Regression of Fibrosis & Reversal of Diastolic Dysfunction in HFpEF Patients Treated With Allogeneic CDCs (RegressHFpEF)

NCT02941705

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Item 6: Clinical Protocol: [redacted] [redacted]

Study Title: **Regress-HFpEF: Regress**ion of fibrosis & reversal of diastolic dysfunction in **HFpEF** patients treated with allogeneic CDCs

A Phase 2 Study of the safety and feasibility of intracoronary delivery of allogeneic human cardiosphere-derived stem cells (CDCs) in patients with heart failure and a preserved ejection fraction (HFpEF).

Study Phase: Phase 2

Product Name: CAP-1002, with allogeneic human cardiosphere-derived cells as the active ingredient

Indication: Heart failure with a preserved ejection fraction

Investigators: Michael R. Zile, MD, Sheldon Litwin, MD, Valerian Fernandes, MD, Eduardo Marbán, MD, PhD

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Confidentiality Statement

TABLE OF CONTENTS

STUDY SYNOPSIS

Sponsor: Eduardo Marbán, MD, PhD - Cedars-Sinai Heart Institute Investigators:

Michael R Zile, MD, Sheldon Litwin, MD, Valerian Fernandes, MD, Eduardo Marbán, MD, PhD

Name of Study Therapy:
Allogeneic Cardiosphere-Derived Cells - CAP-1002

Title of Study:

Regress-HFpEF: Regression of fibrosis & reversal of diastolic dysfunction in **HFpEF** patients treated with allogeneic CDCs

Study Phase: 2 Objectives:

Primary: To determine the safety profile of CAP-1002 administered by intracoronary infusion in patients with Heart Failure and a Preserved Ejection Fraction (HFpEF).

Secondary: To assess exploratory efficacy endpoints to determine whether treatment of HFpEF patients with intracoronary allogeneic CDCs affects clinical functional status (QOL scores), exercise tolerance (6 Minute Walk Test - 6MWT), exercise hemodynamics (supine exercise ergometry during right heart catheterization), myocardial interstitial fibrosis (MRI with native T1 mapping and calculation of extracellular volume [ECV] after gadolinium administration), macroscopic fibrosis by delayed gadolinium enhancement (DGE), and diastolic function (catheterization, echocardiography, BNP).

Study Rationale:
HFpEF is a distinct clinical heart failure syndrome and represents a critical unmet need in cardiovascular medicine. [1-4] HFpEF patients have a marked increase in morbidity and mortality and a profound clinical disability. [5, 6-13] However, to date, no management strategies have been definitively demonstrated to decrease morbidity and mortality or decrease the clinical disability suffered by HFpEF patients. [14-20] We postulated that one pivotal reason that previous randomized clinical studies have failed to show efficacy in HFpEF trials centers around the incomplete understanding of the pathophysiologic mechanisms underlying the development of HFpEF. Studies in patients with HFpEF and in relevant animal models of HFpEF have demonstrated that one critical mechanism contributing to HFpEF involves changes in the cardiac interstitium and extracellular matrix (ECM) fibrillar collagen homeostasis. [21,22]

[redacted]

Study Design:

Patients with HFpEF meeting all inclusion and no exclusion criteria will be enrolled. A randomized, double blind, placebo-controlled (RCT) Phase 2 feasibility study will be conducted. This Phase 2 RCT will study a reasonably homogeneous HFpEF patient population. The goal is to recruit an enriched sample of patients with structural/functional abnormalities like those in the pre- clinical rat model, with a limited number/extent of co-morbid conditions. A randomized, double blind, placebo-controlled design in 40 patients with 1:1 randomization (20 placebo, 20 CDC treated) will be performed. Patients will be assessed at screening, post-infusion, 2 weeks, 3, 6, and 12 months after treatment. The effects of one-time administration of CDCs in patients with HFpEF will be examined.

Patient Population:
Three (Zile, Litwin, Fernandes) of the 4 study investigators have dual appointments at the RHJ Department of Veterans Administration Medical Center (VAMC) and Medical University of South Carolina Hospital Authority (MUSC). These individuals will be the ones responsible for clinical trial execution, including patient enrollment. Patients referred from either center are screened at MUSC, where all tests, procedures and study visits are performed and which will have sole responsibility for the conduct of the trial. Screening for enrollment is from three primary sources: patients hospitalized for HF, patients in primary and specialty care clinics with HF as a listed problem, and patients undergoing echocardiography with a request listing HF as a problem or a result identifying evidence of increased LV filling pressures. Over the last 6 months, these screening methods have yielded a list of 337 patients that would fulfill the inclusion and exclusion criteria for Regress-HFpEF listed below. Our previous studies indicate that we have been successful in recruiting 54–69 % of eligible subjects into RCTs and investigator initiated studies. Therefore, recruitment expectations are justifiable.

Recruitment time-line: 2.0 patients / month, 40 patients by month 20 (approximately 20 males and 20 females from VAMC or MUSC), 6 month endpoints at month 26, 12 month endpoints at month 32, complete analysis finished by month 36. (See Appendix 2).

Main Criteria for Inclusion/Enrollment:

Inclusion Criteria:

- ≥ 18 years old, male or female
- LVEF ≥ 50%
- Symptoms and physical findings of chronic heart failure (NYHA class II- ambulatory IV)
- Treatment with a stable, maximally tolerated dose of diuretic(s) for a minimum of 30 days prior to randomization.
- Left atrial (LA) enlargement [defined by at least one of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20 cm^2 or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m^2] or LV concentric remodeling (LV posterior or septal wall thickness ≥ 1.2 cm) using echo or MRI
- BNP > 125 pg/ml for patients in NSR or > 150 pg/ml for patients in AF or resting PCWP > 15 mmHg, or exercise PCWP > 18 mmHg
- Ability to provide informed consent and follow-up with protocol procedures.

Exclusion Criteria:

- Any confirmed prior echocardiographic measurement of LVEF < 40%
- Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery, or percutaneous coronary intervention (PCI) within the 3 months prior to randomization or previous CABG or Non-revascularized, hemodynamically significant CAD (FFR < 0.75)
- Current acute decompensated HF
- Alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms such as severe pulmonary disease (i.e., requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy); hemoglobin (Hgb) < 10 g/dl; body mass index (BMI) > 45 kg/m^2
- Use of investigational drugs or treatments at the time of enrollment
- Systolic blood pressure > 150 mmHg unless receiving ≥ 3 antihypertensive drugs
- History of any dilated cardiomyopathy; right sided HF in the absence of left-sided structural heart disease; pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy; clinically significant congenital heart disease; hemodynamically significant valvular heart disease
- Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within 3 months
- Uncontrolled dysrhythmia; symptomatic or sustained ventricular tachycardia or atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute
- Prior major organ transplant or intent to transplant (i.e., on transplant list)
- Hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin > 1.5 mg/dl; history of chronic viral hepatitis
- Chronic Kidney Disease with eGFR < 30 mL/min/1.73 m2; serum potassium > 5.5 mmol/L (mEq/L)
- History or presence of any other disease with a life expectancy of < 3 years
- Non-compliance to medical regimens
- Drug or alcohol abuse within the last 12 months
- Devices that are MRI incompatible

- History of malignancy within the past 5 years
- Pregnant or nursing (lactating) women confirmed by a positive human chorionic gonadotropin (hCG); women of child-bearing potential (physiologically capable of becoming pregnant), unless using highly effective contraception methods during study
- Diagnosis of active myocarditis
- Known hypersensitivity to contrast agents
- Known hypersensitivity to dimethyl sulfoxide (DMSO)
- Known hypersensitivity to bovine products
- History of heparin induced thrombocytopenia (HIT)
- Active infection not responsive to treatment
- Active allergic reactions or connective tissue diseases.
- History of cardiac tumor or cardiac tumor demonstrated on screening
- History of previous stem cell therapy
- Human Immunodeficiency Virus (HIV) infection

OUTCOME MEASURES

Primary Safety endpoints:

The primary endpoint is the proportion of subjects experiencing any of the following safety-related events during or post intracoronary delivery during the six and twelve month follow-up period:

- TIMI myocardial perfusion grade: New TIMI flow 0–2 or TIMI myocardial perfusion grade (TMPG) 0–2, noted immediately following intracoronary infusion of CAP-1002 and persisting > 3 min after cell infusion, despite intracoronary vasodilator administration.
- Acute myocarditis within one month of intracoronary infusion, possibly attributable to CAP-1002, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002, humoral or cellular immune reaction specific to CAP-1002 must also be documented.
- 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) resulting in death, or requiring medical intervention, within 72 hours of intracoronary infusion.
- Sudden unexpected death within 72 hours of intracoronary infusion defined as occurring within 1 hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
- Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and re-hospitalization for

cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin I and CK- MB will be obtained in a serial fashion over 24 hours after CAP-1002 infusion.

Secondary Safety endpoints (Short and Long Term):

- Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations), emergency room treatment for heart failure (including outpatient infusion).
- Any hospitalization due to a cardiovascular cause or related to CAP-1002.
- Any inter-current cardiovascular illness or one related to CAP-1002. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol, troponin I and CKMB levels.
- Development of increased DSA levels specific to the CAP-1002 CDC donor at immunologically significant titers.

Efficacy Endpoints (Exploratory): 6- and 12-month follow-up periods*:

- Absolute and relative change in myocardial structure and function: measured by echocardiogram, MRI:
- LV volume, mass, EF, regional wall motion. Based on rodent data, none of these parameters are expected to change either as a function of time or treatment.
- Regression of myocardial fibrosis ECV by MRI T1 mapping.
- Improvement of diastolic dysfunction by echo parameters and reduction in LV filling pressures by catheterization and exercise hemodynamics.
- Absolute and relative reduction in BNP.
- Absolute and relative increase of 6MWT Distance
- Absolute and relative improvement in Quality of Life (QOL) questionnaire MLWHF.
- Absolute and relative reduction in pro-inflammatory and pro-fibrotic signaling measured by plasma biomarkers and plasma proteomics.
  * Cath and MRI will only be done at the 6-month time point.

- **Transthoracic Echocardiogram:**

  - **Rationale:** evaluate indices of LV systolic and diastolic function and LV and left atrial structure estimates to characterize any improvement or stability over time with the use of CDCs
  - **Indices for safety:**
    EF, LVEDV, regional wall motion
  - **Indices for efficacy:**
    E/E', LA Volume, RV systolic pressure estimates, LV mass

- **Cardiac MR (with and without contrast):** Unless known contra-indications

- **Rationale:** evaluate myocardial interstitial fibrosis
- **Indices:**
  MRI with native T1 mapping and calculation of extracellular volume [ECV]
  Macroscopic fibrosis by delayed gadolinium enhancement (DGE)

- **Right Heart Catheterization:**

- **Rationale:** assess LV diastolic function at rest and during supine bicycle ergometry.

- **Indices:** PCWP, PA systolic and diastolic pressure, cardiac output

- **BNP:**

- **Rationale:** Reflects changes in LV filling pressure using non-invasive method

- **6MWT:**

- **Rationale:** Assess exercise capacity using noninvasive method

- **Quality of Life Questionnaire (QOL):**

- **Rationale:** to obtain baseline and follow-up evaluation of QOL spanning key domains pertinent to HFpEF

- **Tool:** Minnesota Living with Heart Failure (MLWHF)

Test Product, Dose, and Mode of Administration:

Non-occlusive, sequential, three-vessel intracoronary delivery of 25 million CDCs (or placebo) in each of the three coronary arteries, as used safely to date in 14 subjects in the DYNAMIC trial. This method achieves broad myocardial coverage and is atraumatic to vessel walls, as a flexible guiding catheter is used to deliver the cells. [redacted]

Using SAS or comparable software, the company will provide the master randomization list of a 1:1 (CAP-1002 to placebo) randomization using permuted blocks with random block sizes of 2 or 4 without stratification. In addition, the company, through its third-party drug depot, will ship investigational product to the MUSC research pharmacy on a just in time, per patient basis before each scheduled infusion.

Duration of Treatment:

All patients will be followed until they have reached 12 months follow-up.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

µl	Microliter
AE	Adverse Event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (same as SGPT)
AST	Aspartate aminotransferase (same as SGOT)
ATM	Atmospheres
β-HCG	Beta Human Chorionic Gonadotropin
BP	Blood Pressure
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
C	Celsius
CCU	Critical (or Coronary) Care Unit
CDC	Cardiosphere Derived Cell
ceMRI	Contrast-Enhanced Magnetic Resonance Imaging
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Cardiac Index
CK-MB	Creatine phosphokinase MB isoenzyme
CMV	Cytomegalovirus
CO	Cardiac output
CRF	Case Report Form
CRP	C-reactive protein
CS	Clinically Significant
CT	Computerized Tomography
DLCO	Diffusing Capacity for Carbon Monoxide
DMSO	Dimethyl Sulfoxide
DSMB	Data Safety Monitoring Board
DCE-CMR	Dynamic Contrast Enhanced Cardiac Magnetic Resonance
ECG	Electrocardiogram
EDV	End-Diastolic Volume
ESR	Erythrocyte Sedimentation Rate
ESRP	Expedited Safety Report
ESV	End-Systolic Volume
F	Fahrenheit
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GCP	Good Clinical Practice

GFR	Glomerular Filtration Rate
HR	Heart Rate
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus
HF	Heart Failure
Hb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
K	Potassium
kg	Kilogram
LDH	Lactate dehydrogenase
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
M	Million
MACE	Major Adverse Cardiac Event
mcg	Microgram
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
min	Minute
mL	Milliliter
mm	Millimeters
mmol	Millimole
Na	Sodium
NCS	Not clinically significant
NYHA	New York Heart Association
p	Probability
PA	Pulmonary Artery
PBS	Phosphate buffered saline
PCWP	Pulmonary capillary wedge pressure
mPAP	Mean pulmonary artery pressure
PRA	Panel Reactive Antibodies
PSP	Patient Specific Probability
PT	Prothrombin time
PTT	Activated partial thromboplastin time
r	Correlation coefficient
RBC	Red blood cell

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SVT	Supraventricular Tachycardia
6MWT	Six Minute Walk Test
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPRO	Serious Procedure Related Outcome
TTE	Transthoracic Echocardiography
UA	Urinalysis
VGEF	Vascular Endothelial Growth Factor
VT	Ventricular Tachycardia
WBC	White Blood Cell

1.1 Rationale for Study and Patient Population:

HFpEF is a distinct clinical heart failure syndrome and represents a critical unmet need in cardiovascular medicine. [1-4] HFpEF patients have a marked increase in morbidity and mortality and a profound clinical disability. [5, 6-13] However, to date, no management strategies have been definitively demonstrated to decrease morbidity and mortality or decrease the clinical disability suffered by HFpEF patients. [14-20] We have postulated that one pivotal reason that previous randomized clinical studies have failed to show efficacy in HFpEF trials centers around the incomplete understanding of the pathophysiologic mechanisms underlying the development of HFpEF. Studies in patients with HFpEF and in relevant animal models of HFpEF have demonstrated that one critical mechanism contributing to HFpEF are changes in the cardiac interstitium and extracellular matrix (ECM) fibrillar collagen homeostasis. [21, 22] Preliminary studies presented demonstrate that a highly novel application of stem cell therapy to a rodent model of HFpEF results in regression of ECM fibrosis and reversal of LV diastolic dysfunction[57]. These preliminary studies form the foundation for this proposed application in HFpEF.

Health care utilization and costs in HFpEF: HFpEF patients consume an enormous percentage of all health care utilization costs. Previous studies and preliminary data demonstrate that HFpEF health care utilization costs are driven in part by very high hospitalization and repeat hospitalization rates. [1,11,12] Hospitalization for HFpEF exceeds 15%/year in selected patients in RCTs, 25 %/year in unselected epidemiologic studies, and 25% / year in our preliminary VA data. We reviewed 800 consecutive HF hospitalizations at the Charleston VA site in patients with an echocardiogram at the time of hospitalization to determine presence of HFpEF, frequency and costs. There were 412 HFpEF admissions, mean age 72 ± 10 (SD) years, length of stay 5 ± 2 (SD) days, total inpatient cost $13,322 ± 5,5051 (SD) including bed day, laboratory, radiology, pharmacy and other costs and a frequency of 1.5 ± 0.5 (SD) HF hospitalizations/patient/2 years observation. Once hospitalized for HFpEF, the incidence of re-hospitalization is ~50% in 6 months and patients require frequent outpatient visits by primary and specialty care, frequent tele-health care visits, diagnostic testing and medications. In addition, there is a high risk of death with a 5-year mortality rate ~50%. The annual VA cost / HFpEF patient is ~$15,000; based on one five-day hospitalization ($12,500), four outpatient visits ($500), four medications ($100/month), annual echo, blood tests, X-rays ($1,500). Thus, HFpEF represents an important target for cost and health care utilization reduction.

Quality of life (QOL) in HFpEF: HFpEF patients have a low QOL with debilitating symptoms. This cardiac disability has been objectively assessed by a 6-minute hall walk (6-MHW), standard exercise treadmill, and cardiopulmonary exercise testing. [1,11,12] Our studies have demonstrated that serial 6-MHW performed successfully in > 92% of our HFpEF patients has very high reproducibility and is significantly reduced (220 m vs 550 m in age- and sex-matched controls). [24] Cardiac symptom status can be assessed by QOL tools validated in HFpEF, including New York Heart Association Class (NYHC), Quality of Life in Severe Heart Failure Questionnaire (QLSHFQ), the Chronic Heart Failure Questionnaire (CHQ), the Left Ventricular Dysfunction Questionnaire (LVD), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). MLHFQ has been successfully applied in HFpEF RCTs and correlates well with our preliminary studies. [8] In addition, preliminary studies indicate that overall VA-specific QOL tool (VA SF-12) is abnormal in HFpEF.

[redacted]

1) CADUCEUS (**CA**rdiosphere-**D**erived **aU**tologous **S**tem **CE**lls to reverse ventric**U**lar dy**S**function), IND #13930, NCT00893360; first-in-human trial demonstrated preliminary safety and efficacy of autologous CDCs in reducing fibrosis post-myocardial infarction (MI) in patients with pre-symptomatic HFREF. Once the indirect mechanism of CDC action became evident, [34,32] emphasis shifted to the allogeneic product (CAP-1002).

2) ALLSTAR (**ALL**ogeneic heart **ST**em cells to **A**chieve myocardial **R**egeneration), IND #15118, NCT01458405; a randomized, double-blind, placebo-controlled Phase 1/2 study of the safety and efficacy of intracoronary delivery of CAP-1002 in subjects with an MI and pre-symptomatic ischemic HFREF. ALLSTAR did not reveal an increase in adverse events. In the completed 14-patient Phase 1 portion, a relatively small, non-clinically significant increase in cardiac enzymes of the scale common with any intracoronary intervention, the lack of high level immune response to donor cells, and the absence of any immune-related clinical sequelae support the safety of CAP-1002. [35] The randomized, double-blind multicenter Phase 2 portion of ALLSTAR is currently undergoing final analysis. A prespecified 6-month administrative interim analysis demonstrated a low probability (futility) of achieving a statistically-significant difference in the 12-month primary efficacy endpoint of percent change from baseline in infarct size as a percent of left ventricular mass as measured by cardiac magnetic resonance imaging (MRI). At 6 months, a near-statistically significant (p=0.05) reduction of mean end-diastolic volume as well as a trend of reduction of mean end-systolic volume, were seen in the CAP-1002 treatment group. There was no notable difference between treatment groups with respect to the change in ejection fraction. There were no safety signals in the CAP-1002 treatment cohort.

[redacted]

[redacted]

[redacted]

2. STUDY OBJECTIVES

2.1. Primary Objective

To determine the safety profile of CAP-1002 administered by intracoronary infusion in patients with Heart Failure and a Preserved Ejection Fraction (HFpEF).

2.2. Secondary Objective

To assess exploratory efficacy endpoints to determine whether treatment of HFpEF patients with intracoronary allogeneic CDCs affects clinical functional status (QOL scores), exercise tolerance (6MWT), exercise hemodynamics (supine exercise ergometry during right heart catheterization), myocardial interstitial fibrosis (MRI with native T1 mapping and calculation of extracellular volume [ECV] after gadolinium administration), macroscopic fibrosis by delayed gadolinium enhancement (DGE), and diastolic function (catheterization, echocardiography, BNP).

3. STUDY ENDPOINTS

3.1 Primary Endpoints:

3.1.1 Primary Safety Endpoints

The primary endpoint is the proportion of subjects experiencing any of the following safety-related events during or post intracoronary delivery during the six and twelve month follow-up period:

- TIMI myocardial perfusion grade: New TIMI flow 0–2 or TIMI myocardial perfusion grade (TMPG) 0–2, noted immediately following intracoronary infusion of CAP-1002 and persisting > 3 min after cell infusion, despite intracoronary vasodilator administration.
- Acute myocarditis within one month of intracoronary infusion, possibly attributable to CAP-1002, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002, humoral or cellular immune reaction specific to CAP-1002 must also be documented.

- 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) resulting in death, or requiring medical intervention, within 72 hours of intracoronary infusion.

- Sudden unexpected death within 72 hours of intracoronary infusion defined as occurring within 1 hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.

- Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and re-hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin I and CK-MB will be obtained after CAP-1002 infusion.

3.1.2 Secondary Safety endpoints (Short and Long Term):

- Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations or emergency room treatment for heart failure).
- Any hospitalization due to a cardiovascular cause or related to CAP-1002.
- Any inter-current cardiovascular illness or one related to CAP-1002. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol, troponin I and CKMB levels.
- Development of increased DSA levels specific to the CAP-1002 CDC donor at immunologically significant titers.

3.2 Secondary Endpoints

3.2.1. Efficacy Endpoints (Exploratory): 6- and 12-month follow-up periods*:

- Absolute and relative change in myocardial structure and function: measured by echo, MRI:
  - LV volume, mass, EF, regional wall motion. Based on rodent data, none of these parameters are expected to change either as a function of time or treatment.
  - Regression of myocardial fibrosis ECV by MRI T1 mapping.
- Improvement of diastolic dysfunction by echo parameters and reduction in LV filling pressures by catheterization and exercise hemodynamics.
- Absolute and relative reduction in BNP.
- Absolute and relative increase of 6MWT Distance.
- Absolute and relative improvement in Quality of Life (QOL) questionnaire, MLWHF.

- Absolute and relative reduction in pro-inflammatory and pro-fibrotic signaling measured by plasma biomarkers and plasma proteomics.

  * Cath and MRI will only be done at the 6-month time point.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Hypothesis: Treatment of patients with symptomatic hypertensive heart disease-induced HFpEF with allogeneic CDCs will be safe and will improve clinical functional status, exercise tolerance/hemodynamics, myocardial interstitial structure, and diastolic function; the mechanisms underlying these improvements will be reflected in changes in plasma biomarkers that indicate a reduction in pro-inflammatory and pro-fibrotic signaling.

Specific Aims:

Perform a randomized, double blind, placebo-controlled Phase 2a feasibility study to determine whether treatment of HFpEF patients with intracoronary allogeneic CDCs affects clinical functional status (QOL scores), exercise tolerance (6MWT), exercise hemodynamics (supine exercise ergometry during right heart catheterization), myocardial interstitial fibrosis (MRI with native T1 mapping and calculation of extracellular volume [ECV] after gadolinium administration), macroscopic fibrosis by delayed gadolinium enhancement (DGE), and diastolic function (catheterization, echocardiography, BNP).

Determine whether treatment with CDCs affects plasma biomarkers that indicate alterations in proinflammatory and profibrotic mechanisms and whether these biomarker changes correlate with alterations in clinical symptom status, myocardial structure and/or diastolic function.

Use these feasibility and exploratory efficacy data study data to 1) confirm that the application of CDCs is safe in HFpEF patients and 2) optimize the design of a Phase 2b trial including determination of sample size power estimates and appropriate primary and secondary endpoints.

Research Strategy / Clinical Trial Design: This Phase 2a RCT will study a reasonably homogeneous HFpEF patient population. The goal is to recruit an enriched sample of patients with structural/functional abnormalities like those in the DS rat model [57], with a limited number/extent of co-morbid conditions. A randomized, double blind, placebo-controlled design in 40 patients with 1:1 randomization (20 placebo, 20 CDC treated) will be performed. Patients will be assessed at baseline, post-infusion, pre-discharge, 24-48 hours post discharge, 0.5, 3, 6, and 12 months after treatment.

Here we are studying the effects of one-time administration of CDCs in patients with HFpEF. While CDCs benefits persist for at least several weeks in the DS rat model, it is possible that benefits in humans may wear off over time. Thus, one of the objectives here is obtain preliminary indications of the duration of therapeutic benefits over the year of follow-up. If benefits are evident initially but wane over time, future clinical studies may be designed to include multiple repeated doses.

Team: The clinical study will be conducted by Dr. Zile and colleagues in Charleston, SC. Dr Eduardo Marbán will collaborate on study design and analysis. [redacted] Inc., a NASDAQ-traded biotechnology company (ticker symbol CAPR), has licensed all relevant intellectual property and is conducting the ongoing ALLSTAR, DYNAMIC, and HOPE-Duchenne trials. [redacted] will collaborate by providing at-cost investigational product (CAP-1002 or placebo) produced under Good Manufacturing Practices (GMP) standards approved for Phase 2 clinical testing, as well as randomization services, and immunological assays performed through its contracted central immunology laboratory.

Pre-Screen: Patients will be referred from either the RHJ Department of Veterans Administration Medical Center (VAMC) or the Medical University of South Carolina Hospital Authority (MUSC) and identified from three primary sources: patients hospitalized for HF, patients in primary and specialty care clinics with HF as a listed problem, and patients undergoing echocardiography with a request listing HF as a problem or a result identifying evidence of increased LV filling pressures. Over the last 6 months, these screening methods have yielded a list of 337 patients that would fulfill the inclusion and exclusion criteria for Regress-HFpEF listed below. The referred Veterans, will be predominantly male, and MUSC will provide the necessary additional female patients to reflect the real-world demographic sex distribution of HFpEF. Our previous studies indicate that we have been successful in recruiting 54–69 % of eligible subjects into RCTs and investigator initiated studies. Therefore, recruitment expectations are justifiable.

Consent and Screen: If a patient fulfills the inclusion criteria of clinical HF, preserved EF, increased BNP or increased PCWP, and increased LA size or concentric LVH and has none of the exclusion criteria (see details below), they will be consented and undergo CT coronary angiography (to define the coronary anatomy; CT scan will not be needed if patient has had a recent coronary arteriogram or previous CT scan within 1 year showing no significant CAD). If significant CAD is identified by CT and confirmed by subsequent coronary arteriography and FFR, subjects will be referred to their physician for consideration of a revascularization procedure. If such subjects undergo a revascularization procedure, they may be reconsidered and rescreened for the study, minus a repeat CT, after a minimum of 3 months post- revascularization.

The originally approved protocol called for HLA typing and testing for donor-specific antibodies (DSAs), and using this information to choose a CAP-1002 master cell bank that lacks expression of the relevant antigen(s), if applicable. We now have clinical information from the randomized placebo-controlled ALLSTAR trial of 134 subjects treated with CAP-1002, some of whom were cross-matched and others (n=13) of whom had no possible cross-match and so were treated with cells from randomly selected CAP-1002 master cell banks. There was no difference in efficacy or safety between the cross-matched and non-cross-matched groups, with a tendency to larger therapeutic responses (i.e., greater attenuation of adverse remodeling after myocardial infarction) in the non-cross-matched subjects. Accordingly, we made a protocol modification to eliminate the cross-matching requirement for investigational product CAP-1002. We will still perform HLA typing and measure DSAs pre and post-treatment (for documenting de novo immune responses if any) but not cross-match cells. We will also eliminate ELISpot testing, as its value is theoretical and there has been no evidence of a clinically significant cell-mediated immune response in any of the N=95 subjects tested to date.

Endpoint measurement: Prior to randomization, the patient will undergo measurement of all exploratory efficacy endpoints as listed below:

Echocardiography and MRI: Assess myocardial structure, function, fibrosis using previously published methods; [36, 37-41] interpretation in our imaging core lab by Dr. Litwin.

Catheterization and bicycle ergometry: Assess hemodynamics at rest and during exercise using previously published methods; [10,42-46] interpretation in our hemodynamics core lab by Dr. Fernandes. If PCWP ≥ 20 mmHg at rest, bicycle ergometry will not be performed.

Biomarkers: Blood will be drawn for the assessment of various candidate biomarkers indicative of inflammation (IL1, 6), fibrosis (Gal-3, sST-2, collagen pro- and telo-peptides), ECM homeostasis (MMPs, TIMPs, SPARC, other matricellular proteins/peptides, TGF-b), and t-tubule remodeling (BIN-1) from a peripheral vein. [47-50]

Quality of life: Six-minute hall walk, NYHA class, MLWHF questionnaire.

Randomization: Non-occlusive, sequential, three-vessel intracoronary delivery of 25 million CDCs (or placebo) in each of the three coronary arteries, as used safely to date in the DYNAMIC trial. This method achieves broad myocardial coverage and is atraumatic to vessel walls, as a flexible guiding catheter is used to deliver the cells. [redacted] Using SAS or comparable software, the company will provide the master randomization list of a 1:1 (CAP-1002 to placebo) randomization using permuted blocks with random block sizes of 2 or 4 without stratification. In addition, the company, through its third-party drug depot, will ship investigational product to the MUSC research pharmacy on a just in time, per patient basis before each scheduled infusion.

Follow-up: Safety measurements will be made immediately post infusion, pre-discharge, 24-48 hours post-discharge at 2 weeks and at 3, 6, and 12 months after treatment (described below). Efficacy measurements and safety measurements will be made at 6 and 12 months.

Inclusion criteria:

1. ≥ 18 years old, male or female
2. LVEF ≥ 50%
3. Symptoms and physical findings of chronic heart failure (NYHA class II- ambulatory IV)
4. Treatment with a stable, maximally tolerated dose of diuretic(s) for a minimum of 30 days prior to randomization.
5. Left atrial (LA) enlargement defined by at least one of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20 cm^2 or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m^2 or LV concentric remodeling (LV posterior or septal wall thickness ≥ 1.2 cm) using echo or MRI.
6. BNP > 125 pg/ml for patients in NSR or > 150 pg/ml for patients in AF or resting PCWP > 15 mmHg, or exercise PCWP > 18 mmHg
7. Ability to provide informed consent and follow-up with protocol procedures.

Exclusion criteria-Specific to HFpEF

1. Any confirmed prior echocardiographic measurement of LVEF < 40%
2. Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery, or percutaneous coronary intervention (PCI) within the 3 months prior to randomization or previous CABG or Unrevascularized, hemodynamically significant CAD (FFR < 0.75)
3. Current acute decompensated HF
4. Alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue) such as severe pulmonary disease (i.e., requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy); hemoglobin (Hgb) < 10 g/dl; body mass index (BMI) > 45 kg/m^2
5. Use of investigational drugs or treatments at the time of enrollment
6. Systolic blood pressure > 150 mmHg but < 180 mmHg unless receiving 3 or more antihypertensive drugs
7. History of any dilated cardiomyopathy; right sided HF in the absence of left-sided structural heart disease; Pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy; clinically significant congenital heart disease; hemodynamically significant valvular heart disease
8. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months
9. Uncontrolled dysrhythmia; symptomatic or sustained ventricular tachycardia or atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm)
10. Prior major organ transplant or intent to transplant (i.e., on transplant list)
11. Hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin > 1.5 mg/dl; history of chronic viral hepatitis
12. Chronic Kidney Disease with eGFR < 30 mL/min/1.73 m^2; serum potassium > 5.5 mmol/L (mEq/L)
13. History or presence of any other disease with a life expectancy of < 3 years
14. Non-compliance to medical regimens
15. Drug or alcohol abuse within the last 12 months
16. History of malignancy within the past 5 years
17. Pregnant or nursing (lactating) women confirmed by a positive human chorionic gonadotropin (hCG); women of child-bearing potential (physiologically capable of becoming pregnant), unless using highly effective contraception methods during study
18. Devices that are MRI incompatible

Exclusion criteria-Specific to CAP-1002 (not listed above)

1. Diagnosis of active myocarditis
2. Known hypersensitivity to contrast agents
3. Known hypersensitivity to dimethyl sulfoxide (DMSO)
4. Known hypersensitivity to bovine products
5. History of heparin induced thrombocytopenia (HIT)
6. Active infection not responsive to treatment
7. Active allergic reactions or connective tissue diseases
8. History of cardiac tumor or cardiac tumor demonstrated on screening
9. History of previous stem cell therapy

10. Human Immunodeficiency Virus (HIV) infection

Endpoints: The primary objective is to determine the safety of CAP-1002 administered by multi-vessel, non-occlusive intracoronary infusion in subjects with HFpEF. A secondary objective is to explore, in a non-hierarchical manner, efficacy end-points that will be of value intrinsically as indicators of bioactivity as well as in guiding future trials with CAP-1002.

Safety endpoints: The primary endpoint is the proportion of subjects experiencing any of the following safety-related events during or post intracoronary delivery during the six and twelve month follow-up period:

1. New TIMI flow 0–2 or TIMI myocardial perfusion grade (TMPG) 0–2, noted immediately following intracoronary infusion of CAP-1002 and persisting > 3 min after cell infusion, despite intracoronary vasodilator administration.
2. Acute myocarditis within one month of intracoronary infusion, possibly attributable to CAP-1002, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002, humoral or cellular immune reaction specific to CAP-1002 must also be documented.
3. 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) resulting in death, or requiring medical intervention, within 72 hours of intracoronary infusion.
4. Sudden unexpected death within 72 hours of intracoronary infusion defined as occurring within 1 hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
5. Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and re-hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin I and CK-MB will be obtained after CAP-1002 infusion.

Secondary safety endpoints:

1. Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations and emergency room treatment for heart failure).
2. Any hospitalization due to a cardiovascular cause or related to CAP-1002.
3. Any inter-current cardiovascular illness or one related to CAP-1002. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol, troponin I and CKMB levels.
4. Development of increased DSA levels specific to the CAP-1002 CDC donor at immunologically significant titers.

Efficacy endpoints (exploratory): 6- and 12-month follow-up periods*:

1. Absolute & relative change in myocardial structure & function: measured by echo, MRI:
a) LV volume, mass, EF, regional wall motion. Based on rodent data, none of these parameters are expected to change either as a function of time or treatment.
b) Regression of myocardial fibrosis ECV by MRI T1 mapping.
c) Improvement of diastolic dysfunction by echo parameters and reduction in LV filling pressures by cath and exercise hemodynamics.
2. Absolute and relative reduction in BNP.
3. Absolute and relative increase of 6MWT distance.
4. Absolute and relative improvement in Quality of Life (QOL) questionnaires VA SF-12, MLWHF.
5. Reduction in pro-inflammatory and pro-fibrotic signaling.

* Cath and MRI will only be done at the 6-month time point.

Statistical analysis: An independent DSMB, with roles and responsibilities defined in a written charter, was appointed to oversee safety of the study. The DSMB will consist of three heart failure cardiologists, one with additional expertise in interventional cardiology, one with additional expertise in imaging, one with additional expertise in transplant/immunology, and a statistician. The DSMB may 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 be reported to the DSMB Chair and will be reviewed by the DSMB. The DSMB will have access to reports evaluating group trends for CAP-1002 vs. Control as well as data from the literature for CAP-1002-treated subjects. In addition, any external concerns regarding CDC safety will be brought to the attention of the DSMB.

The proportion of subjects experiencing an adverse event or a protocol-specific safety event (PSE) will be monitored at pre-planned intervals set by the DSMB. A futility chart will be created to allow for DSMB safety monitoring. The excess for CAP-treated subjects is of primary concern as Phase 2a data accrue. The boundaries are computed using StatXact v7 (CyTel, Cambridge MA); a one-sided 95% exact test is performed assuming binomially distributed outcomes. The chart will be applied to any binary outcome pertaining to safety. The chart will be computed over a broad range of possible PSE outcomes. No adjustment for Type I error will be made for repeated looks since the ultimate decision regarding safety represents a clinical decision involving all safety endpoints in the context of efficacy. Descriptive summaries will be provided for all primary and secondary endpoints for both safety and efficacy. A prospective statistical analysis plan (SAP) will be generated for DSMB review with their input. All analyses and reports will be developed per Good Clinical Practices. All analyses will be performed using SAS Version 9.2 or greater.

Efficacy data will be presented as mean changes from screening at designated visits. These Phase 2a data will be used to calculate effect sizes for planning subsequent Phase 2b studies. If there are sufficient follow-up data, longitudinal models (SAS PROC MIXED for continuous endpoints and SAS PROC GENMOD for binary endpoints) will be explored. A formal SAP will be developed in a collaboration between Dr. Zile, MUSC statistician Dulaney Wilson (in the Department of Public Health Sciences), CSMC and [redacted]. Dr. Wilson, Professor, MUSC Department of

Public Health Sciences, and the PI/PD Dr. Zile have collaborated on development of SAPs for a number of published studies.

4.2 Study Duration and Dates

Recruitment time line: 2.0 patients / month, 40 patients by month 20 (approximately 20 males and 20 females from the VAMC and MUSC), 6 month endpoints at month 26, 12 month endpoints at month 32, complete analysis finished by month 36. (See Appendix 2) Covid-19 pandemic and FDA review postponed completion of recruitment and established new time line.

5. STUDY POPULATION SELECTION

5.1 Study Population

Research Strategy / Clinical Trial Design: This Phase 2a RCT will study a reasonably homogeneous HFpEF patient population. The goal is to recruit an enriched sample of patients with structural/functional abnormalities like those in the DS rat model[57], with a limited number/extent of co-morbid conditions. A randomized, double blind, placebo-controlled design in 40 patients with 1:1 randomization (20 placebo, 20 CDC treated) will be performed. Patients will be assessed at screening, post infusion, pre-discharge, 24-48 hrs post-discharge, 0.5, 3, 6, and 12 months after treatment.

Here we are studying the effects of one-time administration of CDCs in patients with HFpEF. It is possible that benefits in humans may wear off over time. Thus, one of the objectives here is obtain preliminary indications of the duration of therapeutic benefits over the year of follow-up. If benefits are evident initially but wane over time, future clinical studies may be designed to include multiple repeated doses.

Consent and Screen: If a patient fulfills the inclusion criteria and has none of the exclusion criteria (see details below), they will be consented and undergo CT coronary angiography (to define the coronary anatomy; CT scan will not be needed if patient has had a recent coronary arteriogram within 3 months showing no significant CAD) and donor-specific antibodies (DSA). If significant CAD is identified by CT and confirmed by subsequent coronary arteriography and FFR, the patient will be referred to their physician for consideration of a

revascularization procedure. After a minimum of 3 months following such a revascularization procedure, the patient can be reconsidered and rescreened for the study, minus a repeat CT.

[redacted]

5.2 Inclusion Criteria

Inclusion criteria:

Inclusion criteria:

1. ≥ 18 years old, male or female
2. LVEF ≥ 50%
3. Symptoms and physical findings of chronic heart failure (NYHA class II- ambulatory IV)
4. Treatment with a stable, maximally tolerated dose of diuretic(s) for a minimum of 30 days prior to randomization.
5. Left atrial (LA) enlargement defined by at least one of the following: LA width (diameter) ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20 cm^2 or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m^2 or LV concentric remodeling (LV posterior or septal wall thickness ≥ 1.2 cm) using echo or MRI.
6. BNP > 125 pg/ml for patients in NSR or > 150 pg/ml for patients in AF or resting PCWP > 15 mmHg, or exercise PCWP > 18 mmHg.
7. Ability to provide informed consent and follow-up with protocol procedures.

5.3 Exclusion Criteria

Exclusion criteria-Specific to HFpEF

1. Any prior echocardiographic measurement of LVEF < 40 %
2. Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery, or percutaneous coronary intervention (PCI) within the 3 months prior to randomization or previous CABG or Unrevascularized, hemodynamically significant CAD (FFR < 0.75)
3. Current acute decompensated HF
4. Alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue) such as severe pulmonary disease (i.e., requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy);

hemoglobin (Hgb) < 10 g/dl; body mass index (BMI) > 45 kg/m2
5. Use of investigational drugs or treatments at the time of enrollment
6. Systolic blood pressure > 150 mmHg but < 180 mmHg unless receiving 3 or more antihypertensive drugs
7. History of any dilated cardiomyopathy; right sided HF in the absence of left-sided structural heart disease; Pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy; clinically significant congenital heart disease; hemodynamically significant valvular heart disease
8. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months
9. Uncontrolled dysrhythmia; symptomatic or sustained ventricular tachycardia or atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm)
10. Prior major organ transplant or intent to transplant (i.e., on transplant list)
11. Hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin > 1.5 mg/dl; history of chronic viral hepatitis
12. Chronic Kidney Disease with eGFR < 30 mL/min/1.73 m2; serum potassium > 5.5 mmol/L (mEq/L)
13. History or presence of any other disease with a life expectancy of < 3 years
14. Non-compliance to medical regimens
15. Drug or alcohol abuse within the last 12 months
16. History of malignancy within the past 5 years
17. Pregnant or nursing (lactating) women confirmed by a positive human chorionic gonadotropin (hCG); women of child-bearing potential (physiologically capable of becoming pregnant), unless using highly effective contraception methods during study
18. Devices that are MRI incompatible

Exclusion criteria-Specific to CAP-1002 (not listed above)
1. Diagnosis of active myocarditis
2. Known hypersensitivity to contrast agents or previous H/O HIT
3. Known hypersensitivity to dimethyl sulfoxide (DMSO)
4. Known hypersensitivity to bovine products
5. History of heparin induced thrombocytopenia (HIT)
6. Active infection not responsive to treatment
7. Active allergic reactions or connective tissue diseases
8. History of cardiac tumor or cardiac tumor demonstrated on screening
9. History of previous stem cell therapy
10. Human Immunodeficiency Virus (HIV) infection

Endpoints: The primary objective is to determine the safety of CAP-1002 administered by multi-vessel, non-occlusive intracoronary infusion in subjects with HFpEF. A secondary objective is to explore, in a non-hierarchical manner, efficacy end-points that will be of value intrinsically as indicators of bioactivity as well as in guiding future trials with CAP-1002.

6. STUDY TREATMENT(S)

[redacted]

6.2 Treatment Administered

[redacted] All patients will receive 25 million cells (CAP-1002) or placebo in each of the 3 coronary arteries. Prior to infusion of the investigational product, the lumen of the catheter is flushed with saline-heparin wash solution (with or without nitroglycerin depending on individual patient tolerance) for approximately 30 seconds (±5 seconds). [redacted]

[redacted] During and in between infusions, multiple measures of O2 sat, hemodynamics, including blood pressure and heart rate and monitoring for any arrhythmias (ventricular and supra-ventricular). Fluids are permitted for hypotension during the procedure, as are low dose inotropes such as dobutamine and use of inhaled nitric oxide. VPCs or NSVT can be seen with insertion of the PA catheter as it traverses the RV and is easily remedied by catheter withdrawal. Oxygen will be used if needed to treat temporary hypoxia should this occur. If significant adverse events occur, the infusion will be terminated (see details below).

6.3 Selection and Timing of Dose

This Phase 2 cohort will include 40 patients randomized in a double-blind fashion to receive either CAP-1002 or placebo in a 1:1 ratio. CAP-1002 will be grown from unrelated donors. After completion of the screening and baseline procedures, patients will receive either CAP-1002 or placebo Infusions within 3 weeks of screening and completion of any outstanding baseline studies required to confirm a diagnosis of HFpEF. All patients (those who have undergone CAP-1002 or placebo infusion) will be followed until the last enrolled patient has reached 12-month follow-up. Patients will be followed post infusion, pre-discharge, 24-48 hrs post-discharge, at week 2 and at months 3, 6, and 12 after CAP-1002 or placebo infusion.

6.4 Method of Assigning Patients to Treatment Groups

[redacted] Using SAS or comparable software, [redacted] will prepare the master randomization list of a 1:1 (CAP-1002 to placebo) randomization using permuted blocks with random block sizes of 2 or 4 without stratification. Following randomization, [redacted], through its third-party drug depot vendor, will ship out investigational product (CAP-1002 or placebo) on a just in time, per patient basis to the MUSC Center for Cellular Therapy.

6.5 Concomitant Therapy

Concomitant therapies are defined as all therapies received on or after the day of infusion. Those received before the day of infusion are considered prior therapies. Prior therapies will be recorded during initial screening. Concomitant therapies with HFpEF –specific agents will be recorded at each study visit, beginning with the day

of infusion, as well as all other medications. All patients with HFpEF will be on stable background diuretic therapy prior to enrollment as well as any adjunctive therapies for HFpEF deemed to be necessary in that particular patient.

6.6 Restrictions

6.6.1 Prior Therapy

Patients who have had previous stem cell therapy or any organ transplant may not participate in this study. There are no medication restrictions except those listed in Appendix 3. Individual patient medication will be advised by the patient's physician according to the usual practice of the study site. Coumadin / other anticoagulant discontinuation prior to catheterization will be managed according to standard of care practices.

6.6.2 Fluid and Food Intake

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

6.6.3 Patient Activity Restriction

Patients should follow the activity recommendations prescribed by their physician.

6.7 Treatment Compliance

Since the treatment is a one-time procedure, dosing compliance is not a concern. Study site personnel will document compliance with medications and study follow-up procedures at each study visit.

6.8 Packaging and Labeling

[redacted]

6.9 Storage and Accountability

[redacted]

[redacted]

6.10 Investigational Product Retention at Study Site

[redacted]

7. STUDY PROCEDURES

7.1. Informed Consent

Before being admitted to the clinical study, all patients must consent in writing to participate. An Informed Consent Form (ICF) will be given to each patient, 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 patient. The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference on Harmonization (ICH) requirements, and local laws. The Investigator will review the study with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review will be in a form understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient 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 patient 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 patient 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 patients and repeat the consent process with the amended ICF for any ongoing patients.

7.2. Medical History

A complete medical history, including all elements pertinent to HFpEF (e.g., effort intolerance, NYHA FC, exercise–induced chest pain or dizziness/syncope, edema, etc., medications, etc.) of patients enrolled in the study will be documented as part of the screening process and reviewed prior to enrollment into the study. At subsequent visits (day of infusion forward), medications, general health and cardiopulmonary

health will be reviewed including all elements pertinent to HFpEF at each patient visit and new information will be updated in the patient's study documentation.

7.3. Physical Examination

A qualified physician, either the Principal Investigator or Sub-Investigators will perform a comprehensive physical examination aimed at examining all signs pertinent to HFpEF at each study visit.

7.4. Vital Signs

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

7.4.1. Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following:

List of laboratory tests

Hematology: *CBC with differential* Immunology: HLA/DSA ***Urine Pregnancy Test*** (for women of childbearing potential Biomarkers HIV Hepatitis panel	***Serum Chemistry:*** Albumin (ALB) Alkaline phosphatase (ALK-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Brain natriuretic peptide (BNP) Creatinine Creatine kinase and subtypes Glucose Lactate dehydrogenase (LDH) Potassium (K) Sodium (Na) Total bilirubin Direct bilirubin Total protein Troponin I (baseline and as needed) ***Coagulation:*** Prothrombin time (PT) Activated partial thromboplastin time (PTT) International Normalized Ratio (INR)

7.5 12-Lead ECG

Beginning at the screening period, a 12 lead ECG will be performed and then post infusion, day of discharge from the hospital, day14, and months 3, 6 and 12. The purpose will be to assess any change in axis, look for new features of LVH, MI, and assess rhythm.

7.6 Echocardiography

An echocardiogram will be performed during the screening period as well as at months 6 and 12 visits. Echocardiography will be performed to measure LV structure, systolic and diastolic function.

7.7 Holter Monitor (24 Hour ECG)

The 24-hour ECG (Holter) will be performed during the screening phase, 0.5, and 6 months after Cap-1002 to rule out the presence of significant arrhythmias or conduction defects.

7.8 Six Minute Walk Test

The 6MWT will be performed at screening and at 6 and 12-month follow-up visit. While we will be looking for an improvement in 6MWT distance, a ≥ 15% reduction in 6MWT distance from baseline will be consider a significant decline.

7.9 Magnetic Resonance Imaging Protocol

With the exception of those patients with a known contra-indication for MRI, all patients will undergo contrast-enhanced magnetic resonance imaging (ceMRI) at screening and at month 6. 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 such that there is standardization regarding acquisition of the studies. Specific measures of note will include LV structure and function. Delayed contrast enhancement can also reflect the presence of myocardial fibrosis. This will not be required in patients in whom there are contraindicated to undergo an MRI.

7.10 Image Analysis

The imaging data will be read by cardiovascular imaging expert: Sheldon Litwin, MD.

7.11 Cardiac CT

A computerized tomography (CT) of the chest and heart will be performed at the screening visit to ensure that there are no clinically significant pre-existing abnormalities particularly calcification, atherosclerosis in the coronary arteries. The CT will be performed with (provided no renal dysfunction) and without contrast. If any

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

7.12 Clinical Functional Capacity and Quality of Life Measures

New York Heart Association (NYHA) functional status will be evaluated at screening, 0.5, 3, 6 months, 12 months. A MLWHF QOL questionnaire will be completed at baseline, 6 months and 12 months.

7.13 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject 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 the medicinal product. 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 patient'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 patient'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 or his/her designee will then record all relevant information regarding an AE/SAE into the CRF. It is not acceptable for the Investigator to send photocopies of the patients' medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when the DSMB Chair requests copies of medical records for certain cases. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the DSMB Chair.

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.

7.13.1 Timing

Adverse event assessment and documentation will occur at each study visit from during and immediately after infusion and then throughout the study. On the day of treatment administration, a patient's medical complaint will be considered to be a treatment-emergent adverse event if the event occurs any time after the infusion of CAP-1002 or placebo.

7.13.2 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 patient, 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 7.13.7.1, Serious Adverse Events.

7.13.3 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 (CAP-1002 or placebo) will be defined according to one of the following categories:

Related: The AE/SAE is clearly related to the investigational product.
Not related: The AE/SAE is clearly NOT related to the investigational product.
Unable to Determine: The investigator should make every attempt to assign causality based on his best clinical judgment, all available information about the investigational product, and consultation with the Capricor chief medical officer. In the rare case causality cannot be determined, "unable to determine" may be used; however, for determining whether an event meets expedited reporting requirements, "unable to determine" shall be treated the same as a "related" event.

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.

7.13.4 Expectedness

The following events are those that could be expected to occur as a result of the catheterization and infusion procedure:

- Premature ventricular contractions, non-sustained ventricular tachycardia
- Possible atrial tachyarrhythmias (e.g. atrial fibrillation).
- Possible bradycardias and conduction block
- Hypotension (Systolic Blood Pressure <80mmHg) with symptoms, requiring intravenous fluid administration, during the cell infusion procedure
- Desaturation below 90% requiring O_2 administration or up titration of O_2
- Bleeding and /or hematoma formation at the site of vascular access for the cell infusion procedure. Complications such as pneumothorax or pulmonary artery rupture are extremely rare SAE of any cath procedure and are not anticipated. (Access using ultrasound guidance and safe process for balloon inflation to determine PCWP)

  Note: For this study, the standard definitions of *non-sustained and sustained ventricular tachycardia* will be employed:
  - *non-sustained VT:* "ventricular tachycardia with a heart rate of at least 120 beats per minute, lasting for at least three beats and persisting less than 30 second"
  - *sustained VT:* " ventricular tachycardia that lasts more than 30 seconds and leads to hemodynamic collapse

All adverse events expected or otherwise, should be reported in the patient data. Serious adverse events should be reported to the Sponsor within 24 hours of the site learning of the event.

7.13.5 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 indicate whether the abnormal result is clinically significant (CS) or not clinically significant (NCS) on the source document and CRF. The Investigator will also date and sign the source document next to the circled abnormal result.

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.

7.13.6 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 7.13.5 and will be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 7.13 or SAE, as defined in Section 7.13.7.1.

Clinically significant abnormal laboratory findings that are detected during the study or are present at baseline 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 patient'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.

7.13.7 Serious Adverse Events

7.13.7.1 Definition

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect or important medical event.

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 patient 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.

7.13.7.2 Reporting Serious Adverse Events

Step 1- If an SAE occurs that is possibly related to protocol, procedure or product, the study site will notify the following within 24 hours:
1- Sponsor (Cedars-Sinai Heart Institute)
2- Regress-HFpEF DSMB
3- MUSC IRB
4- [redacted]

Step 2- Send most current, updated SAE CRF and other available documentation to DSMB within 72 hours (3 days). Every attempt will be made to obtain all necessary documentation from all involved health care providers and facilities both MUSC and any other location. However, even if documents and information are "pending", the DSMB will be sent all currently available information in this timely fashion.

Step 3- DSMB will complete adjudication using the adjudication SAE form within 5 days. However, if the DSMB requests additional information, documentation or primary documents or if the study site receives additional information, revised adjudication by the DSMB may occur. The DSMB will send the results of the adjudication to the study site who will in turn send the adjudication result to the Sponsor.

Step 4- FDA will be informed by the Sponsor of the DSMB adjudication within 5 days after the adjudication is completed by the DSMB.

Step 5- If, based on the DSMB adjudication, and, at the request of the DSMB, a change in the Clinical Protocol needs to be made, the following sequential steps will be taken and completed within 30 business days after the adjudication is completed:
1- The study site will revise the Clinical Protocol.
2- The study site will submit these changes to the MUSC IRB for review and approval.
3- The study site will send the revised clinical protocol to the Sponsor for review and approval.
4- The Sponsor will send the revised clinical protocol to the FDA for review and approval.

After DSMB review of an SAE is completed, a clear record will be established of the adjudication, recommendations, and sponsor follow-up.
Site notification of SAE and all other communications regarding the SAE will be sent to sponsor, DSMB, IRB as appropriate by email together with all appropriate SAE CRFs and a paper copy of this email and any email response will be kept in the individual patient binder. The DSMB completed SAE adjudication form will be sent to sponsor by email and a paper copy of this email and any email response will be kept in the individual patient binder. All communications regarding SAE will be sent to FDA by the sponsor.

Specific SAEs to our patient population are those included in the definition of clinical worsening as defined above. For example:

- Death (all-cause mortality)
- Hospitalization for worsening HFpEF:
  - Non-elective hospitalization for ≥ 24 hours

- Signs and symptoms of LV failure to include one or more of**:** increased dyspnea, clinically significant deterioration in exercise capacity, syncope or pre-syncope, hypoxemia, edema, hepatomegaly, ascites

Per ICH E2A and 21 CFR 312, regulatory agencies will be notified by the Sponsor by telephone or fax of any unexpected, serious adverse event potentially associated with treatment as soon as possible, but in no event later than 14 business 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 14 business days. Follow-up information will be provided as required.
After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information to the medical monitor on the patient's condition. All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

Adverse events and SAEs will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a patient experiencing a critical adverse event is treated successfully and stabilized even though they may continue to experience lingering sequelae that may never resolve), until the patient is lost to follow-up, or until it is agreed that further follow-up of the event is not warranted (e.g. non-serious, study therapy unrelated, mild or moderate adverse events ongoing at a patient's final study visit). If a patient dies during participation in the study or during a recognized follow-up period, the DSMB 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 paper CRFs.

The Investigator will promptly report all SAEs within the timeframes specified above. The Investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to his or her Institutional Review Board (IRB).
This protocol is being filed under an Investigational New Drug (IND) application with the FDA in the US. A given SAE may qualify for an Expedited Safety Report (ESRP) if the SAE is both attributable to study therapy and unexpected. 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.

7.13.7.3 Sponsor Monitoring of Adverse Events

This study will be overseen by an independent data safety monitoring board (DSMB) appointed by the Sponsor, which will have access to all the reports of patients receiving CAP-1002 infusion.

- The following list summarizes the Sponsor's role in monitoring AE/SAEs:
- All AEs will be reviewed on a monthly basis by the study site.
- All SAEs will be reviewed by the DSMB within 5 days of receiving the adverse event form from the clinical center.
- If the DSMB requires additional information to make an assessment, the clinical centers will respond to the request for additional information as soon as the requested information is made available.
- 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 attribution, and expected/unexpected nature of event as assessed by the clinical center, will be provided to the DSMBs within 5 days of receiving the report.
- All SAEs deemed at least possibly related to study treatment will also be sent to the DSMB within 72 hours of the Sponsor becoming aware of the event.

The Sponsor will prepare summary reports every annually of all AEs/SAEs occurring in all enrolled patients for the DSMB.

7.13.7.4 DSMB Monitoring of Adverse Events

The following list summarizes roles of the DSMBs in monitoring AE/SAEs:

- The DSMB will review SAEs with at least a possible relationship to study treatment within 5 days and all other SAEs in advance of every DSMB meeting. The Sponsor anticipates (1) phone conversation with DSMB chair within 5 days of every death or life-threatening event, and (2) communications within 5 days for all other SAEs with at least a possible relationship to the study therapy. The DSMB chair (or designee) will be requested to acknowledge receipt of SAEs within 5 days of notification.
- On an annual basis the DSMB will be provided with a summary 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 DSMB.
- The DSMB Chair (or designee) 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 and study site regarding continuation of the study.

7.13.7.5 Data Safety Monitoring Board: Further Specifics

An independent Data Safety and Monitoring Board (DSMB) will oversee the safety of all subjects. Interim data reviews will be conducted at times coincident with regularly scheduled meetings of the DSMB in accordance with reaching accrual and follow up milestones. The DSMB Chair will be notified each time that an SAE occurs. The DSMB will evaluate blinded AE data (including SAEs) as group A vs B without identification as CDC vs Control unless there is a safety signal present in one of the 2 groups, then the data will be reviewed in an unblinded manner. The DSMB will review data after all 10 subjects have completed their three-month study visit. The DSMB will then review the data after 20 subjects have completed their month 3 follow up visits. The DSMB will then review the data after 40 subjects have completed their month 3 follow up visits. All patients will continue to undergo protocol assessments through 12 months of follow-up, including DSMB reviews.

The DSMB will review all safety parameters. Monitoring of key safety endpoints will be conducted as described above. Policies of the DSMB are described in the DSMB Charter. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and do not mandate automatic closure of study enrollment. Stopping will be at the discretion of the Sponsor, after consideration of DSMB recommendation. The Sponsor always retains the final responsibility to stop a study. Given the complexities of the disease and treatment there cannot be more specific stopping rules.

After DSMB review of an SAE is completed, a clear record will be established of the adjudication, recommendations, and sponsor follow-up. Site notification of SAE and all other communications regarding the SAE will be sent to sponsor, DSMB, IRB as appropriate by email together with all appropriate SAE CRFs and a paper copy of this email and any email response will be kept in the individual patient binder. The DSMB completed SAE adjudication form will be sent to sponsor by email and a paper copy of this email and any email response will be kept in the individual patient binder. All communications regarding SAE will be sent to FDA by the sponsor.

7.13.8 Post-Study Adverse Events and Serious Adverse Events

The Sponsor will notify the DSMB of any death or SAE occurring at any time after a patient 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.

7.13.9 Treatment-Emergent Adverse Events

Adverse event assessment and documentation will occur at every study visit from screening throughout the study. On the day of treatment administration, a patient's medical complaint will be considered to be a treatment-emergent adverse event if the event occurs any time after the infusion of CAP-1002 or placebo.

7.14 Concomitant Medication Assessments

Study personnel will record both general and cardiac medication use at each study visit beginning at the time of enrollment. Concomitant medications are defined as those received on or after the day of infusion. All medications will be reviewed by the Investigator at individual study sites and will then be entered into the CRF for each study visit.

7.15 Removal of Patients from the Trial or Study Drug

The Investigator may withdraw a patient from participation in the study for any of the following reasons:

- A protocol violation occurs
- A serious or intolerable adverse event occurs
- A clinically significant change in a laboratory parameter occurs
- The Sponsor or Investigator terminates the study, or
- The patient requests to be discontinued from the study.

7.16 Other Study Procedures

For patients who so consent, serum for clinical research into biomarkers will be collected at every scheduled visit.

7.17 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 have been mentioned under primary and secondary end-points.

This is a phase IIa study with a primary objective to evaluate the safety of the coronary artery infusion of CAP-1002 in patients with HFpEF. In addition to the safety end-points, information on numerous potential measures of efficacy, as mentioned previously, will also be collected, which will be considered only exploratory to help guide possible future clinical trials.

8. STUDY ACTIVITIES

Patients qualifying as potential candidates for the study, based on initial preliminary screening, will be consented for the procedure. Patients meeting the screening criteria for the study will be consented for CAP-1002 infusion.

The final eligibility of the patient for the study will depend on the hemodynamic profile of the patient with patient meeting all inclusion and exclusion criteria. Patients who meet all of the inclusion criteria and none of the exclusion criteria will receive intracoronary infusion of CAP-1002. Study patients will be observed in the hospital with continuous cardiac and respiratory monitoring for at least 24 hours afterwards.

8.1 Pre-Treatment Screening Phase (Days -28 to -1)

No screening exams will take place until the patient is fully informed of the research and signs the informed consent.

Screening tests and procedures include:

- History and physical examination
- Vital Signs
- Medication review
- NYHA functional class assessment
- 12 lead ECG
- Biomarkers
- 24-hour ECG
- Echocardiography
- 6MWT
- Laboratory tests (hematology, chemistry, BNP, pregnancy test [if applicable] and HLA/DSA, troponin-I, CPKMB)
- Chest CT
- Cath and bicycle ergometry
- Baseline contrast enhanced cardiac MRI; (unless contraindicated);
- Baseline Patient Quality of Life Questionnaire (MLWHF)

Following screening examinations, once a patient has met all of the inclusion criteria and none of the exclusion criteria, the patient will undergo further hemodynamic screening. For those enrolled in the study, dosing and randomization will be coordinated with [redacted] and the Research Pharmacy at MUSC. The test agent will be prepared according to instructions in the Pharmacy Manual. The test agent will then be drawn into the syringes using sterile technique for administration during the cath procedure.

8.2 Hemodynamic Screening

The final eligibility of the patient will be determined based on the presence of hemodynamic inclusion criteria and absence of hemodynamic exclusion criteria. Patients who do not proceed to infusion due to violation of eligibility criterion at screening will be withdrawn from the study as screen failures and will have no further follow up.

8.2.1 Intracoronary Infusion Procedure (Day 0)

During the infusion period, patients will be clinically stable as judged by no evidence of infection, and stable blood pressure, pulse and pulse Ox.

A patient is enrolled and randomized in the study once the patient receives any amount of test agent. Conversely, a patient who does not receive any test agent is not considered enrolled or randomized in the study. If the operator decides not to administer the test agent, the patient is not enrolled or randomized, and subsequent treatment will be determined by the responsible physician and will not be protocol- driven. In addition, only those subjects that are enrolled, randomized, and receive any amount of test agent will be considered in the statistical analysis plan.

Prior to cell infusion, all patients will have a pulmonary artery catheter inserted and coronary catheters using standard technique in the cardiac catheterization laboratory. Baseline (pre-infusion) hemodynamics will be made. Provided no hemodynamic contra-indications to proceed, cell infusion will be done. During the infusions, vital signs, SP_{O2} and pulmonary artery hemodynamics will be monitored

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

- Hypotension unresponsive to IV fluids that require pharmacologic intervention
- VT/ventricular fibrillation that require cardioversion or administration of an antiarrhythmic.
- Changes in cardiac rhythm or conduction (such as SVT, atrial fibrillation with rapid ventricular response or heart block) that requires cardioversion or administration of an antiarrhythmic.
- Significant hypoxemia/desaturation not corrected by supplemental oxygen or IV diuretic (if volume overloaded) or reversal of sedation (if over sedated)
- Suspected or confirmed pulmonary artery rupture.
- Suspected or confirmed coronary dissection.
- Acute onset of rigors or elevated temperature above 99.8^{o}F (symptoms indicative of acute sensitivity or infection)

Following infusion, patients will be observed in the hospital for at least 24 hours with continuous cardiac and respiratory monitoring. Note, hemodynamic measurements will be obtained if clinically indicated (e.g. fall in blood pressure), prior to withdrawal of PA catheter in the cardiac catheterization laboratory over the 1-hour time frame post CDC infusion, at which time the patient will be assessed as stable to transfer to the hospital. Additionally, troponin I and CK-MB will be obtained.

Cardiac Arrhythmia Monitoring: The electrocardiogram will be continuously monitored during the intracoronary infusion and while patients are in the hospital after the procedure. IND Submission: Revision #1

Prior to discharge from the hospital, a physical assessment will be performed. The latter includes evaluation of symptoms of dyspnea, chest pain, and dizziness with effort. The following will also be assessed: O_2 needs, serial BP and HR, administration of an antiarrhythmic or cardioversion, administration of an inotrope, review of laboratory results, ECG, and assessment of adverse events. In the absence of serious adverse events, patients will be discharged per standard of care practice.

The timing of follow-up visits is based on the date of study therapy administration.

8.2.1.1 Post infusion of CAP-1002

- History and physical examination
- Medication review
- Adverse events assessment
- 12 lead ECG
- Laboratory examinations (including troponin I and CK-MB)
- Troponin and CK-MB will be drawn 8, 16 and 24 hours post infusion
- If Troponin is not down trending at 24 hours post infusion, the patient will remain in hospital until they reach down trending pattern.

Pre Discharge an instruction sheet will be given to patient and reviewed with study coordinator

24-48 hours after discharge, the patient will be contacted by the study coordinator to check on patient condition and r/o AE or SAE occurance.

8.2.2 2 Week Visit (Day 14 +/- 4 days) Procedures

The following will be performed at the 2-week visit:

- History and physical examination
- Medication review
- Adverse events assessment
- 12 lead ECG
- Laboratory examinations (hematology, chemistry, DSA, BNP)
- Biomarkers
- NYHA functional class assessment
- 24 hour ECG

Outpatient visits will be completed as close to the scheduled visit dates as possible. The visit window is ± 4 clinic days from the intended date of the visit.

8.2.3 3 Month Visit (Day 90 +/- 14 days) Procedures

The following will be performed at the 3-month visit:

- History and physical examination
- Medication review
- Adverse events assessment
- 12 lead ECG
- Laboratory examinations (hematology, chemistry, DSA, BNP)
- Biomarkers
- NYHA functional class assessment

8.2.4 6 Month Visit (Day 180 +/- 14 days) Procedures

The following will be performed at the 6-month visit:

- History and physical examination
- Medication review
- Adverse events assessment
- 12 lead ECG
- 24 hour ECG
- Echo
- MRI
- Laboratory examinations (hematology, chemistry, DSA, BNP)
- Biomarkers
- NYHA functional class assessment
- 6MWT
- Quality of Life assessment
- Cath / ergometry

8.2.5 12 Month Visit (Day 360 +/- 30 days) Procedures

The following will be performed at the 12-month visit:

- History and physical examination
- Medication review
- Adverse events assessment
- 12 lead ECG
- Echo
- Laboratory examinations (hematology, chemistry, DSA, BNP)
- Biomarkers
- NYHA functional class assessment
- 6MWT
- Quality of Life assessment

Note: Outpatient visits will be completed as close to the scheduled visit dates as possible. The visit window is ± 30 clinic days from the intended date of the visit.

8.3 Payments to Patients

Patients will be reimbursed $50 for each of the 2-week, 3-month and 6 and 12-month visits. 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.

8.4 Early Termination Procedures

Every reasonable effort will be made to retain patients in the study. In the event that a patient must be withdrawn from the study early, study personnel should attempt to obtain testing and data required for the 1-month primary safety end-point visit (See Section 8.3.3) as well as the reason for withdrawal, if known. If the patient permits, he or she should be contacted by study personnel at the time of their usual study visits to obtain adverse event information.

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

Patients who withdraw from the study due to pregnancy will be followed during the pregnancy and through birth of the newborn.

A patient 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 patient is not accomplished, study personnel will follow-up with certified mail in the following manner:

1. Mail a certified letter with return receipt requesting contact and expressing concern for the patient’s well-being.
2. If the patient does not respond within seven days, mail another certified letter with return receipt stating that the patient’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 patient signed it. Otherwise, record the termination date as the date the second letter was mailed.

Stopping Rules Statement:

Stopping Rules that will result in temporary suspension of enrollment and dosing until the situation can be fully assessed and addressed will be defined by the independent DSMB. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study. Monitoring of primary safety endpoints will be conducted. All SAEs will be reported to the DSMB for review.

The DSMB will carefully evaluate the safety of all patients, including the following:

- Death (all-cause mortality)
- Hospitalization for worsening HFpEF:

- Non-elective hospitalization for ≥ 24 hours
- Signs and symptoms of LV failure to include one or more of: increased dyspnea, clinically significant deterioration in exercise capacity, syncope or pre-syncope,
- hypoxemia, edema, hepatomegaly, ascites

9. QUALITY CONTROL AND ASSURANCE

Data will be entered into the REDCap clinical database. A detailed description of the data collection tools and data management process can be found in the CRF completion guidelines and other data management materials. The study site must ensure appropriate source data documentation. The Investigator or designee must enter all required patient data in a timely fashion and an explanation must be documented for any missing data.

10. PLANNED STATISTICAL METHODS

Statistical analysis: An independent DSMB, with roles and responsibilities defined in a written charter, was be appointed to oversee safety of the study. The DSMB will consist of a three heart failure cardiologists, one with additional expertise in an interventional cardiology, one with additional expertise in imaging, one with additional expertise in transplant/immunology, and a statistician. 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 reports evaluating group trends relative to CAP-1002 vs. Control as well as relative to the literature for CAP-1002-treated subjects. In addition, any external concerns regarding CAP-1002 safety will be brought to the attention of the DSMB.

The proportion of subjects experiencing an adverse event or a protocol-specific safety event (PSE) will be monitored at pre-planned intervals set by the DSMB. A futility chart will be created to allow for DSMB safety monitoring. The excess for CAP-treated subjects is of primary concern as Phase 2a data accrue. The boundaries will be computed using StatXact v7 (CyTel, Cambridge MA); a one-sided 95% exact test was performed assuming binomially distributed outcomes. The chart will be applied to any binary outcome pertaining to safety. The chart will be computed over a broad range of possible PSE outcomes. No adjustment for Type I error will be made for repeated looks since the ultimate decision regarding safety represents a clinical decision involving all safety endpoints in the context of efficacy. Descriptive summaries will be provided for all primary and secondary endpoints for both safety and efficacy. A prospective statistical analysis plan (SAP) will be generated with DSMB review and input. . All analyses will be performed using SAS Version 9.2 or greater.

Efficacy data will be presented as mean changes from screening at designated visits. This Phase 2a data will be used to calculate effect sizes for planning subsequent Phase 2b studies. If there are sufficient follow-up data, longitudinal models (SAS PROC MIXED for continuous endpoints and SAS PROC GENMOD for binary endpoints) will be explored.[52-56] A formal SAP will be developed in a collaboration as described earlier.

10.1 General Considerations

Descriptive summaries will be provided for all primary and secondary end-points. All analyses will be performed using SAS Version 9.2 or greater. An independent DSMB will monitor the study and make recommendations, if needed, regarding stopping the study due to safety concerns.

10.2 Analysis Populations

Patients receiving CAP-1002/placebo infusion will be followed for 12 months. Patients will have study visits at 24-48 hours post discharge 2 weeks, 3, 6 & 12 months following infusion.

The analysis population for assessing safety objectives will consist of all patients who received an infusion of CAP-1002. For patients with missing follow-up data points, missing data will be imputed using predefined rules detailed in the SAP.

10.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics of all accrued patients such as race, ethnicity, gender and age will be summarized and reported. The gender and minority distributions are expected to reflect the HFpEF population in the United States. There are no particular recruitment strategies for gender or minorities. We expect a high percentage of women in the HFpEF population.

10.4 Interim Analysis

The DSMB will be reviewing the data over the course of the study to assess the safety of CAP-1002 infusion. All interim analysis are described above.

11. ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Information regarding the study 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 or should a SAE occur, the staff should contact the **Regress-HFpEF** DSMB using the contact information below:
Theo Meyer
meyert@ummhc.org
(508) 856-2224

The lead Principal Investigator is Michael R. Zile, MD,

MUSC. MUSC will be responsible for enrolling subjects.

A core imaging group (Dr. Litwin, MUSC) will be used to centrally read all echocardiography, CT, MRI studies and a core laboratory (UCLA Immunogenetics Center) will be used to analyze samples for HLA/donor specific antigens. A core hemodynamics lab (Dr. Fernandes, MUSC) will read all cath data.

In order to ensure quality and continuance of patient care, the PI will inform patients primary cardiac care physician of his/her participation in **HFpEF** Study.

11.2 Institutional Review Board (IRB) 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). The composition and conduct of this committee shall conform to the United States CFR and ICH E6.

The IRB will also review and approve the site's informed consent form (ICF), other written information provided to the patient and all advertisements that may be used for patient 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 reviews and approves these amended documents. An IRB approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new patients are consented to participate in the study using the amended version of the ICF.

11.3 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 Harmonization 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.

11.4 Patient Information and Consent

Before being admitted to the clinical study, all patients must consent in writing to participate. An ICF will be given to each patient, 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 patient.

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 patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review will be in a form understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient 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 patient 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 patient 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 patients and repeat the consent process with the amended ICF for any ongoing patients.

11.5 Patient Confidentiality

Patients' names will remain confidential and will not be included in the database. Only patient number, patient initials, and birth date will be recorded in the data system. If the patient 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 paper CRFs. The patients 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.

Patients 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 patient 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 patient 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 patient's personal physician or to other appropriate medical personnel when required in connection with the patient's continued health and welfare.

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

11.6 Study Monitoring

The DSMB Chair will also serve as study monitor and will determine the frequency of monitoring visits primarily based on enrollment and compliance with protocol-dictated procedures, with visits generally occurring once every 12 months. The DSMB Chair will have continuous access to the electronic data capture system to review completion of study documents, and data and adverse event reporting in a timely manner.

11.7 CRFs and Study Records

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

REDCap will be utilized to record all of the protocol-required information to be reported to the Sponsor on each trial subject. Study personnel will be trained in how to access and use the REDCap to enter and transmit data for the study. Study personnel will be trained regarding proper correction of data entries in the REDCap.

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. REDCap will not serve as source documents.

11.8 Protocol Violations/Deviations

As they occur, deviations and violations will be documented and reported to the DSMB, Sponsor and MUSC IRB. 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 Site investigator and the Sponsor and statistician will review the circumstances of each violation (in a blinded fashion) to determine whether the data can reasonably be included in the patient data in the final study analysis.

11.9 Access to Source Documentation

The Investigator, Sponsor 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 review, and regulatory inspection(s), with direct access to source data and documents.

11.10 Data Generation and Analysis

REDCap will be utilized to collect data and generate a database. Study site will be responsible for entering data collected at the site and external data sources (i.e., central lab and core imaging center) are expected to provide data sets to be entered into the database.

11.11 Retention of Data

In accordance with 21 CFR 312.62, an Investigator participating in this study shall retain records, including the CRFs 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 FDA, until 2 years after the investigation is discontinued and FDA is notified. In any case, the Sponsor should be notified prior to the destruction of any study records.

11.12 Financial Disclosure

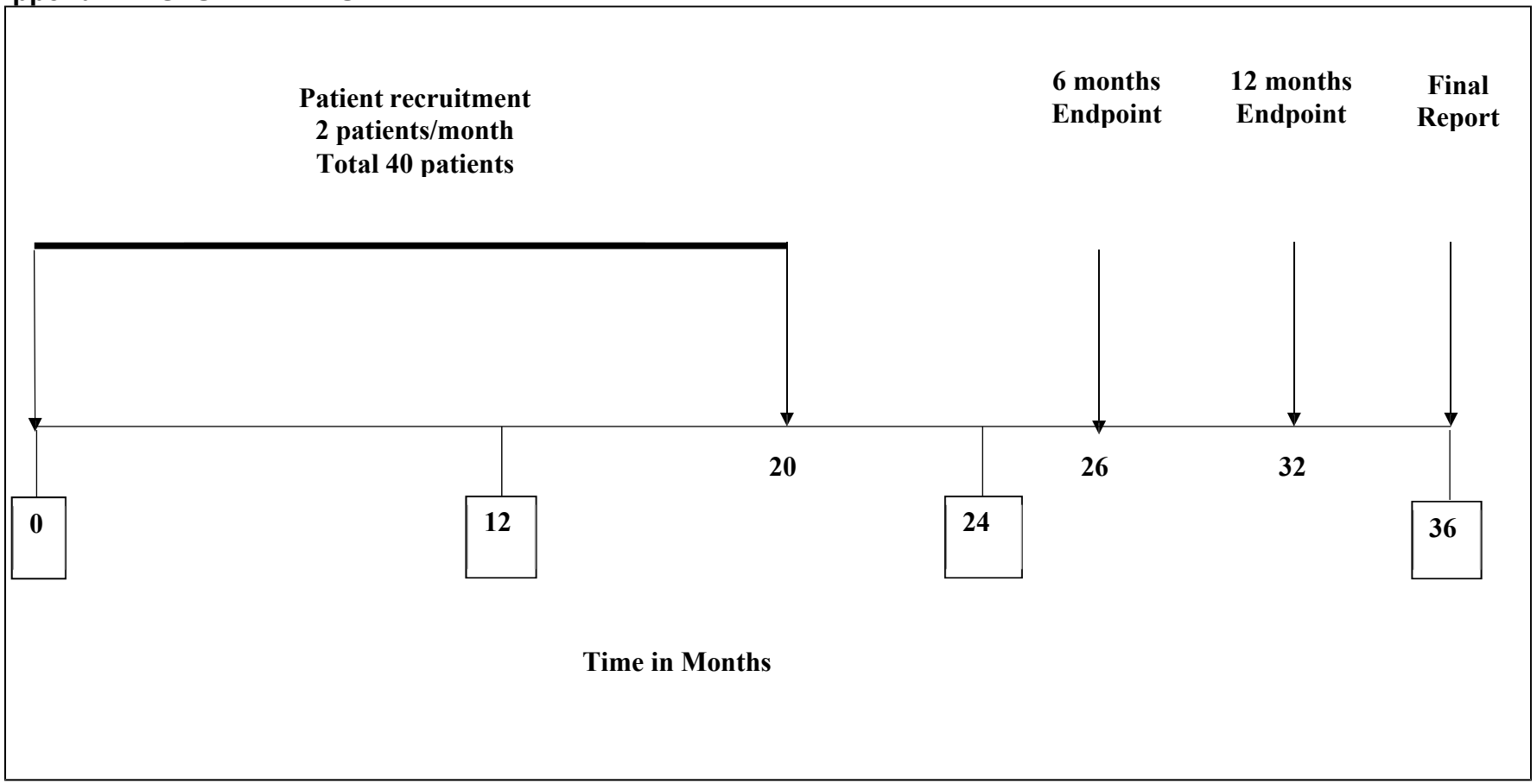
In accordance with FDA regulatory requirements, 21 CFR 54.4, study personnel who are required to complete a financial disclosure form will do so prior to participation in the study. Designated individuals shall provide sufficient and accurate financial information to allow the Sponsor to submit complete and accurate certification or disclosure statements (Forms 3454 and/or 3455) as required by the FDA regulations. Those individuals shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

LIST OF APPENDICES

Appendix 1: SCHEDULE OF STUDY ACTIVITIES/ASSESSMENTS

		Post Infusion		Months				
Study Procedure	**Screening**	**Pre D/C**	**Post D/C Phone 24-48 Hr**	**0.5**	**3**	**6 - Pre D/C**	**6 - Post D/C phone 24-48 hr**	**12**
Informed Consent	x							
Medical History	x	x	X	x	x	X	X	x
Physical Exam	x	x		x	x	X		x
Medication Review	x	x		x	x	X		x
AE Assessment		x	X	x	x	X	X	x
ECG	x	x		x	x	X		x
Labs	x	x		x	x	X		x
Biomarkers	x			x	x	X		x
HLA	x							
DSA	x			x	x	X		x
Chest CT	x							
Cath/Ergometry	x					X		
Cardiac MRI	x					X		
24-hour ECG	x			x		X		
Troponin I & CK-MB	x	x* See 8.2.1.1						
Echocardiography	x					X		x
Six Minute Walk	x					X		x
QOL	x					X		x
NYHA Assessment	x			x	x	X		x
D/C Instructions		X				X		

Appendix 2: STUDY RECRUITMENT TIMELINE



Appendix 3: 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®
Basiliximab	Simulect®
Bleomycin	Blenoxane®
Busulfan	Myleran®
Capecitabine	Xeloda®
Carboplatin	Paraplatin®
Carmustine	BiCNU® (BCNU)
Certolizumab pegol	Cimzia®
Chlorambucil	Leukeran®
Cidofovir	Vistide®
Cisplatin	Platinol®
Cladribine	Leustatin®
Cyclosporine	Gengraf®
Cyclosporine	Neoral®
Cyclosporine	Sandimmune®
Cytarabine	
Cytarabine	DepoCyt®
Dacarbazine	DTIC-Dome®
Daclizumab	Zenopax®
Dactinomycin	Cosmegan®
Darunavir	Prezista®
Dasatinib	Sprycel®
Daunorubicin	Cerubidine®
Delavirdine	Rescriptor®
Denileukin diftitox	Ontak®
Didanosine	Videx®
Docetaxel	Taxotere®
Docetaxel	Docefrez®

Doxorubicin	Adriamycin®
Doxorubicin	Doxil®
Efavirenz	Sustiva®
Efavirenz/emtricitabine/tenofovir disoproxil	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
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 HCl	Mustargen®
Megestrol	Megace®
Melphalan	Alkeran®
Mercaptopurine	Purinethol®
Methotrexate	Rheumatrex®
Methotrexate	Trexall™
Mitomycin	Mutamycin®
Mitotane	Lysodren®
Mitoxantrone	Novantrone®
Muromonab-CD3	Orthoclone-OKT3
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®
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®
Tacrolimus	Prograf®
Tamoxifen citrate	Nolvadex

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

Appendix 4: Approved [redacted]

Please see attached

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