Official Title: Double-blind, Randomized, Sham–procedure–controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology: DREAM HF-1

NCT Number: NCT02032004

Document Date: Protocol Version 7.0: 06-October-2017

A Double-blind, Randomized, Sham–procedure–controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology: DREAM HF-1

STUDY PROTOCOL

Protocol Number: MSB-MPC-CHF001

Clinical Development: Phase 3

Version: 7.0

IND Number: 15715

Protocol Date: 04 October 2017

Sponsor: Mesoblast, Ltd. c/o Mesoblast, Inc.
505 Fifth Avenue, 3rd Floor
New York, NY 10017 USA

Monitor: **INC Research**/inVentiv Health
504 Carnegie Center
Princeton, NJ 08540 USA

Sponsor Authorized Representative:

[redacted] Digitally signed by [redacted]
DN: [redacted]
email=[redacted]
Date: 2017.10.06 11:08:02 -04'00'

[redacted] MD

Mesoblast Inc.

Confidentiality Statement

The information in this document is confidential and is provided to you as an investigator, potential investigator, or consultant for review by you, your staff, and applicable Institutional Review Board/Ethics Committee members. This information shall not be disclosed to others without prior written authorization from Mesoblast, Inc. except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

INVESTIGATOR'S SIGNATURE (HEART FAILURE SPECIALIST)

Study Title: Double-blind, Randomized, Sham–procedure–controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology: DREAM HF-1

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes.

I agree to report to the Sponsor adverse experiences that occur in the course of the investigation(s)

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance and to make those records available for inspection.

I will ensure that an IRB/EC completed the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Agreement Signature:

_____	_____	_____
Principal Investigator (Please print)	Principal Investigator (Signature)	Date

INTERVENTIONAL CARDIOLOGIST'S SIGNATURE

Study Title: Double-blind, Randomized, Sham–procedure–controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology: DREAM HF-1

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes.

I agree to report to the Sponsor adverse experiences that occur in the course of the investigation(s)

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

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Agreement Signature:

_____	_____	_____
Interventional Cardiologist (Please print)	Interventional Cardiologist (Signature)	Date

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Clinical Laboratory
For United States and Canada:
Pharmaceutical Product Development Inc. (PPD) Global Central Lab
2 Tesseneer Road
Highland Heights, Kentucky 41076
USA

For Europe:
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Cluster Park
Kleine Kloosterstraat 19
B-1932 Zaventem, Belgium

Immunogenicity Testing Laboratory
For panel-reactive antibody (PRA) and donor-specific antibody (DSA):
Rabin Medical Center
Petach Tikva, Israel 49100

For anti-murine and anti-bovine antibody:
Global Bioassays & Technology Israel
Teva Pharmaceutical Industries, Ltd.
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Electronic Data Capture
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Central Institutional Review Board (IRB)
Quorum IRB
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Core Cardiac Imaging and Electrocardiography Laboratory
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Interactive Response Technology (IRT)
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Medical Device Manufacturer
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3333 Diamond Canyon Road
Diamond Bar, California 91765
USA

- NOGA® XP Cardiac Navigation System and NovaStar® Catheter
- CARTO® 3 Cardiac Navigation System and NovaStar® Catheter
- MyoStar™ Injection Catheter.

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the medical monitors listed below:

In the USA, Canada, and rest of the world outside of the European Union:

Medical Monitor (Blinded)
[redacted] MD
[redacted] INC Research/inVentiv Health
Tel: [redacted]
Fax: [redacted]

Medical Monitor (Unblinded)
[redacted] MD
[redacted] INC Research/inVentiv Health
Tel: [redacted]
Fax: [redacted]

In the European Union:

[redacted] MD
Medical Monitor, INC Research/inVentiv Health
Tel: [redacted]
Fax: [redacted]
Cel: [redacted]

For operational issues, contact the operational lead:

[redacted]
INC Research/inVentiv Health
Tel: [redacted]
Fax: [redacted]
Cell: [redacted]

FOR SERIOUS ADVERSE EVENTS (SAES):

Contact the Clinical Study Medical Monitor responsible for medical issues (see above) only if needed.

For events which occur from Day 0 through hospital discharge for the index cardiac catheterization, contact the unblinded medical monitor. For events which occur after hospital discharge for the index cardiac catheterization, contact the blinded medical monitor.

Any serious adverse event (SAE), whether deemed related or not to the investigational product, must be reported. To report the SAE, the investigator or designee will complete the SAE information electronically in the electronic case report form (eCRF). When it is completed, Mesoblast Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible to access the eCRF, the investigator or designee should complete the backup paper SAE form and e-mail it at [redacted] to Mesoblast Safety with 24 hours of awareness. In case of difficulty transmitting the form, contact the Sponsor study personnel identified in the front matter of this protocol for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Sponsor: Mesoblast Inc., Inc.

Title of Study: A Double-blind, Randomized, Sham–procedure–controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology: DREAM HF-1

Study Number: MSB-MPC-CHF001

Name of Active Ingredient: Human bone marrow-derived allogeneic mesenchymal precursor cells (MPCs)

Name of Investigational Product: Rexlemestrocel-L

Phase of Clinical Development: 3

Number of Investigational Centers Planned: Approximately 80-100 sites are planned.

Countries Planned: United States, Canada, Europe, Australia, and Singapore

Number of Patients Planned: Approximately 600 heart failure (HF) patients (approximately 300 patients per treatment group). However, since this is an events-driven study, the total number of patients may change. It is anticipated that at least 531 recurrent (multiple events per patient) non-fatal heart failure–related major adverse cardiac events (HF-MACE) will be obtained and positively adjudicated by an independent Clinical Endpoints Adjudication Committee (CEC) to complete the study. These non-fatal HF-MACE will include patients with recurrent non-fatal decompensated HF events and/or successfully resuscitated cardiac death (RCD) events.

Study Population: Adult men and women with chronic HF due to left ventricular (LV) systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy

Estimated Planned Study Period: 2014 to 2020

Primary Objectives: The primary objectives of this study are to:

1. Determine whether transendocardial delivery of 150 million (M) allogeneic human bone marrow-derived MPCs (rexlemestrocel-L) administered during a single index cardiac catheterization and intracardiac mapping procedure is more effective than a scripted sham cardiac mapping and cell delivery procedure in risk reduction for recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully RCD events, in the presence of TCEs in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.
2. Evaluate the safety and tolerability of transendocardial delivery of rexlemestrocel-L in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.

Key Secondary Objective: The key secondary objective of this study is the assessment of time from Day 0-to-first terminal cardiac event (TCE) (cardiac death, left ventricular assist device [LVAD] placement, heart transplant, or artificial heart implantation), whichever event occurred first, to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-first TCE for the Cell Therapy vs. Control (Sham) group.

Day 0 Definition: Day 0 for all time-to-event analyses is defined as follows:

1. For patients who are randomized but **DO NOT** undergo the index cardiac catheterization as the date of the disqualifying event (i.e., violation of at least 1 inclusion/exclusion criterion);
2. For patients who are randomized and **DO** undergo the index cardiac catheterization as the date of the index cardiac catheterization.

Secondary Objectives: The secondary objectives of this study are the assessment of various aspects of recurrent non-fatal HF-MACE (i.e., decompensated HF events and/or successfully RCD events). Other secondary objectives of the study relate to LV remodeling by echocardiography, functional exercise capacity using the 6-minute walk test, functional status assessed by New York Heart Association Classification, and quality of life [QoL].

Immunogenicity Objective: The immunogenicity objective of this study is to evaluate the immunogenic potential of rexlemestrocel-L by evaluating the results of the following assays performed as specified in the protocol:

- panel reactive antibodies (PRA)
- donor specific antibodies (DSA) (if test for PRA is positive)
- antibodies against bovine and murine proteins (*i.e.,* BSA [bovine serum albumin] and MIgG [mouse immunoglobulin G]).

[redacted]

- study the association of changes from baseline levels of the biomarkers high-sensitivity C-reactive protein (hsCRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) with disease severity and clinical outcomes
- [redacted]
- collect and store blood samples for possible use in future pharmacogenomic (PGx) analyses in the assessment of associations between genetic polymorphisms and the response to rexlemestrocel-L therapy in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.

NOTE: Current entry criteria are included in the synopsis and main text of the protocol. In the trial, replaced and/or deleted entry criteria from the time the 1st patient was enrolled through the final amendment to this protocol are included in Section 17.

Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

a. The patient is 18 to 80 years of age, inclusive; both men and women will be enrolled.

b. **Inclusion criterion b was replaced by b1.**
(b1) The patient has a diagnosis of chronic HF of ischemic or nonischemic etiology for at least 6 months before the initiation of screening procedures, with New York Heart Association (NYHA) Functional Class II or Functional Class III symptoms. Chronic HF of ischemic etiology includes epicardial coronary artery disease [CAD] defined as documented stenosis of at least 50% in one or more major epicardial

coronary arteries, documented prior coronary revascularization, and/or documented prior MI.

c. The patient is on stable, optimally tolerated dosages of HF therapies including beta-blockers (approved for country-specific usage), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), and/or aldosterone antagonists and/or neprilysin inhibitor, without change in dose for at least 1 month before study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

d. **Inclusion criterion d was replaced by d1**
(d1) The patient is on a stable, outpatient, oral diuretic dosing regimen in which the patient remains clinically stable during screening. Flexible diuretic dosing that allows the patient to titrate the dose or add a dose of a second diuretic during screening is permitted provided that the dosing regimen is not further altered and the patient remains stable during this period or the patient is not on a regular dose of diuretics but takes diuretics as needed based on daily weight or the appearance of symptoms.

e. The patient is not a candidate for either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery as determined by the Principal Investigator (or designee) during screening.

f. **Inclusion criterion f was replaced by f1.**
(f1) The patient may be on the cardiac transplant list. However, the patient must have low priority status with low probability of having a transplant procedure performed over the next 12 months (*i.e.,* cannot be United Network for Organ Sharing [UNOS] status 1A or 1B).

g. The patient has a LVEF by the Core Cardiac Image Laboratory of 40% or less as measured by 2-D echocardiogram, or 35% or less as measured by radionuclide ventriculography (RVG) within 42 days prior to study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

h. **Inclusion criterion h was replaced by h1**
(h1) The patient has 1 or more of the following:
- at least 1 HF hospitalization more than 1 month, but 9 months or less before initiation of screening procedures
- at least 1 outpatient visit requiring intravenous (IV) diuretic, vasodilator, and/or positive inotropic therapy more than 1 month, but 9 months or less before initiation of screening procedures
- plasma levels of NT-proBNP as measured by the central laboratory of greater than 1000 pg/mL (1000 ng/L SI units; 118 pmol/L) or 1200 pg/mL (1200 ng/L SI units; 141.6 pmol/L) for patients with atrial fibrillation.

i. **Inclusion criterion i was replaced by i1**
If the patient has an implantable cardioverter defibrillator (ICD) (or any implanted device capable of defibrillation) in place, the placement must have occurred at least 1 month before initiation of screening procedures.

j. If the patient has had cardiac resynchronization therapy (CRT), the procedure must have occurred at least 3 months before screening.

k. The patient has an LV end-diastolic wall thickness of at least 8 mm at potential myocardial target sites for cell delivery.

l. Women must be surgically sterile, 1 year post-menopausal, or must have a negative urine or serum pregnancy test at screening.

m. **Inclusion criterion m1 was replaced by m2**
(m2) Women must be surgically sterile, 1 year post-menopausal, or, if of childbearing potential, currently using a medically accepted method of contraception, and must agree to continue to use this method of contraception after initiation of screening procedures and for 6 months after study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Acceptable methods of contraception include barrier method with spermicide, abstinence, intrauterine device (IUD) (known to have a failure rate of less than 1% per year), or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. Men must be surgically sterile, or, if capable of producing offspring, currently using an approved method of contraception and must agree to continue to use this method of contraception after initiation of screening procedures and for 16 weeks after study intervention. Acceptable methods of contraception include abstinence, female partner's use of steroidal contraceptive (oral, implanted or injected) in conjunction with a barrier method, female partner's use of an IUD (known to have a failure rate of less than 1% per year), or if female

partner is surgically sterile or 1 year post-menopausal. In addition, men may not donate sperm for16 weeks after study intervention.

n. The patient must be willing to return for required follow-up visits.
o. Written informed consent is obtained for the study before any study-specific procedures are performed. A separate written informed consent for an exploratory PGx substudy will be obtained before any PGx-specific procedures are performed. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). A patient will not be excluded from participation in the study if he/she chooses not to provide consent for the additional procedures that are required as part of the exploratory PGx substudy.
p. Prior to the initiation of any procedures on Day 0, the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable.
q. The patient must be able to receive systemic anticoagulant therapy.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has NYHA Functional Class I or Functional Class IV symptoms.
b. The patient has had an acute MI within 1 month before initiation of the screening procedures.
c. The patient has unstable angina pectoris within 1 month before initiation of screening procedures; unstable angina is defined as the occurrence of chest pain more frequently than usual, pain at rest or upon minimal exertion, or protracted episodes of pain without any discernible trigger, and/or chest pain that persists despite use of vasodilatory therapy (*e.g.,* nitroglycerin) and or aggravation of stable angina or new onset angina.
d. The patient has peri- or postpartum cardiomyopathy (CM).
e. The patient has ischemic or hemorrhagic stroke as diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) within 3 months prior to study enrollment.
f. The patient has had a coronary arterial or peripheral arterial revascularization procedure within 2 months before initiation of screening procedures.
g. The patient has had IV therapy with diuretic, vasodilator, and/or positive inotropes or aquapheresis within 1 month before initiation of screening procedures, and/or during the screening period.

h. Exclusion criterion h was replaced by h1
(h1) The patient, who in the absence of an ICD (or any implanted device capable of defibrillation), has a history of malignant ventricular arrhythmia or sustained ventricular tachycardia (VT), with sustained VT demonstrated by QRS complexes wider than 120 milliseconds, lasting more than 30 seconds, and with a rate of more than 100 beats per minute on screening ECG or other data supporting this diagnosis.

i. The patient has restrictive, obstructive, or infiltrative CM, pericardial constriction, amyloidosis, or uncorrected thyroid disease.

j. The patient has moderate to severe aortic stenosis as determined by the Core Cardiac Imaging Laboratory echocardiography-Doppler assessment with a valve area less than 1.0 cm^2.

k. The patient requires valve or other cardiac (e.g., pericardectomy) surgery.

l. The patient has had LV reduction surgery, implanted LVAD, cardiac transplantation or artificial heart placement. The patient may be on the cardiac transplant list, but must have low probability of having a transplant procedure over the next 12 months.

m. The patient has an LV thrombus diagnosed by echocardiography, left ventriculogram, or other cardiac imaging.

n. The patient has cardiogenic shock that is dependent upon mechanical or inotropic support at the time of study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery), as defined by Killip Class IV physiology indicative of cardiogenic shock and/or requirement of intra-aortic balloon pump or IV inotropic support for the maintenance of mean arterial blood pressure at least 60 millimeters of mercury (mmHg).

o. The patient is known to have unprotected left main CAD greater than 50%.

p. **Exclusion criterion p1 was replaced by p2.**
(p2) The patient has known hypersensitivity to radiocontrast media or dimethyl sulfoxide (DMSO), murine, and/or bovine products with the exception of patients with mild hypersensitivity to radiocontrast media, who may be pretreated with corticosteroids and/or antihistamines.

q. The patient has a known active malignancy within the past 3 years except for localized prostate cancer, cervical carcinoma in situ, breast cancer in situ, or non-melanoma skin cancer that has been definitively treated.

r. **Exclusion criterion r was replaced by r1**
(r1) The patient has acute bacterial or viral infectious disease, or acute exacerbation of a chronic infectious disease at the time that Day 0 intervention is planned. However, patients with an upper respiratory infection diagnosed at screening that is

cleared by Day 0 (maximum of 42 days from signing of informed consent form) may undergo the procedure.

s. **Exclusion criterion s was replaced by s1**
(s1) Patients with severe chronic obstructive pulmonary disease (COPD) or who require home oxygen for any kind of pulmonary disease; home oxygen use as part of CPAP (continuous positive airway pressure) for the indication of sleep apnea in patients living at high altitude is permitted, and as-needed home oxygen use solely as therapy for HF is permitted. A patient with moderate COPD without severe right ventricular dilatation and dysfunction on echocardiogram may be included in the study if the patient has a documented HF history that meets qualifying HF criteria. A patient who has a forced expiratory volume in one second (FEV_1) of less than 1.0 L will be excluded. A given patient will be excluded from serial echocardiographic imaging assessments if his/her heart is difficult to image adequately using standard precordial echocardiographic techniques. In that case, RVG estimations of LVEF will be used for screening inclusion criteria as well as for serial changes in overall cardiac performance after study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). A patient with clinically meaningful COPD will be excluded from serial 6MWT evaluations if the patient's exercise limitation is thought to be due predominantly to the patient's intrinsic pulmonary disease rather than from the patient's HF state.

t. The patient has a bleeding diathesis disorder such as abnormal coagulation profile, precluding study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

u. **Exclusion criterion u was replaced by u1**
(u1) The patient has 1 or more clinical laboratory test value(s) performed by the Central Clinical Laboratory that are outside the range for 1 or more of the tests specified below, or any other clinically significant abnormality as determined by the investigator or medical monitor as follows (note: repeat of suspected spurious laboratory abnormalities may be permitted after consultation with the medical monitor):
   - aspartate aminotransferase (AST/SGOT)/alanine aminotransferase (ALT/SGPT) greater than 3 times upper limit of normal (ULN) range
   - estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 (calculated by the central clinical laboratory using the Modification of Diet in Renal Disease (MDRD) formula); measures to minimize the risk of contrast-induced nephropathy will be taken at the discretion of the investigator

- hemoglobin less than 9 g/dL
- platelets less than $100 \times 10^3/mm^3$
- hemoglobin A1c (HBA1c) of 10% or greater

v. The patient has any concurrent disease or condition that in the opinion of the investigator would make the patient unsuitable for participation in the study.

w. The patient has previously participated in any stem cell or regenerative medicine study, in which he/she received active agent.

x. The patient has received hematopoietic growth factors within 12 months preceding study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

y. **Exclusion criterion y was replaced by y1**
(y1) The patient has had treatment and/or an uncompleted follow-up treatment of any investigational therapy within 6 months before study intervention and/or intends to participate in any other investigational drug or cell therapy study in the 3 years after study intervention (*i.e.*, hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

z. The patient has hemodynamically compromised, complex congenital heart disease.

aa. **Exclusion criterion aa1 was replaced by aa2**.
(aa2) A patient with an ICD (or any implanted device capable of defibrillation) in place who has had a device firing within 1 month of Day 0.

bb. A patient has had angina on the average of more than 3 times per week.

cc. **New exclusion criterion**
The patient completes two 6MWTs with either test being a distance >450 meters during screening

dd. **New exclusion criterion**
The patient is unable to perform the 6MWT due to concurrent medical conditions; the exception is those patients with NT-proBNP >2000 pg/mL (2000 ng/L SI units; 236 pmol/L).

ee. **New exclusion criterion**
The patient has an aortic valve prosthesis.

Study Drug Dose, Mode of Administration, and Administration Rate

Investigational Product: Rexlemestrocel-L consists of human bone marrow-derived allogeneic MPCs that have been isolated from bone mononuclear cells with anti-STRO 3 antibodies, expanded ex vivo, and cryopreserved. The allogeneic MPCs are cryopreserved at a concentration

of [redacted] Rexlemestrocel-L must be thawed before use. Patients randomly assigned to active treatment with rexlemestrocel-L who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo intracardiac mapping to receive 150 M completely thawed rexlemestrocel-L, which will be delivered transendocardially into the myocardium, using a specially designed catheter (MyoStar™ Injection Catheter) that is placed through a sheath that has been previously inserted into the femoral artery. This catheter is then advanced through the arterial system to the left ventricle. Transendocardial delivery into the myocardium will require the placement of the catheter needle into the LV wall.

During the index cardiac catheterization, contrast left ventriculography as well as evaluations for stable myocardium will be performed. The latter will utilize either the NOGA® XP or CARTO® 3 Cardiac Navigation System [also referred to as NOGA® or CARTO®, respectively). Data will be generated to visualize and map myocardial locations that are potential targets for delivery of rexlemestrocel-L. Of note, the techniques utilized for mapping and cell delivery with either the NOGA® or CARTO® system are highly similar to each other. Myocardial locations will be defined within the left ventricle by imaging and electrical mapping as viable for cell delivery. After the completion of the mapping procedure, 15 to 20 appropriate myocardial sites will be identified (20 sites is ideal). The injection sites will be captured by NOGA® or CARTO® and transcribed into electronic data capture (EDC). Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to the imaging identified myocardial locations; the total volume of study product administered must not exceed 4.0 mL. The total duration of the transendocardial delivery procedure must not exceed 90 minutes from the time of completion of thaw of rexlemestrocel-L.

Control: Patients randomly assigned to the control group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted sham intracardiac mapping and cell delivery procedure that includes an index cardiac catheterization with left ventriculography. The sham intracardiac mapping and cell delivery procedure will be staged to script and will not include intracardiac mapping or transendocardial delivery of rexlemestrocel-L.

Definition of Treatment: Treatment is defined as all patients who underwent Day 0 index cardiac catheterization (with or without intracardiac mapping and cell delivery) and in whom the interventional cardiologist was able to advance the pigtail catheter across the aortic valve and into the LV chamber.

Duration of Follow-up: Duration of treatment for an individual patient will be determined from Day 0 to either death or the end of the study for that patient.

Method of Blinding and Randomization: This is a double-blind study. Patients enrolled in the study will be randomly assigned in a 1:1 ratio to receive active treatment (*i.e.,* intracardiac mapping and transendocardial delivery of rexlemestrocel-L) or control treatment (*i.e.,* a scripted sham intracardiac mapping and cell delivery procedure without rexlemestrocel-L).

After confirmation of all eligibility criteria, patients will be randomly assigned to the active or control treatment group (approximately 300 patients per group) by means of a computer-generated randomization list, and stratified by the following:

- baseline NYHA Class (Functional Class II versus Functional Class III)
- geographic region (US versus ex US), and
- presence of epicardial coronary artery disease (CAD) (ischemic versus nonischemic).

Epicardial CAD is defined as documented stenosis of at least 50% in one or more major epicardial coronary arteries, documented prior coronary revascularization, and/or documented prior MI. The randomization list and treatment group will be assigned via interactive response technology (IRT). The IRT will be used to track and monitor enrollment of female patients as well as patients with baseline NYHA Class III versus Class II functional status in the study. To ensure that approximately 20% of the patient population in the study will be women, frequent discussions with the site staff will take place during the recruitment phase and will include discussion of the current rate of recruitment of women to the study. If there is a large disparity between the number of men and the number of women randomized to the study, the randomization may be limited to women until women represent approximately 20% of the study population.

Patient enrichment and replenishment will be performed such that by the end of the trial, the ratio of enrolled patients with baseline NYHA Class III to baseline NYHA Class II will be approximately 2:1. With this ratio, it is estimated that approximately 600 randomized patients will be needed to achieve a minimum of 531 recurrent non-fatal HF-MACE at the end of the

trial. Based on current enrollment projections, at the end of the trial it is estimated that there will be ~200 baseline NYHA Class II patients and ~400 baseline NYHA Class III patients who have undergone the Day 0 index cardiac catheterization resulting in a baseline Class III/Class II ratio of 2:1. In order to achieve this target, an enrollment cap of ~200 baseline NYHA Class II patients will be instituted. It is anticipated that any baseline NYHA Class II patients who are inadvertently screened but not randomized during the suspension of NYHA Class II enrollment will be considered screen failures. The enrollment process will be overseen by the trial's treatment blinded Medical Monitor in conjunction with current computer-generated randomization and interactive response technology (IRT) enrollment methodologies.

The success of this study depends on several factors including: a) the safety of patients enrolled and randomly assigned to treatment; b) demonstration of the potential clinical benefit from transendocardial delivery of rexlemestrocel-L; c) maintenance of the treatment blind as it relates to clinical follow up and decision making.

Patients will be screened at recruiting HF study centers. The timing of randomization relative to Day 0 will vary based on study drug availability and Biologics Delivery System [BDS] availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0.

Hospitalization for index cardiac catheterization (with or without intracardiac mapping and cell delivery) will occur at a cell injection center; the interventional cardiologist who will perform the catheterization procedure will be unblinded to treatment assignment. Not all HF study sites will be cell injection centers and not all cell injection centers will be HF study centers. However, it is anticipated that the majority of cell injection centers will also be HF study centers. Screening and follow-up evaluations will be performed at HF study sites by study personnel who will be blinded to study treatment for the duration of the study. The interventional cardiology site staff, who are unblinded to study treatment, may participate in screening procedures but will not be involved in follow-up evaluations.

Study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery) for all randomized patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will be performed at a cell injection center by an unblinded interventional cardiology team not involved with data collection for safety and

efficacy evaluations during the follow-up period. Patients, as well as noninterventional investigators and HF study center personnel responsible for efficacy and safety evaluations of patients after hospital discharge, will remain blinded to the study treatment provided to the patients at the cell injection center. Once a physician has been designated as either the blinded or unblinded cardiologist, he/she may not change his/her blinded vs. unblinded role within the trial.

Maintaining the blind of study participants and study site personnel during the follow-up period will help to protect the integrity of study data and may reduce the risk of introducing physician bias into the clinical decision-making process. Knowledge of which treatment was received by a patient could influence a treating physician's decision to hospitalize a patient for HF. For example, knowledge that a given patient did not receive rexlemestrocel-L could result in a lower threshold for hospitalization because the physician would not expect the sham intracardiac mapping and cell delivery procedure to have a beneficial effect on the patient's long-term clinical state. Maintenance of the blind is particularly important in this study because a biased decision relating to HF hospitalization would directly impact the study's primary efficacy endpoint.

During the course of the study, the Sponsor Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities.

There will be three oversight committees: an independent Data Monitoring Committee (DMC), an Executive Steering Committee (ESC), and an independent CEC. Both the ESC and the CEC will be blinded to study treatment; the DMC will be unblinded.

The **Data Monitoring Committee (DMC)**, which will be unblinded to study treatment, will oversee the study with primary responsibility for ensuring patient safety. Specific goals and responsibilities of the DMC are outlined in the Data Monitoring Committee Manual of Operations. These responsibilities include the following:

- Oversight of the study with primary responsibility for insuring patient safety
- Review on a regular predefined basis the occurrence of adverse events including TCEs (cardiac death, LVAD placement, heart transplant, or artificial heart implantation), non-fatal HF-MACE (including recurrent non-fatal decompensated HF events and/or successfully RCD events), overall survival, non-fatal CVA, non-fatal MI, and other arrhythmic events.

- Perform pre-specified serial assessments of patient safety and monitor treatment effects to assess whether the objectives of the ongoing trial can be met. Periodically, the DMC will conduct unblinded analyses of clinical events that have been adjudicated by the independent CEC. Additionally, the DMC may formulate recommendations to the unblinded sponsor study team regarding the conduct and execution of the protocol as issues arise (see Blinding Plan for more information).
- Review of planned interim analyses.

The **Executive Steering Committee (ESC)** will perform the following:

- Oversight for the operation of the study, including working with national leaders and local HF study site investigators to achieve goals for enrollment of patients into the study
- Reviewing recommendations from the project team for study conduct
- Reviewing recommendations from the DMC for patient safety
- Reviewing recommendations from the DMC for Interim Analysis #2.

The independent **Clinical Endpoints Adjudication Committee (CEC)**, which will be blinded to study treatment, will adjudicate all potential efficacy endpoint events and cardiac events of special interest in accordance with pre-specified criteria. The events include all-cause death (i.e., including non-cardiac and cardiac death), LVAD placement, heart transplant, artificial heart implantation, hospitalization for non-fatal decompensated HF, urgent care outpatient HF visit, successfully RCD, non-fatal MI, hospitalization for unstable angina, non-fatal CVA, coronary artery revascularization, and [redacted] (refer to the CEC charter).

Duration of Study/Patient Participation: This is an events-driven study and the study duration will be determined by a minimum length of time and cumulative total number of recurrent non-fatal HF-MACE (*i.e.,* recurrent non-fatal decompensated HF events and/or successfully RCD events). Patients are expected to participate in this study until the required minimum number of recurrent non-fatal HF-MACE occur. The End-of-Study will occur when the two following conditions have been met: 1) at least 531 recurrent non-fatal HF-MACE have occurred and 2) all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up.

General Design and Methodology: This is a multinational, multicenter, double-blind, randomized, scripted sham procedure-controlled, parallel-group study to evaluate the efficacy and safety of rexlemestrocel-L (human bone marrow-derived adult allogeneic MPCs) during a single treatment index cardiac catheterization involving intracardiac mapping in patients with

chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy. Overall, it is anticipated that known epicardial CAD (documented stenosis of at least 50% in one or more major epicardial coronary arteries, documented prior MI, and/or documented coronary artery revascularization) will be present in approximately 60% of patients who are randomly assigned to treatment. The randomization code for the study will be maintained by a Mesoblast-independent third party provider.

The study comprises 3 main time periods:

- Screening and randomization designation period: A patient's eligibility to participate in the study will be determined during this period and will be based on the study's inclusion and exclusion criteria for screening. If the patient is deemed eligible to participate in the study, randomization will occur.
- Study intervention: Study intervention will involve hospitalization on Day 0 for a single index cardiac catheterization (with or without intracardiac mapping and cell delivery). For all patients who are randomized and **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization, study intervention will be performed at a cell injection center by an interventional cardiology team not involved with long-term follow-up of patients' safety and efficacy evaluations. Interventional cardiologists and the unblinded team performing the study intervention may participate in screening evaluations (follow-up evaluations will be performed by blinded team members only).
- Follow-up period: For patients who are randomized and **DO** undergo the index cardiac catheterization, the follow-up period begins after hospital discharge from the cell injection center and includes safety and efficacy evaluations for a minimum of 6 months for all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit; and until the minimum of 531 required recurrent non-fatal HF-MACE is obtained. Patients, as well as non-interventional investigators and study site personnel at the HF study sites who conduct screening and follow-up (including long-term follow-up) evaluations after hospital discharge of patients from the cell injection center, will remain blinded to the study treatment provided at the cell injection center. In general, mid-term safety and efficacy evaluations for patients who are randomized and **DO** undergo the index cardiac catheterization will be conducted through 12 months follow-up while long-term follow-up after Month 12 will continue every 6 months until study conclusion. Also, any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary

and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study; additional assessments other than vital status and AE and endpoint collection will **NOT** be performed. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

Written informed consent will be obtained for the study before any study-specific procedures are performed. A separate written informed consent for an exploratory pharmacogenomics (PGx) substudy will be obtained before any PGx-specific procedures are performed. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). A patient will not be excluded from participation in the study if he/she chooses not to provide consent for the additional procedures that are required as part of the exploratory PGx substudy.

After informed consent is obtained, the patients will be screened for eligibility to participate in the study. This will be based during the screening period on the study's pre-specified inclusion and exclusion criteria. During the screening period, patients will undergo cardiac imaging, which will consist, at a minimum, of 2-D echocardiogram (with or without contrast). Contrast imaging will be performed for enhanced LV chamber imaging as determined by the investigator or designee. If echocardiographic imaging is of insufficient technical quality for LV volume and LV ejection fraction estimation, then a radionuclide ventriculogram (RVG) will be performed to assess LV ejection fraction as part of the patient's screening procedures for inclusion in the trial. The Principal Investigator (or designee) will assess the need for coronary revascularization before the patient is randomly assigned to receive active or control treatment. If it is determined that a patient requires coronary revascularization, it should be performed at least 2 months before reinitiating any study screening procedures. Patients who are screen failures may be re-screened with approval from the medical monitor. Randomization should occur as close as possible to the scheduled index cardiac catheterization date for potential delivery of study product. The pre-randomization criteria, such as echocardiographic criteria (restrictive, constructive or obstructive physiology, LV wall thickness, mural or arterial thrombus and prosthetic valve) are to be met by all patients and confirmed by both HF referral physician and the interventional cardiologist.

Echocardiographic criteria must be confirmed and signed off by interventional cardiologist prior to randomization.

Patients who are randomized and experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization procedure will be included as part of the ITT analysis and cannot be re-screened. Also, any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study; additional assessments other than vital status and AE and endpoint collection will **NOT** be performed. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

Patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned in a 1:1 ratio to receive either active treatment (*i.e.,* intracardiac mapping and transendocardial delivery of rexlemestrocel-L) or control treatment (*i.e.,* a scripted sham intracardiac mapping and cell delivery procedure without rexlemestrocel-L). After randomization, all patients who **DO NOT** experience an inclusion/exclusion criterion violation before the scheduled index cardiac catheterization procedure will be hospitalized at a cell injection center for index cardiac catheterization (with or without intracardiac mapping and cell delivery) and will remain hospitalized on telemetry for a minimum of 1 night. Prior to the initiation of any procedures, the study personnel at the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable.

All patients randomly assigned to the active treatment group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo an index cardiac catheterization with left ventriculography followed by cardiac mapping and transendocardial delivery of rexlemestrocel-L. Myocardial locations for transendocardial delivery of rexlemestrocel-L will be defined by means of imaging and left ventricular electrical mapping of the myocardium using the NOGA® or CARTO® Cardiac Navigational System in combination with the NogaStar® Mapping Catheter. Fifteen to

20 appropriate myocardial sites will be identified (20 sites is ideal) by imaging and electrical mapping as viable for cell delivery. The injection sites will be captured by NOGA® or CARTO® and transcribed into EDC. Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to the imaging identified myocardial locations; the total volume of study product administered must not exceed 4.0 mL. The total duration of the transendocardial delivery procedure must not exceed 90 minutes from the time of completion of thaw of rexlemestrocel-L.

All patients randomly assigned to the control group who **DO NOT** experience an inclusion/exclusion criterion) violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted sham cardiac mapping and cell delivery procedure that will include index cardiac catheterization with left ventriculography and a simulation of cardiac mapping and cell delivery. The scripted sham cardiac mapping and cell delivery procedure will be staged to script and will not include actual cardiac mapping or transendocardial delivery of rexlemestrocel-L but is designed to correspond to the operational steps that are used for intracardiac transendocardial delivery. These patients will not undergo placement of the NogaStar® navigation catheter and the MyoStar™ catheters. The scripted sham cardiac mapping and cell delivery procedure will be led by the interventional cardiologist and will be approximately 60 to 90 minutes in duration. As with the active treatment group, after the completion of the mapping procedure, 15 to 20 appropriate myocardial sites will be identified, but by means of a scripted sham cardiac mapping procedure followed by a scripted sham cell delivery procedure, and will simulate the exact full procedural requirements used for the actual treatment cohort. Thus, the patients will be blinded to study treatment. The total duration of the scripted sham cell delivery procedure will not exceed 90 minutes.

Index cardiac catheterization (with or without intracardiac mapping and cell delivery) will be performed only by interventional cardiologists who have successfully completed the NOGA® System/MyoStar™ Catheter or CARTO® System/MyoStar™ Catheter training program required by BDS. In addition, these individuals must be confirmed as having an active status in the BDS database and are experienced in performing cardiac interventional procedures. Retraining in the use of Global NOGA® System/MyoStar™ Catheter or CARTO® /MyoStar™ Catheter must take place for interventionalists who have not performed the NOGA® or CARTO® system procedure in over 1 year. Current American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) Practice Guidelines will be followed in managing any procedure-related cardiac arrhythmias.

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

For randomized patients who **DO** undergo study treatment in the cardiac catheterization laboratory, the following assessments will be performed at follow-up: evaluations of LVEF, exercise capacity as determined by the 6MWT, biomarkers (NT-proBNP and hsCRP), functional status by the NYHA functional class assessment, QoL as measured by the MLHF and EQ-5D questionnaires, immunogenicity testing, and safety evaluations of adverse events, CVA, and MI, clinical laboratory tests, urinalysis, vital signs measurements, physical examinations, ECG recordings, 24-hour Holter monitor recordings (randomized patients across the US and EU), and use of concomitant medication and therapy. In addition, for echo-qualifying patients only, serial assessment of cardiac remodeling will be performed based on 2-D echocardiographic estimations (without or with contrast) of left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV) and reviewed by the core imaging laboratory. Serial assessment of LVEF will be performed in selected patients using either echocardiographic imaging or RVG, depending upon which technique was used to qualify the patient during screening. Separate serial assessments will be performed for RVGs and echocardiograms, as applicable. For patients with an ICD (or any implanted device capable of defibrillation), rhythm analysis by device interrogation (performed at regularly scheduled intervals by appropriate site personnel) will be conducted. These episodes will be assessed at each site and captured as adverse events or non-fatal HF-MACE, as appropriate. When a non-fatal HF-MACE or a TCE is suspected, the rhythm strips obtained by device interrogation and relevant clinical context will be provided to the CEC for their review and adjudication.

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-human leukocyte antigen (HLA) DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who

were randomized and underwent the index cardiac catheterization. All serum samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). [redacted] serum samples [redacted] rexlemestrocel-L will be analyzed for anti-murine (MIgG) and anti-bovine (bovine serum albumin [BSA]) antibodies. The serum samples will be analyzed for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies) [redacted]

Blood samples will be collected after randomization from patients who **DO NOT** experience an inclusion/exclusion criterion violation and provided informed consent for possible use in future PGx analyses for the assessment of possible associations between genetic polymorphisms and the response to rexlemestrocel-L therapy in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy. Blood samples for PGx evaluations will be collected at the end of screening and stored for future use.

The screening period may last up to 42 days before the scheduled index cardiac catheterization. For patients who are randomized and **DO** undergo the index cardiac catheterization, during the first 12 months after the Day 0 index cardiac catheterization, follow-up assessments will be scheduled at Day 10 and Months 1, 3, 6, and 12. A telephone follow-up inquiry will be made at Months 2, 4, 5, 7, 8, 9, 10, and 11 (±14 days). For the long-term follow-up evaluations, which will begin after Month 12, patients will return to the study site approximately every 6 months for follow-up of patients' safety and efficacy evaluations until study conclusion. Telephone follow-up inquiries will be made every 2 months between study visits during the long-term follow-up period (Months 14, 16, 20, and 22). These long-term follow-up visits and telephone contacts will continue until study conclusion.

For patients who are randomized and **DO NOT** undergo the index cardiac catheterization, follow-up consists of determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential

primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

Enrollment in this study will end at or before the time that a minimum number of pre-specified recurrent non-fatal HF-MACE (i.e., decompensated HF events and/or successfully RCD events) have been positively adjudicated and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up. Patients are expected to participate in this study until the required minimum number of recurrent non-fatal HF-MACE occur; they will remain in the study until the Sponsor declares the study has reached completion. Patients who complete or withdraw from the study before or after the Month 12 follow-up visit will be evaluated at the time of study completion/withdrawal, using the same assessments that are specified for the Month-12 visit. Any surviving patient with a prior history of TCE may have their EOS visit conducted by phone. When a minimum of 95% of the positively adjudicated non-fatal HF-MACE has occurred, patients may have EOS assessments performed at their next scheduled visit if they already have a minimum of 18 months of follow-up. An echocardiogram or RVG will also be performed if more than 6 months have passed since the patient's last echocardiogram or RVG.

During the course of the study, the occurrence of AEs, SAEs, TCEs, non-fatal HF-MACE (*i.e.,* decompensated HF events and/or successfully RCD events), overall survival, coronary artery revascularization procedure, [redacted]), non-fatal CVA, and non-fatal MI will be reviewed, evaluated, processed, and/or reported in accordance with the protocol.

Additionally, the occurrence of all AEs/SAEs on Day 0 through hospital discharge following index cardiac catheterization (with or without intracardiac mapping and cell delivery) will be reported to the the unblinded medical monitor. In addition, Mesoblast Safety will report any AEs/SAEs that have been assessed to be related to either mapping or injection catheters to the medical device manufacturer of the cardiac navigation system and associated catheters (Bioscience Webster, Inc.) within 30 calendar days from the event awareness date. . For reporting of SAEs to the sponsor, the investigator or designee will complete the SAE information electronically in the electronic case report form (eCRF). When it is completed, Mesoblast Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible

to access the eCRF, the investigator or designee should complete the backup paper SAE form and e-mail it at [redacted] to Mesoblast Safety with 24 hours of awareness (see Section 7.1.6.3).

The Sponsor Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities. Additionally, there will be 3 oversight committees: the ESC, an independent CEC, and an independent DMC as described previously.

Primary Efficacy Variable and Endpoint: The primary efficacy measure and endpoint for this study is time-to recurrent non-fatal HF-MACE, which consists of recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully resuscitated cardiac death events. The primary efficacy endpoint only considers non-fatal HF-MACE that occur prior to the first TCE. However, all recurrent and terminal HF-MACE following non-fatal TCEs will be collected and adjudicated for sensitivity analysis based on different definitions of recurrent and TCEs. The following definitions apply to the TWO components of the primary endpoint:

- **Non-fatal decompensated HF event** will be adjudicated when the diagnosis of a non-fatal decompensated HF event demonstrates the presence of signs and symptoms consistent with clinical decompensation of the patient's HF state requiring an in-hospital stay or intravenous (IV) diuretic therapy or aquapheresis during an urgent care outpatient HF visit;
- **Successfully resuscitated cardiac death (RCD)** events will be adjudicated when a subject experiences sudden death or cardiac death and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness (LOC) or syncope and receive a successful appropriate shock from an implantable cardioverter-defibrillator with meaningful recovery will also be designated as successful RCD event. These events will be considered recurrent (non-terminal) events for the purpose of the primary efficacy analysis, and will be considered terminal events in sensitivity analyses.

NOTE: Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be analyzed jointly with recurrent non-fatal HF-MACE within the Joint Frailty Model analysis. It is the intent that a "terminal cardiac event" occurs when the left ventricle (LV) is no longer functioning as an independent viable pumping chamber that provides pulsatile blood flow to the systemic circulation. Time from Day 0-to-first TCE is a

key secondary endpoint that will be evaluated using only TCEs. This analysis, which will be performed utilizing a proportional hazards model, will help assure that any improvement in recurrent non-fatal HF-MACE for the Cell Therapy group is not associated with worsening in time-to-terminal event for the Cell Therapy vs. Control (Sham) group. This analysis will provide assurance that any beneficial difference in recurrent non-fatal HF-MACE for the Cell Therapy vs Sham groups is not due to disproportionate early and/or late TCE rate for the Cell Therapy group.

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

Adjudication of all potential non-fatal HF-MACE or TCEs will be performed by an independent, blinded CEC. Once the first TCE has occurred for a patient, subsequent TCEs and/or non-fatal HF-MACE for that patient will be excluded from the primary JFM analysis. All recurrent non-fatal HF-MACE and TCEs will be collected and adjudicated through end-of-study or patient's death for safety and sensitivity efficacy analysis purposes. (For details on the role and responsibilities of the CEC, please see the CEC Manual of Operations.)

Transendocardial delivery of rexlemestrocel-L into the myocardium will require the placement of the injection catheter needle into the left ventricle wall. In order to accomplish this procedure, there will be significant catheter manipulation within the LV chamber. This normally causes premature ventricular contractions (PVCs) and multiple brief episodes of nonsustained VT during the cardiac mapping and cell delivery procedure. These arrhythmias are usually self-terminated. Sustained ventricular arrhythmias such as VT or ventricular fibrillation (VF) may occasionally be triggered even in the normal heart. Because of the underlying pathology in patients who will be enrolled in this study (which specifies significant LV systolic dysfunction as an inclusion criterion), ventricular arrhythmias may be more pronounced and occur more often than in less ill patients. Because of the close association between ventricular arrhythmias due to LV catheter manipulation and the cell delivery procedure, the occurrence of sustained ventricular arrhythmias that may require cardioversion or defibrillation during index cardiac catheterization

(with or without intracardiac mapping and cell delivery) on Day 0 is expected and will not be considered a non-fatal HF–MACE. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization onward that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

Secondary Efficacy Variables and Endpoints:
The key secondary endpoint, time from Day 0-to-first TCE, will be evaluated to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-TCE for the Cell Therapy vs. Control (Sham) group.

The key secondary endpoint relating to TCEs is as follows:

- Time from Day 0-to-first TCE (cardiac death, LVAD placement, heart transplant, or artificial heart implantation, whichever occurs first).

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control.

Secondary efficacy measures and endpoints for this study comprise a comparison of study treatment groups for the following:

- time-to-hospital admissions for decompensated HF events beginning on Day 1
- time-to-urgent care outpatient HF visits beginning on Day 1
- time-to-successfully RCD events beginning on Day 1
- total length of in-hospital stay in intensive care unit for decompensated HF events beginning on Day 1
- time-to-first major cardiac event, defined as a composite of hospital admissions for decompensated HF, urgent care outpatient HF visits, and successfully RCD events.
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated heart failure, urgent care outpatient HF visits, successfully RCD events, or TCE
- time-to-cardiac death
- time-to-all-cause death
- time-to-non-fatal MI, non-fatal CVA, or coronary artery revascularization, whichever comes first.

Other secondary efficacy measures and endpoints relating to LV remodeling, functional exercise capacity, functional status, and QoL, and comprise the following:

- LV remodeling as assessed by change from baseline in LVESV as determined by 2-dimensional (2-D) echocardiography (echo-qualifying patients only).
- Sensitivity analyses would, at a minimum, include the following:
  - Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE)
  - Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and change in month 6 – baseline LVESV (increase or no change vs. decrease) and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE)
  - LV remodeling as assessed by change from baseline in LVEDV as determined by 2-D echocardiography (echo-qualifying patients only)
  - LV systolic performance as assessed by change from baseline in left ventricular ejection fraction (LVEF)
  - functional exercise capacity as assessed by change from baseline in distance covered during the 6-minute walk test (6MWT)
  - functional status as assessed by change from baseline in NYHA Functional Class
  - QoL as assessed by change from baseline in the Minnesota Living With Heart Failure (MLHF) questionnaire score
  - QoL as assessed by change from baseline in the EuroQol 5-dimensional Quality of Life (EQ-5D) questionnaire score.

Safety Variables and Endpoints: The safety and tolerability of rexlemestrocel-L will be assessed throughout the study by evaluating AEs, clinical laboratory test results, vital signs measurements, concomitant medication and therapy usage, ECG, 24-hour Holter monitoring (randomized patients across the US and EU), echocardiographic, and physical examination results. In addition, important cardiovascular safety events will be reviewed from CEC-adjudicated data. The safety variables and endpoints for this study are as follows:

- occurrence of adverse events relative to index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 hospitalization through discharge for that hospitalization
- occurrence of adverse events
- clinical laboratory tests (serum chemistry and hematology) results
- urinalysis
- vital signs measurements
- ECG findings

- Telemetry findings
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- 24-hour Holter monitoring (randomized patients across the US and EU)
- physical examination findings
- review of important cardiovascular safety events from CEC adjudicated data for all-cause death (*i.e.,* including non-cardiac and cardiac death) and hospitalizations for non-fatal decompensated HF, successfully RCD events, overall survival, coronary artery revascularization procedure, pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE, non-fatal CVA, and non-fatal MI.

Immunogenicity Variables and Endpoints: The immunogenicity variables and endpoints are as follows:

- PRA
- DSA (if the test for PRA is positive)
- antibodies against bovine or murine proteins (*i.e.,* BSA and MIgG).

[redacted]:

- biomarkers as assessed by changes from baseline in NT-proBNP and hsCRP
- [redacted]
- [redacted]
- [redacted]
- PGx analyses to determine whether gene variants found in some patients will predict how they respond to rexlemestrocel-L therapy.

[redacted]

[redacted]

Pharmacodynamics: Blood samples for analysis of the biomarkers NT-proBNP and hsCRP will be collected at screening and at Months 3, 6, and 12 (randomized and treated patients who **DO NOT** experience a disqualifying event). Blood samples will be collected every 12 months thereafter during long-term follow-up evaluations until study conclusion.

Immunogenicity: The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-HLA DSA formation. Blood serum samples will be collected for immunogenicity analyses during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who were randomized underwent the index cardiac catheterization. All serum samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). [redacted] serum samples [redacted] of rexlemestrocel-L will be analyzed for anti-murine (MIgG) and anti-bovine (BSA) antibodies. The serum samples will be analyzed for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies) [redacted]

Pharmacogenomics: Blood samples will be collected after randomization from patients who have signed the pharmacogenomics informed consent form and who **DO NOT** experience an inclusion/exclusion criterion violation. Samples will be stored for possible use in future PGx analyses to determine whether gene variants found in some patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology will predict how those patients will respond to therapy with rexlemestrocel-L.

Statistical Considerations: This is an events-driven study using the Intent-to-Treat (ITT) population as the primary analysis dataset. The sample size is based on Monte-Carlo simulations: 600 patients, with an estimated total of 531 recurrent non-fatal HF-MACE defined as recurrent non-fatal decompensated HF events and/or successfully resuscitated cardiac death (RCD) events adjusted for TCEs. These non-fatal HF-MACE will provide approximately 93.5% power (with 91.4% for the low limit of 95% confidence interval (CI) for the powers from all the simulations) at the 0.05 two-sided (0.025 one-sided) significance level to detect at least a 40% risk reduction (hazard ratio of 0.6) in recurrent non-fatal HF-MACE adjusted for TCEs. The simulations to determine the sample size were based on the following assumptions:

- overall recurrent event rate of 1.06 (based on the Phase 2 study data)

- median follow-up period of at least 2 years (patients who were enrolled early in the study and followed for recurrent non-fatal HF-MACE through the end-of-study would have a follow-up period substantially longer than 2 years, unless they experienced a TCE).

The assumption regarding TCE rate was based on data from the Phase 2 study ([redacted] and ESSENTIAL study (evaluated patients with entry criteria similar to this study[1] and was assumed to be between 25% and 31% based on an approximate 2-year median follow-up (27% was used in the simulation for the sample size in this study). This sample size of 600 patients also considers and includes a potential 4% patient drop-out rate during the study.

Two interim analyses were planned and have been conducted. Details for both interim analyses are provided in the statistical analysis plan (SAP) V5.0.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
2-D	2-Dimensional
3-D	3-Dimenstional
6MWT	6-Minute Walk Test
ACE	Angiotensin Converting Enzyme
ACC/AHA/ESC	American College of Cardiology/American Heart Association/European Society of Cardiology
ACT	Activated Clotting Time
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARB	Angiotensin-Receptor Blocker
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BDS	Biologics Delivery System
bpm	Beats Per Minute
BSA	Bovine Serum Albumin
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CEC	Clinical Endpoints Adjudication Committee
CFR	Code of Federal Regulations
CHMP	Committee For Medicinal Products For Human Use
CI	Confidence Interval
CIOMS	Council For International Organizations of Medical Sciences
CK-MB	Creatine Kinase-Myocardial Band
CLIA	Clinical Laboratory Improvement Amendments
CM	Cardiomyopathy
cMRI	Cardiac Magnetic Resonance Imaging
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CSC	Clinical Supply Chain
CRT	Cardiac Resynchronization Therapy
CRT-D	An implantable CRT defibrillator
CT	Computed Tomography
CVA	Cerebrovascular Accident
CVMP	Committee For Medicinal Products For Veterinary Use
DC	Direct Current
DSA	Donor-Specific Antibodies
DMC	Data Monitoring Committee
DMSO	Dimethyl Sulfoxide
ECG	Electrocardiography, Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency

Abbreviation	Term
EQ-5D	Euroqol 5-Dimensional Quality of Life Scale
ESC	Executive Steering Committee
EU	European Union
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume In 1 second
FDA	US Food And Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HF	Heart Failure
HF-MACE	Heart Failure–Related Major Adverse Cardiac Event (NOTE: Non-Fatal HF-MACE Are Defined As the Composite of Recurrent Non-Fatal Decompensated HF Events And/Or Successfully Resuscitated Cardiac Death Events)
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
hsCRP	High-Sensitivity C-Reactive Protein
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IB	Investigator's Brochure
ICH	International Conference On Harmonisation
ICD	Implantable Cardioverter Defibrillator
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
IUD	Intrauterine Device
JFM	Joint Frailty Model
LAD	Left Anterior Descending
LAO	Left Anterior Oblique
LDH	Lactate Dehydrogenase
LOC	Loss of Consciousness
LLS	Linear Local Shortening
LV	Left Ventricular Or Left Ventricle, Depending On Context
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVEDP	Left Ventricular End-Diastolic Pressure
LVEDV	Left Ventricular End-Diastolic Volume
LVESV	Left Ventricular End-Systolic Volume
M	Million
MACE	Major Adverse Cardiac Event
MDR	Medical Device Safety Reporting
MDRD	Modification of Diet In Renal Disease
MedDRA	Medical Dictionary For Regulatory Activities
MEM	Alpha Modified Eagles Medium

Abbreviation	Term
MI	Myocardial Infarction
MID	Minimum Important Difference
MIgG	Mouse Immunoglobulin G
MLHF	Minnesota Living With Heart Failure
mmHg	Millimeters Mercury
MMRM	Mixed Model For Repeated Measures
MPC	Mesenchymal Precursor Cells
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cells
mV	Millivolts
N	Number
NICM	Nonischemic Cardiomyopathy
NOAC	Novel Oral Anticoagulant
NT-proBNP	N-Terminal-Pro-B-Type Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PDD	Pharmaceutical Product Development, Inc.
PGx	Pharmacogenomic(S)
PRA	Panel Reactive Antibodies
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVC	Premature Ventricular Contraction
QoL	Quality of Life
QRS complex	Name For the Combination of 3 Graphical Deflections Seen on a Typical Electrocardiogram
QT	The Time Interval From the Beginning of the Cardiac QRS Complex To the End of the T Wave
QTc	QT Interval Corrected For Heart Rate
QTcB	QT Interval Corrected Using Bazett Method
QTcF	QT Interval Corrected Using Fridericia Method
RAO	Right Anterior Oblique
RBC	Red Blood Cell
RCD	Resuscitated Cardiac Death
RVG	Radionuclide Ventriculography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Document Verification
SE	Standard Error
SHAPE	Study Group On Heart Failure Awareness And Perception In Europe
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Telephone Contact
TCE	Terminal Cardiac Event
ULN	Upper Limit of the Normal Range
UNOS	United Network for Organ Sharing

Abbreviation	Term
US(A)	United States (of America)
V	version
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WBC	White Blood Cell
WHO	World Health Organization

1. BACKGROUND INFORMATION

1.1 Introduction

A number of therapeutic approaches have been developed in an effort to treat patients with the most severe forms of cardiovascular disease, including chronic heart failure (HF). These approaches have included small molecules, biologics, devices, biventricular pacing, gene therapy, and cellular therapy. [2,11, 17] Whereas some of these therapies have been effective, especially initially, the natural history of advanced chronic HF remains progressive with poor long-term prognosis. For those patients with end-stage disease, very limited options are available, including placement of a left ventricular assist device (LVAD) and heart transplantation. However, an LVAD is costly and generally only provides a short-term solution, and heart transplantation is limited by organ availability and the need for long-term monitoring and complex immunosuppressive therapy. For patients with advanced chronic HF there is an important unmet clinical need to intervene in a manner that halts or, at a minimum, delays disease progression. The use of cellular therapies, such as stem cells, to repair and/or restore the structure and function of the damaged myocardium has the potential to alter the natural history of advanced chronic HF. Indeed, several clinical studies using stem cell therapy have reported promising hypothesis-generating results.[7,12,15,17-21]

Despite substantial advances in the multi-modal treatment of patients with cardiovascular disease, HF continues to place a significant burden on the health care system. In the United States (US), approximately 5.8 million (M) people currently have HF and approximately 670,000 new patients will be diagnosed with HF every year. [22-24] The prevalence of HF is estimated to be 1% to 2% in developed countries, increasing with age. [25]

In the United States, HF is the leading cause of hospitalization for patients older than 65 years of age, raising concerns about the economic burden of this condition.[23-26] Indeed, HF is the only cardiovascular disease that currently has an increasing incidence.[27]

In 2010, the cost of HF in the United States was estimated to be $39.2 billion, a figure that includes health care services, medications, cardiac transplantation, and lost work productivity.[28,29] In 2013, one in nine death certificates (284,388 deaths) in the United States mentioned HF. Heart failure was the underlying cause in 58,309 of those deaths. The number of any-mention deaths attributable to HF was approximately as high in 1995 (287,000) as it was in 2013 (284,000). Additionally, hospital discharges for HF remained stable from 2000 to 2010, with first-listed discharges of 1,008,000 and 1,023,000, respectively.[22,23]

In Europe, HF is also the single biggest reason for acute hospital admission in individuals older than 65 years. Approximately 14 M people in Europe have HF, and the incidence is increasing, with more cases being identified, more people living to an older age, and more patients surviving an acute myocardial infarction (MI) with subsequent adverse ventricular remodeling. More than 3.5 million people are newly diagnosed with HF every year in Europe alone. [25] Similar distribution patterns are seen in European countries as the US national health care budget (~2%) and the percentage of the cost related to hospitalization (60%).[29] According to the Study Group on Heart Failure Awareness and Perception in Europe (SHAPE), the number of people suffering from HF is expected to increase to 30 million by the year 2020.

Heart failure represents the final common pathway in a pathological continuum of clinical, biological, and cellular events that leads to progressive maladaptive ventricular remodeling. [6,30-32] Despite diverse underlying etiologies of structural heart disease (ischemic and nonischemic in etiology), the diseased left ventricle adapts physiologically in order to maintain cardiac output and meet metabolic demands. Ultimately, progressive ventricular dilatation with associated derangements in molecular biodynamics and signaling pathways lead to cellular and genomic responses that ultimately result in adverse remodelling.[33-35] The left ventricular (LV) remodeling process following an MI begins with myocardial necrosis and thinning of the wall of the heart.[36,37] Although fibroblasts and collagen strengthen the necrotic area through a wound-healing response, this thin weakened area is unable to withstand the pressure and volume load on the heart, resulting in LV chamber dilation, decreased myofibril shortening, cardiac dysfunction and circulatory disturbances. Eventually, systolic and diastolic performance decline leading to associated increases in left ventricular end-systolic volume (LVESV) reflecting predominantly diminished contractile performance and increased ventricular afterload, and left ventricular end-diastolic volume (LVEDV) reflecting predominantly increased fiber lengthening or preload immediately prior to ventricular systole.[6,30-32] At a critical juncture in the disease process, symptoms and signs of HF become manifest as a reflection of pulmonary venous hypertension, compromised systemic cardiac output, renal hypoperfusion with sodium and water retention, and neuroendocrine and metabolic derangements.[38-44] The ultimate consequence is significantly increased risk of sudden death due to arrhythmias or death due to progressive pump failure.

Beneficial LV remodeling in patients with HF due to LV systolic dysfunction has been shown in numerous interventional long term follow-up studies to be an important surrogate for improved clinical outcomes. A standard measurement of LV remodeling is 6-month or 12-month change from baseline in LVESV.

a. A meta-analysis by Kramer et al of patients with HF and reduced ejection fraction showed a statistically significant positive correlation between long-term mortality and LV remodeling assessments performed at a mean follow up of 6-months post-baseline.[45] When measurements of beneficial remodeling using LVESV were compared with LVEF, the volume measurement demonstrated a higher incidence of improved longer-term mortality and was a better predictor of therapeutic effects on mortality.
b. In the REVERSE Trial, which included 508 HF patients with systolic dysfunction who received CRT-D (CRT defibrillator) devices, patients were randomized to a CRT ON group or a CRT OFF group.[46,47] There were no significant demographic differences between groups at baseline. In the CRT ON group, those patients with reverse remodeling (significant decrease in echo LVESV at 12-month compared to baseline) had a reduced incidence of VT/VF compared with those patients without LV remodeling (p =.001). Furthermore, the presence of beneficial LV remodeling (decrease in echo LVESV at Month 6 compared to baseline) was associated with a >50% reduction in long term mortality rate.
c. Thus, beneficial LV remodeling (as assessed by decrease in LVESV) should be a goal of therapies designed to treat systolic HF and is an important target for interventions aiming to optimize therapy.

Current treatments for patients with HF, including the administration of neurohormonal antagonists (*e.g.,* ACE inhibitors, ARBs, beta blockers and/or aldosterone antagonists), use of implantable cardioverter defibrillators (ICDs), and/or cardiac resynchronization devices have greatly benefitted many patients with advanced chronic HF as manifested by the following:

- stabilized or improved LVEF and ventricular volumes. [12, 48-50]
- reduced mortality [51,52]decreased number of HF hospitalizations.[10, 53,54]
- improved quality of life.[55]

However, while the administration of neurohormonal antagonists may delay the progression of HF, current treatments usually do not halt the disease.[56,57] In general, pharmacologic attempts at improving exercise capacity in patients with chronic HF due to significant LV systolic dysfunction have met with very limited success. This may reflect the use of drug strategies that attempt to interrupt a single pathologic pathway (*e.g.,* beta adrenergic blockade) rather than addressing the more complex multifactorial nature of the disease process itself.

Whereas ICDs prevent sudden cardiac death due to ventricular fibrillation (VF), they do not diminish the proportion of patients who develop worsening HF.[58] Indeed, because of prolonged

survival, patients with ICDs may progress to a stage of advanced chronic HF characterized by frequent hospitalizations, marked limitation of exercise capacity, poor quality of life, and hemodynamic impairment.[1] Currently, the management of end stage HF prior to transplantation includes cardiac resynchronization therapy[10,48] and LVADs.[59]

Patients who are hospitalized for HF have a highly increased risk of repeat hospital stay and death.[23,29,60,61] Post-hospital discharge mortality and rehospitalization rates reach 10% to 20% and 20% to 30%, respectively, within 3 to 6 months.[23,60-62-64]

Therapies are being developed that offer the potential to interrupt the pathogenic continuum that leads to advanced chronic HF.[2,3,7, 11,12,15] Among these are [redacted] Accordingly, methods to isolate and grow MLCs ex vivo to expand their numbers have been developed to enable assessment of their biology and therapeutic potential. Mesoblast has developed a method to immunoselect a primitive subpopulation of MLCs using a monoclonal antibody raised against the cell surface antigen, STRO-3, a unique epitope on the extracellular domain of tissue nonspecific alkaline phosphatase. The STRO-3 antibody selectively binds to a subset of MLCs that are referred to as mesenchymal precursor cells (MPCs).[70] [redacted]

Rexlemestrocel-L is comprised of adult human bone marrow-derived MPCs that have been culture-expanded and cryopreserved. Mesoblast is developing rexlemestrocel-L for the treatment of chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology. Data from nonclinical and clinical studies provide evidence of the safety and bioactivity of rexlemestrocel-L in this context (Section 1.3). In nonclinical studies in animal models of MI and non-ischemic cardiomyopathy (NICM), intra-myocardial administration of MPCs attenuated left ventricular dysfunction and adverse remodeling. These beneficial effects of MPCs are

attributable, at least in part, to the secretion of bioactive molecules that mediate tissue protection and repair.

Data from the Phase 2 chronic HF study (Study [redacted] performed with rexlemestrocel-L suggest that there is a concordance of long-term benefit relating to clinical outcomes, LV remodeling, and submaximal exercise performance. These findings support the conduct of the current Phase 3 study (Study MSB-MPC-CHF001), which will evaluate the efficacy and safety of rexlemestrocel-L delivered transendocardially into the LV myocardium in patients with chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy.

1.2 Name and Description of Investigational Product

The investigational product rexlemestrocel-L consists of human bone marrow-derived allogeneic MPCs isolated from bone mononuclear cells with an anti-STRO-3 antibody, expanded ex vivo, and cryopreserved. A description of rexlemestrocel-L is provided in Section 3.4.

1.3 Findings from [redacted] and Clinical Studies

Cellular therapy using MPCs was initially investigated by Angioblast Systems, Inc., a subsidiary of Mesoblast, Ltd. (Melbourne, Australia). In 2006, Mesoblast (doing business as Angioblast) incorporated a United States office (New York, New York) and began the clinical development of its cellular therapy products, including rexlemestrocel-L, for cardiovascular and non-cardiovascular conditions.

[redacted]

[redacted]

[redacted]

[redacted]

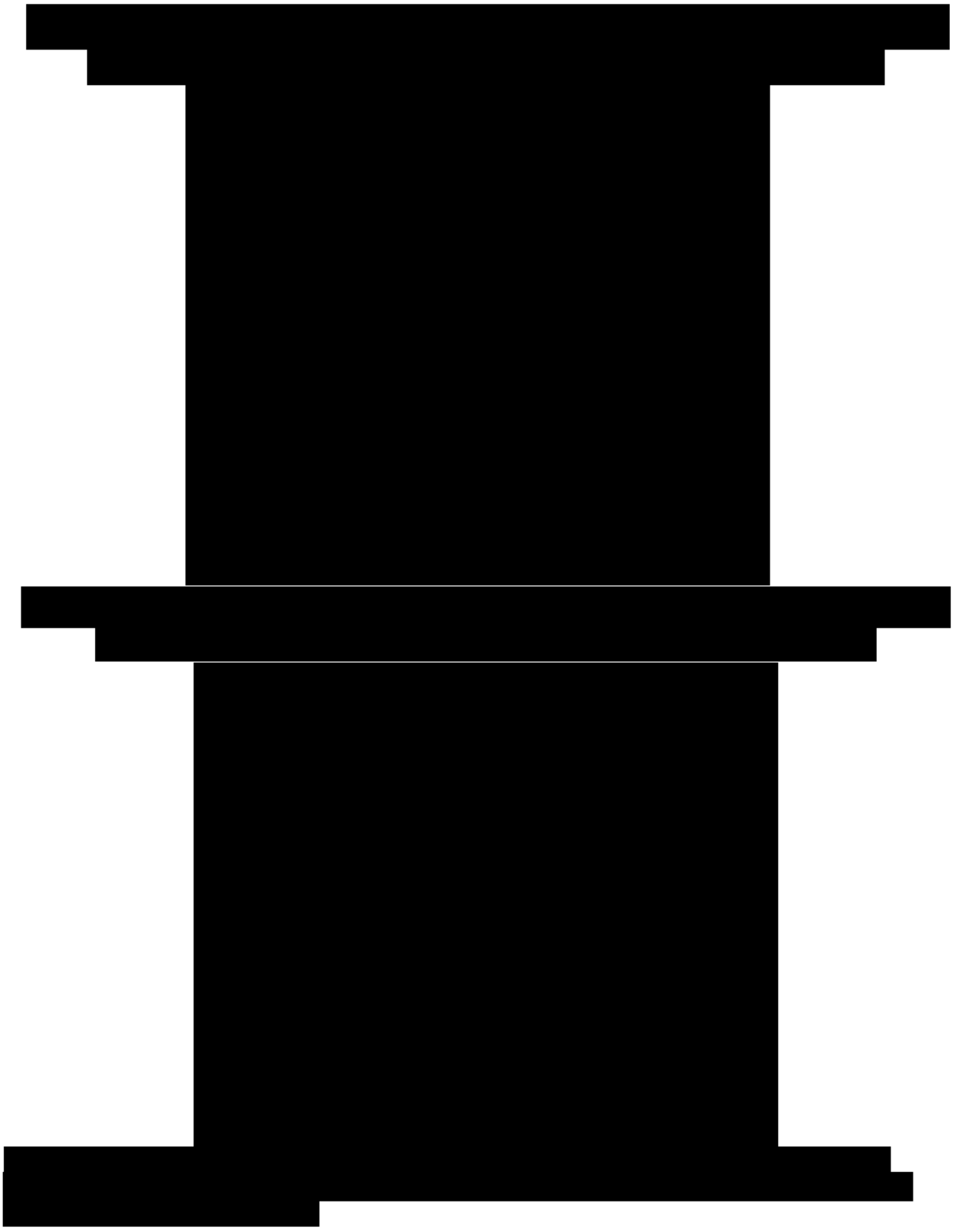
[redacted]

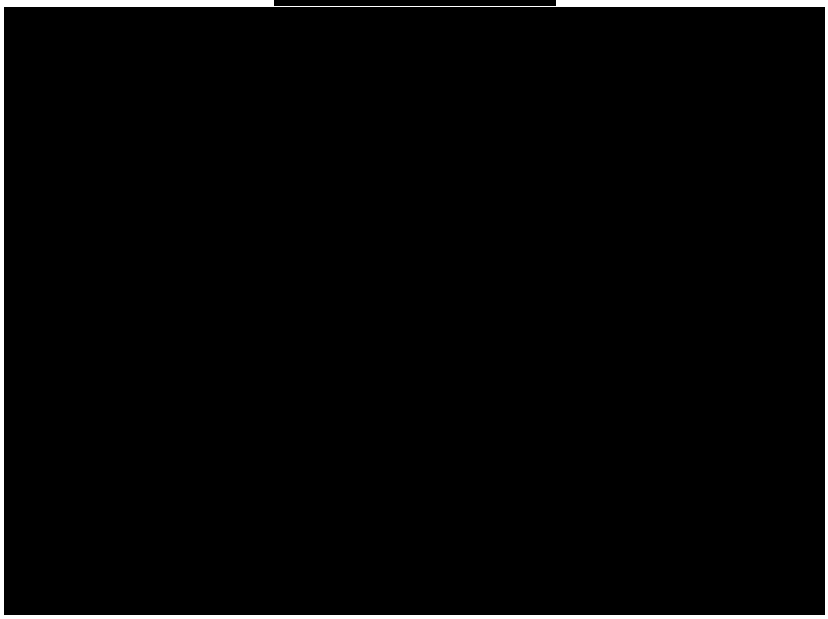
1.3.2.1 Phase 2 Dose-Escalation Study

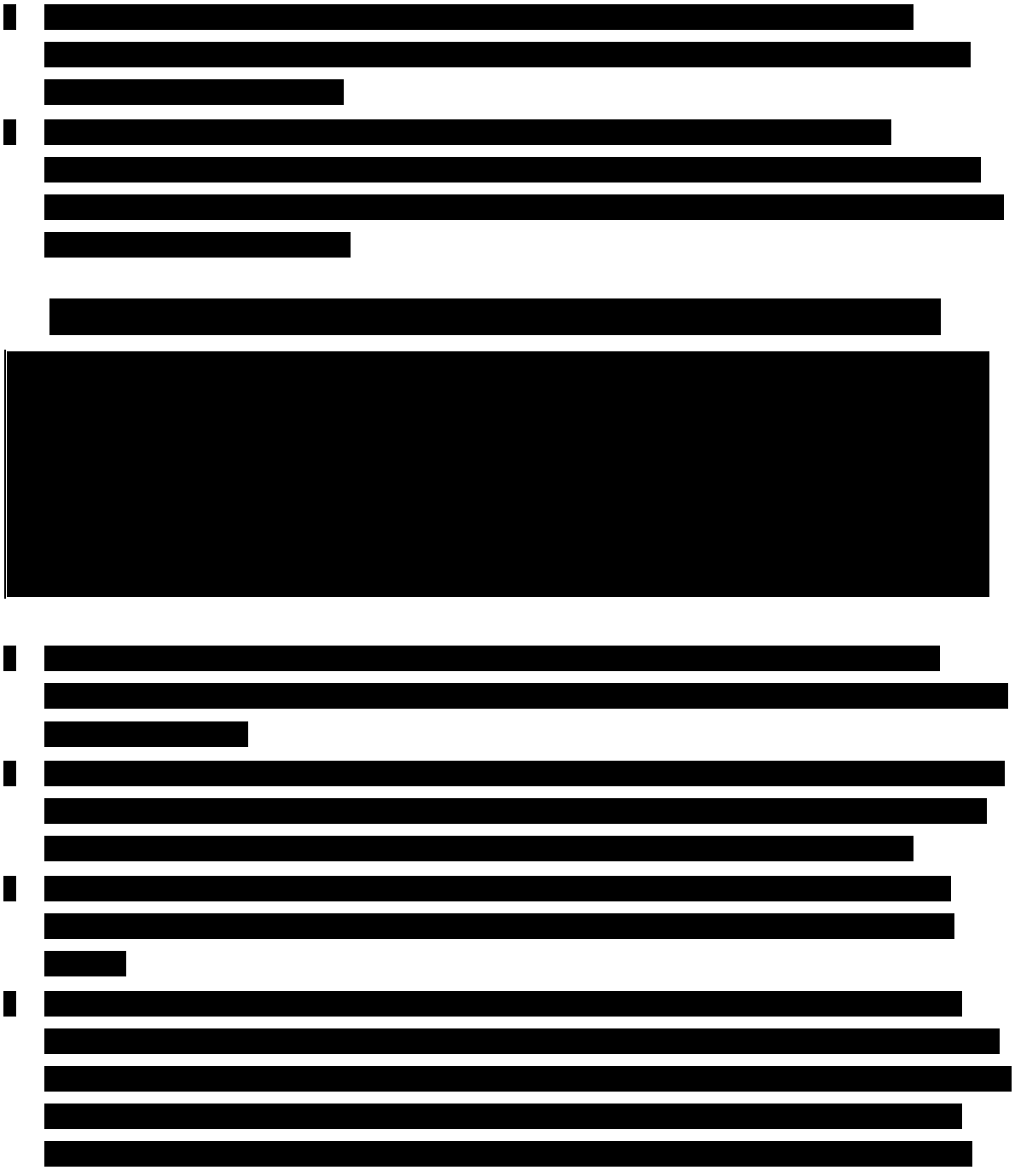
The primary objective of the Phase 2 MPC HF trial was to evaluate the safety and tolerability of three increasing doses (25, 75, or 150 M cells) of immunoselected, culture-expanded allogeneic MPCs in 60 patients with HF due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology. The secondary objective was to explore functional efficacy [redacted] Patients were allocated sequentially to one of three dosing cohorts with randomization to receive either transendocardial injections of allogeneic MPCs or mock mapping/ injection procedures (control). Safety and [redacted] endpoints were evaluated for up to 3 years for all patients. [redacted]

Patients with New York Heart Association (NYHA) Functional Class II or III HF who had a left ventricular ejection fraction (LVEF) <40% by baseline screening echocardiogram were recruited for the study. All patients were between 20 and 80 years old, had either chronic non-ischemic or ischemic cardiomyopathy that was not amenable to percutaneous intervention or surgery, and were on a prescribed regimen of maximal tolerated HF medications. Key exclusion criteria included acute myocardial infarction within 30 days, sustained ventricular tachycardia, unstable angina, or the presence of a left ventricular thrombus.

Patients were randomized to either an injection of 25, 75, or 150 million (M) allogeneic MPC by endomyocardial catheter or scripted mock injections (control group) while in the catheterization laboratory. MPCs were administered into the left ventricle (using the







[redacted]

[redacted]

[redacted]

1.4 Identified and Potential Risks and Benefits of Rexlemestrocel-L to Humans

A number of identified and potential risks associated with rexlemestrocel-L and the products that are used to manufacture rexlemestrocel-L have been recognized. In addition, procedure-related risks associated with cardiac catheterization, transendocardial delivery of MPCs, angiographic

and echocardiographic contrast media, and radionuclide imaging have been identified. Identified important safety concerns in association with rexlemestrocel-L are immunogenic responses, [redacted] Potential risks of rexlemestrocel-L include tumor development and transmission of infections. To date, none of these potential risks have been validated in any treated subjects.

1.4.1 Immunogenic Response

The administration of allogeneic MPCs may elicit immunogenic and/or inflammatory responses resulting from allogeneic exposure to the donor cells and/or manufacturing content. In Study [redacted]

The risks of exposure to MPCs are not fully known but there is the theoretical risk that [redacted]. Patients will be monitored for these responses by performing inflammatory marker tests such as antibody screening tests to [redacted] at designated follow-up visits.

Additionally, for immunoselection of the allogeneic MPCs, the technology incorporates an antibody-based sorting process using [redacted] In the cell expansion process, [redacted] Therefore there is the risk of a hypersensitivity reaction to these [redacted] It is based on these risks that patients with known hypersensitivity to [redacted] are excluded from study participation. The risk of sensitization from this formulation is unknown, but expected to be rare and as mentioned above, it has not been associated to date with clinical signs or symptoms. However, patients will be monitored by collecting serum samples that will be analyzed in batches at intervals during the study. [redacted] will be analyzed for the presence of antibodies specific to mouse IgG (MIgG) and bovine serum albumin (BSA). If sensitization occurs, subsequent therapies containing bovine or murine products may be prohibited for these study patients. Blood samples collected from all treated patients will be stored in a secure laboratory until the laboratory confirms that all testing is complete and the laboratory receives written instruction from the Sponsor to destroy the samples.

1.4.2 Reaction to Dimethyl Sulfoxide

DMSO 7.5% is used as part of the rexlemestrocel-L cryopreservation process. The therapeutic and toxic effects of DMSO include its own rapid penetration and enhanced penetration of other substances across biologic membranes, free radical scavenging, and effects on coagulation, anticholinesterase activity, and DMSO-induced histamine release by mast cells. The systemic toxicity of DMSO is considered to be low. The DMSO exposure in this therapy is minimal and is locally applied. Subjects with any hypersensitivity to DMSO, including mild hypersensitivity, will be excluded from study.

1.4.3 Transmission of Infectious Agents

Potential for disease transmission from cell source and animal derived materials is minimized via thorough risk assessment in line with the Committee for Medicinal Products for Human Use/ Committee for Medicinal Products for Veterinary Use (CHMP/CVMP) Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (European Medicines Agency [EMEA]/410/01). The risk of potential viral contamination is minimized by comprehensive evaluation of prospective donors, which includes completion of a Clinical Bone Marrow Donor Program application, infectious disease testing, hematology, metabolic profiling, and ABO/Rh and HLA typing.

MPCs are an allogeneic, immunoselected, ex-vivo expanded cell product, which has the potential to become contaminated and subsequently cause infection in the study subject at the time of surgical implantation. This risk is greatly minimized by the use of a GMP-compliant production facility. Prior to the release of MPCs from the GMP facility, rigorous screening tests for multiple infectious agents are performed and sterility testing is conducted in order to ensure that no contaminated product is released for use.

There have been no cases of disease transmission reported to date and review of the cumulative safety experience does not suggest an increased risk in the MPC treated group.

1.4.4 Tumor Development

MPCs are living cells that have undergone ex vivo expansion and there is a theoretical risk that these cells could directly or indirectly cause the formation of unwanted tissue growth or a tumor. The possibility of tumor formation consequent to administration of MPCs can be the result either of *in vitro* transformation of the cells resulting in acquisition of a cell autonomous tumor-forming capacity or through the potential for MPCs to augment the growth of nascent/dormant tumors. In

the case *in vitro* transformation of MPCs, nonclinical *in vitro* and *in vivo* data suggest that the theoretical risk of MPC tumorigenicity is very low.[75,76] Nevertheless, the Sponsor remains vigilant in monitoring for signs of tumorigenic potential of rexlemestrocel-L. As part of the CMC process, karyotypic analysis on MPC master cell banks (MCBs) is routinely performed to screen for chromosomal abnormalities. In addition, the *in vivo* tumorigenic potential of MCBs in immunodeficient mice is also assessed. MCBs must be shown to be karyotypically normal and free of tumor-forming cells prior to use in the manufacture of rexlemestrocel-L.

An important factor in the potential risk of MPCs stimulating tumor formation by augmenting growth of malignant cells is the persistence of MPCs following administration. Nonclinical data shown that intramyocardial administration of human and ovine and allogeneic MPC transplantation into animal models of heart failure was associated with short-term and low-level persistence of MPCs.[72,73] These data suggest that MPCs are rapidly cleared following administration, minimizing the risk that MPCs may augment the growth of nascent/dormant tumors.

Tumor formation has not been noted in the Sponsor's preclinical studies employing MPCs delivered by systemic or local routes of administration to various animal models of disease.

To minimize the theoretical risk of tumorigenesis and taking into consideration indication specific risk-benefit, patients with a prior history of malignancy, with the exception of certain treated cancers such as skin cancer and carcinoma in situ, are excluded (see Exclusion Criterion "q" in Section 4.2).

1.4.5 Possible Effects of Cells on Fetus

Because of potential or unknown side effects of the study on the fetus, if the subject is a female of childbearing potential, the subject must have a negative pregnancy test prior to study entry as well as a negative pregnancy test immediately prior to day of the mapping/injection procedure. In addition, women of childbearing potential and men of childbearing age will be included in study participation provided that she or he is willing to use adequate contraception (including hormonal or barrier method or abstinence) from the time of screening and for a period of at least 16 weeks (for men) and 6 months (for women) after study intervention.

In the event that the study subject is confirmed to be pregnant during the study, the Principal Investigator must immediately report and follow the procedure as discussed in Section 7.2.

1.4.6 Cardiac Procedures Risks and Complications

Potential complications during cardiac catheterization include: death, MI, transient ischemic attack and stroke, vascular complications (including bleeding, hematoma, acute thrombosis, distal embolization, pseudoaneurysm, arteriovenous fistula), arrhythmias, perforation of the heart or great vessels, allergic reactions, atheroembolism, acute renal failure, infection, radiation exposure, arterial dissection (aortic), air embolism, and valvular injury.

Potential complications related to the NOGA® XP or CARTO®3 Cardiac Navigation System (also referred to as NOGA® or CARTO®, respectively) used to administer rexlemestrocel-L are perforation, abnormal heart conduction, stroke, MI, pericardial effusion and tamponade, pulmonary embolism, and death.

Possible complications include, but are not limited to:

- vascular bleeding/local hematomas
- thrombosis
- arteriovenous fistula
- pseudoaneurysm formation
- thromboembolism
- vasovagal reactions
- cardiac perforation
- cardiac tamponade
- thrombus
- air embolism
- arrhythmias
- valvular damage
- pneumothorax
- pericardial effusion
- pulmonary embolism
- hemothorax
- infection
- abnormal heart conduction
- stroke
- MI
- Death.

For the most complete information, refer to the NOGA® XP or CARTO® 3 Cardiac Navigation System and MyoStar™ Injection Catheter Instructions for Use (IFU) and user manuals. Note that techniques utilized for mapping and cell delivery with either the NOGA® or CARTO® are highly similar to each other.

1.4.7 Cardiac Potential Benefits of Rexlemestrocel-L

Potential benefits of rexlemestrocel-L therapy in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology are clinically relevant because these patients have very limited therapeutic options including placement of a LVAD and heart transplantation. However, a LVAD is costly and provides only a short-term solution, and heart transplantation is limited by organ availability and the need for long-term monitoring and complex immunosuppressive therapy. Clearly, for patients with chronic HF, there is an important unmet clinical need to intervene in a manner that halts or, at a minimum, delays disease progression and reduces the incidence of recurrent HF hospitalizations. The data generated with rexlemestrocel-L to date in patients with chronic HF suggest the presence of a concordant beneficial effect on 3 key parameters that correlate with long-term prognosis: clinical outcomes (HF–MACE), cardiac remodeling (LVESV), and functional capacity (6MWT distance). Thus, rexlemestrocel-L represents a clinical option that could potentially save lives, improve functional capacity, and decrease disease-related costs by limiting the frequency and/or duration of hospitalizations for decompensated HF.

Additional information regarding risks and benefits to human participants in clinical studies with rexlemestrocel-L may be found in the IB for rexlemestrocel-L.

1.5 Selection of Drugs and Dosage

The dose of rexlemestrocel-L to be evaluated in this study (*i.e.,* 150 M cells) was selected on the basis of the results from 2 nonclinical studies in sheep (see Section 1.3.1) and 1 clinical study with rexlemestrocel-L (see Study [redacted] Section 1.3.2).

[redacted] Intramyocardial administration of 25 x 10^6-225 x 10^6 MPCs attenuated various measures of LV dysfunction and remodeling. Treatment with MPCs at the 225 x 10^6 cell dose level increased myocardial vascular density in the peri-infarct and infarct regions. In the setting of doxorubicin-induced NICM, transendocardial delivery of 110 x 10^6 MPCs using the NOGA® catheter and MyoStar™ Mapping System preserved ejection fraction, attenuated end-systolic dilation, decreased fibrosis

and increased myocardial vascular density compared with vehicle treatment. Intramyocardial administration of MPCs in ovine models of chronic MI and NICM was generally safe and well-tolerated. Collectively, the data from these nonclinical studies support a positive benefit:risk profile for allogeneic MPCs in CHF.

[redacted] transendocardial delivery of 150 M MPCs (rexlemestrocel-L) was the most effective dose. The beneficial effect of 150 MPCs (rexlemestrocel-L) compared with the control group was enhanced when data were analyzed in patients with baseline LVESV > 100 mL (Section Phase 2 Clinical Trial Results).

The transendocardial injection of 150 M MPCs was selected for this study because it was shown to be safe and effective in study [redacted] and was not associated with a clinically significant immune response. It is anticipated that the dosage of 150 M MPCs will provide efficacious treatment for patients with chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy, as well as a satisfactory safety profile. It is important to note that the patient population included in the current trial is enriched for patients with more advanced HF as documented by a recent decompensated HF event and/or significantly elevated plasma NT-ProBNP levels. These are the patients who would be expected to have LVESV > 100 mL at the time of enrollment.

A description of rexlemestrocel-L administration is presented in Section 5.1.

1.6 Compliance Statement

This study will be conducted in full accordance with the GCP: Consolidated Guideline approved by the ICH and any applicable national and local laws and regulations (*e.g.,* Title 21 Code of Federal Regulations [21 CFR] Parts 50, 54, 56, 312, 314). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the ICH and GCP guidelines and for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with

the protocol will be documented in separate study agreements with the Sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in case of a medical emergency. Each investigator must be familiar with the background to and requirements of the study and with the properties of rexlemestrocel-L as described in the current version of the IB for rexlemestrocel-L.

The Principal Investigator at each recruiting HF study site has the overall responsibility for the conduct and administration of the study at that site and for contacts with study management, with the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and with local authorities.

1.7 Population to be Studied

Patients with chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy are eligible for enrollment, provided they meet all additional entry criteria as defined in Section 4.

1.8 Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current version of the IB for rexlemestrocel-L.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The purpose of this study is to assess the efficacy and safety of a single cardiac catheterization involving transendocardial delivery of 150 M human bone marrow-derived allogeneic MPCs (rexlemestrocel-L) in improving clinical outcomes (HF-MACE), preventing cardiac remodeling (LVESV), and increasing exercise capacity (6MWT) in patients with chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives of this study are to:

1. Determine whether transendocardial delivery of 150 M allogeneic human bone marrow-derived MPCs (rexlemestrocel-L) when administered during a single index cardiac catheterization and intracardiac mapping procedure is more effective than a scripted sham cardiac mapping and cell delivery procedure in risk reduction for recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully RCD events, in the presence of terminal cardiac events (TCEs) in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.
2. Evaluate the safety of transendocardial delivery of rexlemestrocel-L in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.

2.2.2 Secondary Objectives

2.2.2.1 Key Secondary Objective

The key secondary objective of the study is the assessment of time from Day 0-to-first TCE (cardiac death, left ventricular assist device [LVAD] placement, heart transplant, or artificial heart implantation), whichever event occurred first, to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-TCE for the Cell Therapy vs. Control (Sham) group.

Day 0 Definition: Day 0 for all time-to-event analyses is defined as follows:

1. For patients who are randomized but **DO NOT** undergo the index cardiac catheterization as the date of the disqualifying event (i.e., violation of at least 1 inclusion/exclusion criterion);
2. For patients who are randomized and **DO** undergo the index cardiac catheterization as the date of the index cardiac catheterization.

2.2.2.2 Secondary Objectives

The secondary objectives of this study are the assessment of various aspects of recurrent non-fatal HF-MACE (i.e., decompensated HF events and/or successfully RCD events). Other

secondary objectives of the study relate to LV remodeling by echocardiography, functional exercise capacity using the 6-minute walk test, functional status assessed by New York Heart Association Classification, and QoL.

2.2.3 Immunogenicity Objective

The immunogenicity objective of this study is to evaluate the immunogenic potential of rexlemestrocel-L by evaluating the results of the following assays performed as specified in the protocol:

- PRA (panel reactive antibodies)
- DSA (if the test for PRA is positive)
- antibodies against bovine or murine proteins (*i.e.,* BSA [bovine serum albumin] and MIgG [mouse immunoglobulin G]).

[redacted]

- study the association of changes from baseline levels of the biomarkers hsCRP and NT-proBNP with disease severity and clinical outcomes

[redacted]

- collect and store blood samples for possible use in future PGx analyses in the assessment of possible associations between genetic polymorphisms and the response to rexlemestrocel-L therapy in patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology who have received optimal medical and coronary revascularization therapy.

3. STUDY DESIGN

3.1 General Design and Study Schema

This is a global, multicenter, double-blind, randomized, scripted sham-procedure controlled, parallel-group, study to evaluate the efficacy and safety of transendocardial delivery of rexlemestrocel-L (human bone marrow-derived adult allogeneic MPCs) during a single treatment index cardiac catheterization involving intracardiac mapping in patients with chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy. Overall, it is anticipated that known epicardial

CAD (documented stenosis of at least 50% in one or more major epicardial coronary arteries, documented prior coronary artery revascularization, and/or documented prior MI) will be present in at least 60% of the patients who are randomly assigned to treatment.

The study comprises 3 main time periods: 1) a screening and randomization designation period; 2) study intervention (*i.e.,* hospitalization on Day 0 for a single index cardiac catheterization with or without intracardiac mapping and cell delivery); and 3) a follow-up period that continues until the required minimum number of recurrent non-fatal HF-MACE (*i.e.,* at least 531 decompensated HF events and/or successfully resuscitated cardiac death events) is obtained and a minimum follow-up of at least 6 months for all surviving subjects without TCEs is achieved. The follow-up period for patients who were randomized and **DID** undergo index cardiac catheterization includes patients' safety and efficacy evaluations for a minimum of 6 months (assuming the patient has survived for that period of time without a TCE and has not discontinued from the study) and long-term safety and efficacy evaluations after the Month-12 visit (every 6 months) until study conclusion. However, if a patient was randomized but **DID NOT** undergo the index cardiac catheterization, the patient will be followed for vital status, AEs, potential primary and key secondary endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

Written informed consent will be obtained for the study before any study-specific procedures are performed. A separate written informed consent for an exploratory PGx substudy will be obtained before any PGx-specific procedures are performed. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). A patient will not be excluded from participation in the study if he/she chooses not to provide consent for the additional procedures that are required as part of the exploratory PGx substudy.

After informed consent is obtained, the patients will be screened for eligibility to participate in the study. During the screening period this will be based on the study's pre-specified inclusion and exclusion criteria. During the screening period, patients will undergo a 2-D echocardiogram

with Doppler. The use of echocardiographic contrast for enhanced LV chamber imaging will be determined by the investigator or designee. If echocardiographic imaging is of insufficient technical quality for LV volume and LV ejection fraction estimation, then a RVG will be performed to assess LV ejection fraction as part of the patient's screening procedures for inclusion in the trial. The Principal Investigator (or designee) will assess the need for coronary revascularization before the patient is randomly assigned to receive active or control treatment. If it is determined that a patient requires coronary revascularization, it should be performed at least 2 months before reinitiating any study screening procedures. Patients who are screen failures may be re-screened with approval from the medical monitor. Randomization should occur as close as possible to the scheduled index cardiac catheterization date for potential delivery of study product. The pre-randomization criteria, such as echocardiographic criteria (restrictive, constructive or obstructive physiology, LV wall thickness, mural or arterial thrombus and prosthetic valve) are to be met by all patients and confirmed by both HF referral physician and the interventional cardiologist. Echocardiographic criteria must be confirmed and signed off by interventional cardiologist prior to randomization.

Patients who experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization procedure will be included as part of the ITT analysis and cannot be re-screened.

Patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned in a 1:1 ratio to receive either active treatment (*i.e.,* intracardiac mapping and transendocardial delivery of rexlemestrocel-L) or control treatment (*i.e.,* scripted sham intracardiac mapping and cell delivery procedure without rexlemestrocel-L) by means of a computer-generated randomization list, and stratified by baseline NYHA Functional Class (Class II versus Class III), geographic region (US versus ex US) and presence of epicardial CAD (ischemic versus nonischemic); randomization will not be stratified by site. The randomization list and treatment group will be assigned via Interactive Response Technology (IRT). The IRT will be used to track and monitor enrollment of female patients as well as patients with baseline NYHA Class III versus Class II status in the study. To ensure that approximately 20% of the patient population in the study will be women, frequent discussions with the site staff will take place during the recruitment phase and will include discussion of the current rate of recruitment of women to the study. If there is a large disparity between the number of men and the number of women randomized to the study, the randomization may be limited to women until women represent approximately 20% of the study population.

Patient enrichment and replenishment will be performed such that by the end of the trial, the ratio of enrolled patients with baseline NYHA Class III to baseline NYHA Class II will be approximately 2:1. With this ratio, it is estimated that approximately 600 randomized patients will be needed to achieve a minimum of 531 recurrent non-fatal HF-MACE at the end of the trial. Based on current enrollment projections, at the end of the trial it is estimated that there will be ~200 baseline NYHA Class II patients and ~400 baseline NYHA Class III patients who have undergone the Day 0 index cardiac catheterization resulting in a baseline Class III/Class II ratio of 2:1. In order to achieve this target, an enrollment cap of ~200 baseline NYHA Class II patients will be instituted. It is anticipated that any baseline NYHA Class II patients who are inadvertently screened but not randomized during the suspension of NYHA Class II enrollment will be considered screen failures. The enrollment process will be overseen by the trial's treatment blinded Medical Monitor in conjunction with current computer-generated randomization and interactive response technology (IRT) enrollment methodologies.

After randomization, all patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo the index cardiac catheterization at a cell injection center and will remain hospitalized on telemetry after index cardiac catheterization for a minimum of one night. Prior to the initiation of any study procedures on the date of index cardiac catheterization, the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable.

All patients randomly assigned to the active treatment group who **DO NOT** experience at least one inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo an index cardiac catheterization with left ventriculography followed by cardiac mapping and transendocardial delivery of rexlemestrocel-L. Myocardial locations for transendocardial delivery of rexlemestrocel-L will be defined by means of imaging and left ventricular electrical mapping of the myocardium using the NOGA® or CARTO® Cardiac Navigational System in combination with the NogaStar® Mapping Catheter (Appendix 1 and Appendix 3). Fifteen to 20 appropriate myocardial locations will be identified (20 sites is ideal) by imaging and electrical mapping as viable for cell delivery. The injection sites will be captured by NOGA® or CARTO® and transcribed into electronic data capture (EDC). Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to imaging identified myocardial locations; the total volume of study product administered must not exceed

4.0 mL. The total duration of the transendocardial delivery procedure must not exceed 90 minutes from the time of completion of thaw of rexlemestrocel-L.

All patients randomly assigned to the control group who **DO NOT** experience at least one inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted sham cardiac mapping and cell delivery procedure that will include catheterization with left ventriculography and a simulation of cardiac mapping and cell delivery (Appendix 2). The scripted sham cardiac mapping and cell delivery procedure will be staged to script and will not include actual intracardiac mapping or transendocardial delivery of rexlemestrocel-L. The scripted sham cardiac mapping and cell delivery procedure will be led by the interventional cardiologist and will be approximately 60 to 90 minutes in duration. As with the active treatment group, 15 to 20 appropriate myocardial locations will be identified but by means of a scripted sham cardiac mapping procedure followed by a scripted sham cell delivery procedure, and will simulate the exact full procedural requirements used for the actual treatment cohort. The total duration of the scripted sham cell delivery procedure will not exceed 90 minutes.

Index cardiac catheterization (with or without intracardiac mapping and cell delivery) will be performed only by interventional cardiologists appropriately trained (including successful completion of the NOGA®/MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System training program and retraining for any interventionalist who has not performed the procedure using this system in over 1 year) and experienced in performing cardiac interventional procedures. Current American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) Practice Guidelines will be followed in managing any procedure-related cardiac arrhythmias.

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

For screening and during the follow-up period (patients who undergo the index cardiac catheterization), the following assessments will be performed: evaluations of LVEF, exercise capacity as determined by the 6MWT (patients will be excluded from participation in the study if they cannot perform the 6MWT due to concurrent medical conditions [the exception is those patients with an NT-proBNP >2000 pg/mL; 2000 ng/L SI units, 236 pmol/L]; patients who complete two 6MWTs during screening with either test being a distance >450 meters will also be excluded), biomarkers (NT-proBNP and hsCRP), functional status as measured by the NYHA Functional Class assessment, QoL as measured by the MLHF and EQ-5D questionnaires, immunogenicity testing, and safety evaluations of adverse events, CVA, MI, clinical laboratory tests, urinalysis, vital signs measurements, physical examinations, ECG recordings, 24-hour Holter monitor recordings (randomized patients across the US and EU), and use of concomitant medication and therapy. In addition, for echo-qualifying patients only, serial assessment of cardiac remodeling will be performed based on 2-D echocardiographic estimations (without or with contrast) of LVESV and LVEDV and reviewed by the core imaging laboratory. Serial assessment of LVEF will be performed in selected patients using either echocardiographic imaging or RVG, depending upon which technique was used to qualify the patient during screening. Separate serial assessments will be performed for RVGs and echocardiograms, as applicable. For patients with an ICD (or any implanted device capable of defibrillation), rhythm analysis by device interrogation (performed at regularly scheduled intervals by appropriate site personnel; see Table 4 and Table 5 will be conducted. These episodes will be assessed at each site and captured as adverse events or non-fatal HF-MACE as appropriate. When a non-fatal HF-MACE or a TCE is suspected, the rhythm strips obtained by device interrogation and relevant clinical context will be provided to the Clinical Endpoint Adjudication Committee (CEC) for their review and adjudication.

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-human leukocyte antigen (HLA) DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, and at Months 1, 3, 6, and 12 (Visit 7) from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who were randomized and underwent the index cardiac catheterization. All samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). [redacted] serum samples [redacted] of rexlemestrocel-

L will be analyzed for anti-murine (MIgG) and anti-bovine (BSA) antibodies. The serum samples will be tested for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies)

Blood samples will be collected from patients who provide informed consent for possible use in future PGx analyses for the assessment of possible associations between genetic polymorphisms and the response to rexlemestrocel-L therapy. Blood samples for PGx analyses will be collected at the end of screening and stored for future use.

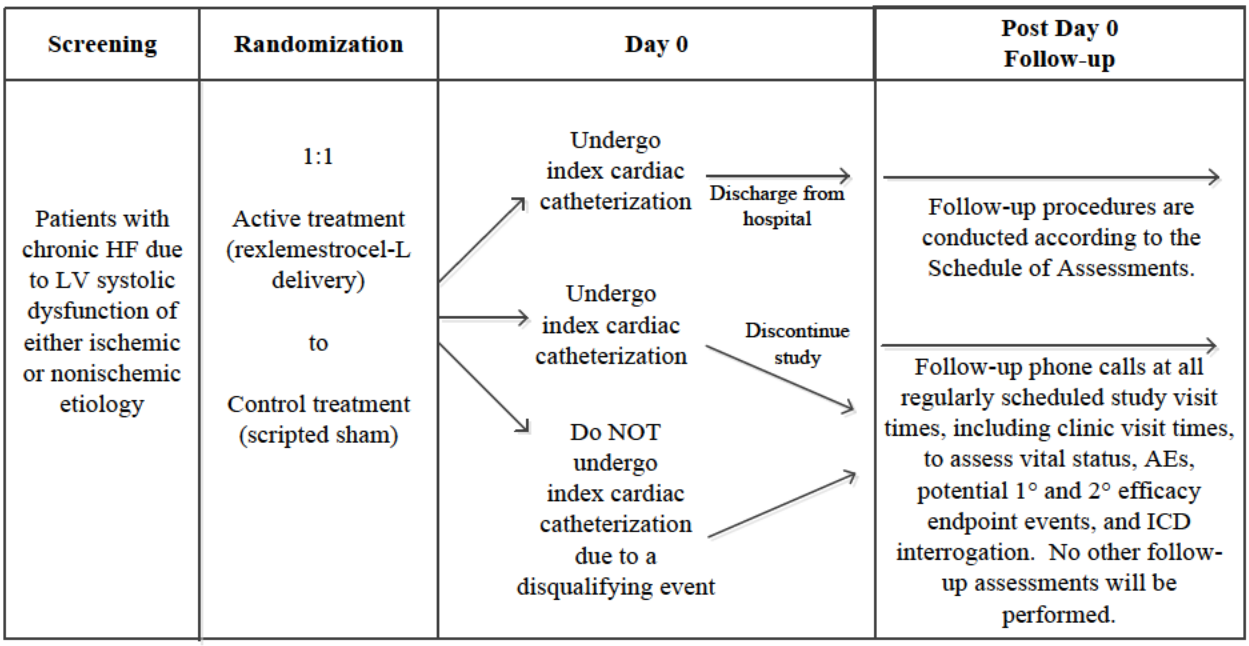
The screening period may last up to 42 days before the scheduled index cardiac catheterization. For randomized patients who **DO** undergo the index cardiac catheterization, during the first 12 months after the Day 0 index cardiac catheterization, follow-up assessments will be scheduled at Day 10 and Months 1, 3, 6, and 12. A telephone follow-up inquiry will be made at Months 2, 4, 5, 7, 8, 9, 10, and 11 (±14 days) (see Table 5). A follow-up period continues until the required number of recurrent non-fatal HF-MACE (*i.e.,* at least 531 decompensated HF events and successfully RCD events) is obtained; a minimum of 6 months is required for all patients who survive, do not discontinue, and are without a TCE. Telephone follow-up inquiries will be made every 2 months between study visits during the long-term follow-up period (at Months 14, 16, 20, and 22). These long-term follow-up visits and telephone contacts will continue until study conclusion. However, patients who are randomized but **DO NOT** undergo the index cardiac catheterization, the patient will be followed for vital status, AEs, potential primary and key secondary endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times for the duration of the study. Similarly, any patients who are randomized, complete Day 0 index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

Patients are expected to participate in this study until the required minimum number of recurrent non-fatal HF-MACE occur and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up. Patients who have a minimum of 6 months follow-up at the time the required number of recurrent non-fatal HF-MACE occur will be evaluated as early as possible using the same

assessments that are specified for the Month 12 visit. An echocardiogram or RVG will be performed only if more than 6 months have passed since the patient's last echocardiogram or RVG.

An overview of the study design is presented in Figure 6.

Figure 6: Study Design



HF=heart failure; ICD=implantable cardioverter defibrillator; LV=left ventricular; R=randomization; TCE=terminal cardiac event; 1°=primary; 2°=secondary.

Note: Important: The timing of randomization relative to Day 0 will vary based on study drug availability and BDS availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0. For patients who are randomized and **DO** undergo the index cardiac catheterization, a follow-up period that continues until the required number of recurrent non-fatal HF-MACE (*i.e.,* at least 531 recurrent non-fatal HF events and/or successfully resuscitated cardiac death events) is obtained; this includes patients' safety and efficacy evaluations for a minimum of 6 months (assuming he/she has survived for that period of time without a TCE and has not discontinued from the study) and long-term safety and efficacy evaluations after the Month-12 visit (patients will have safety and efficacy evaluations performed every 6 months thereafter until study conclusion). However, if a patient was randomized but **DOES NOT** undergo the index cardiac catheterization, the patient will be followed for vital status, AEs, potential primary and key secondary endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, complete Day 0 index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact. Every attempt should also be made to obtain vital status, at a minimum, from patients who withdraw consent to participate in the study after randomization.

During the course of the study, the occurrence of adverse events, SAEs, TCEs, non-fatal decompensated HF-MACE or successfully resuscitated cardiac death events, overall survival (includes all-cause deaths), coronary artery revascularization procedure, [redacted] CVA, and MI will be reviewed, evaluated, processed, and/or reported in accordance with the protocol. Additionally, the occurrence of all adverse events on Days 0 through 7 and all SAEs on Days 0 through Day 30 following index cardiac catheterization (with or without intracardiac mapping and cell delivery) will be reported to the device manufacturer (Bioscience Webster, Inc. for the NOGA®/MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System) and the unblinded medical monitor (See Appendix 4). For reporting of SAEs, see Section 7.1.6.3).

The Sponsor Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities. Additionally, there will be 3 oversight committees: an Executive Steering Committee (ESC), an independent CEC, and an independent DMC.

Both the ESC and CEC will be blinded to study treatment; the DMC will be unblinded.

The Data Monitoring Committee (DMC), which will be unblinded to study treatment, will oversee the study with primary responsibility for ensuring patient safety. Specific goals and responsibilities of the DMC are outlined in the Data Monitoring Committee Manual of Operations. The DMC will review on a regular predefined basis the occurrence of AEs as well as adjudicated clinical endpoints. The DMC will perform prespecified serial assessments of patient safety and monitor treatment effects to assess whether the objectives of the ongoing study can be met (see the DMC charter for more information). The DMC also reviewed the results of futility IA2 and provided pre-specified blinded information regarding study continuation to the ESC and the Sponsor.

Because rexlemestrocel-L is given at a single time point (Day 0) and there is no specific treatment or agent that can reverse the effect of rexlemestrocel-L after administration, it is anticipated that there will be no need to unblind the treatment code to the Sponsor or to the HF study site personnel involved in the follow-up evaluations of the patient. However, for a serious and unexpected adverse event considered related to rexlemestrocel-L or study procedures, the unblinded team (CRO) will have access to unblind the study treatment (on a case-by-case basis) specifically for regulatory reporting purposes. If the treatment code is revealed for this reason, the blinded committees and study team (*e.g.,* the HF study site investigator, clinical scientists,

CEC personnel, Sponsor Pharmacovigilance team), will remain blinded to treatment. In the case of an emergency, if it is necessary to know what treatment a patient has received, the investigator may determine the patient's treatment using IRT after consultation with the Sponsor. In an extreme emergency, if the investigator is unable to contact the Sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. For such an occurrence, the investigator must contact the individual identified in the clinical study personnel contact information section of this protocol immediately. Proper documentation must be maintained when a treatment code is revealed.

The Executive Steering Committee (ESC) will perform the following:

- Oversight for the operation of the study, including working with national leaders and local HF study site investigators to achieve goals for enrollment of patients into the study
- Reviewing recommendations from the project team for study conduct
- Reviewing recommendations from the DMC for patient safety
- Reviewing recommendations from the DMC for Interim Analyses #1 and #2.

The independent Clinical Endpoints Committee (CEC), which will be blinded to study treatment, will adjudicate all potential cardiovascular events and survival in accordance with prespecified criteria. The events include all-cause death (i.e., including non-cardiac and cardiac death), LVAD placement, heart transplant, artificial heart implantation, hospitalization for recurrent non-fatal decompensated HF, urgent care outpatient HF visit, successfully RCD events, nonfatal MI, hospitalization for unstable angina, nonfatal CVA, coronary artery revascularization, and [redacted]

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

Two planned interim analyses have been conducted during the study (Section 9.10).

3.2 Primary and Secondary Measures and Endpoints

3.2.1 Primary Efficacy Measure and Endpoint

The primary efficacy measure and endpoint for this study is time from Day 0-to recurrent non-fatal HF-MACE, which consists of recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully resuscitated cardiac death events.

Day 0 Definition: Day 0 for all time-to-event analyses is defined as follows:

1. For patients who are randomized but **DO NOT** undergo the index cardiac catheterization as the date of the disqualifying event (i.e., violation of at least one inclusion/exclusion criterion);
2. For patients who are randomized and **DO** undergo the index cardiac catheterization as the date of index cardiac catheterization.

The following definitions apply to the TWO components of the primary endpoint:

- **Non-fatal decompensated HF event** will be adjudicated when the diagnosis of a non-fatal decompensated HF event demonstrates the presence of signs and symptoms consistent with clinical decompensation of the patient's HF state requiring an in-hospital stay or intravenous (IV) diuretic therapy or aquapheresis on an urgent care outpatient HF visit;
- **Successfully resuscitated cardiac death (RCD)** events will be adjudicated when a subject experiences sudden death or cardiac death and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness (LOC) or syncope and receive a successful appropriate shock from an implantable cardioverter-defibrillator with meaningful recovery will also be designated as successful RCD event.

NOTE: Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be analyzed jointly with recurrent non-fatal HF-MACE within the Joint Frailty Model analysis. It is the intent that a "terminal cardiac event" occurs when the left ventricle (LV) is no longer functioning as an independent viable pumping chamber that provides pulsatile blood flow to the systemic circulation. Time from Day 0-to-first TCE is a key secondary endpoint that will be evaluated using only TCEs. This analysis, which will be performed utilizing a proportional hazards model, will help assure that any improvement in recurrent non-fatal HF-MACE for the Cell Therapy group is not associated with worsening in

time-to-terminal event for the Cell Therapy vs. Control (Sham) group. This analysis will provide assurance that any beneficial difference in recurrent non-fatal HF-MACE for the Cell Therapy vs Sham groups is not due to disproportionate early and/or late TCE rate for the Cell Therapy group.

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system (Section 7.1.6.4). All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

Adjudication of all potential non-fatal HF-MACE, TCEs, or cardiac events of special interest (regardless of whether they are serious or nonserious) are to be considered by the investigator as events for adjudication by an independent, blinded CEC (Section 7.1.6.4). Once the first TCE has occurred for a patient, subsequent TCEs and/or non-fatal HF-MACE for that patient will be excluded from the primary JFM analysis. All recurrent non-fatal HF-MACE and TCEs will be collected and adjudicated through end-of-study or patient's death for safety and sensitivity efficacy analysis purposes. (For details on the role and responsibilities of the CEC, please see the CEC Manual of Operations.)

Transendocardial delivery of rexlemestrocel-L into the myocardium will require the placement of the injection catheter needle into the left ventricle wall. In order to accomplish this procedure, there is significant catheter manipulation that occurs within the LV chamber. This normally causes premature ventricular contractions (PVCs) as well as multiple brief episodes of nonsustained VT during the cardiac mapping and cell delivery procedure. These arrhythmias are usually self-terminated. Sustained ventricular arrhythmias such as VT or VF may occasionally be triggered even in the normal heart. Because of the underlying pathology in patients enrolled in this study (which specifies significant LV systolic dysfunction as an inclusion criterion), ventricular arrhythmias may be more pronounced and occur more often than in less ill patients. Because of the close association between ventricular arrhythmias due to LV catheter manipulation and the cell delivery procedure, the occurrence of sustained ventricular arrhythmias that may require cardioversion or defibrillation during index cardiac catheterization (with or

without intracardiac mapping and cell delivery) on Day 0 is expected and will not be considered a non-fatal HF-MACE.

3.2.2 Secondary Efficacy Measures and Endpoints

3.2.2.1 Key Secondary Measures and Endpoints Relating to Terminal Cardiac Events

Time from Day 0-to-first TCE will be evaluated to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-first TCE for the Cell Therapy vs. Control (Sham) group.

The key secondary endpoint relating to TCEs is as follows:

- Time from Day 0-to-first TCE (cardiac death, LVAD placement, heart transplant, or artificial heart implantation), whichever occurs first.

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control.

3.2.2.2 Secondary Measures and Endpoints

Secondary efficacy measures and endpoints of the study comprise the following:

- time-to-hospital admissions for decompensated HF events beginning on Day 1
- time-to-urgent care outpatient HF visits beginning on Day 1
- time-to-successfully RCD events beginning on Day 1
- total length of in-hospital stay in intensive care unit for decompensated HF events beginning on Day 1
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated HF, urgent care outpatient HF visits, and successfully RCD events
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated heart failure, urgent care outpatient HF visits, successfully RCD events, or TCE
- time-to-cardiac death
- time-to-all-cause death
- time-to-non-fatal MI, non-fatal CVA, or coronary artery revascularization, whichever comes first.

Other secondary efficacy measures and endpoints for this study relate to LV remodeling, functional exercise capacity, functional status, and QoL, and comprise the following:

- LV remodeling as assessed by change from baseline in left ventricular end-systolic volume (LVESV) as determined by 2-dimensional (2-D) echocardiography (echo-qualifying patients only).

Sensitivity analyses would, at a minimum, include the following:

- Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE)
- Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and change in month 6 - baseline LVESV (increase or no change vs. decrease) and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE).
    - LV remodeling as assessed by change from baseline in left ventricular end-diastolic volume (LVEDV) as determined by 2-D echocardiography (echo-qualifying patients only)
    - LV systolic performance as assessed by change from baseline in left ventricular ejection fraction (LVEF)
    - functional exercise capacity as assessed by change from baseline in distance covered during the 6-minute walk test (6MWT)
    - functional status as assessed by change from baseline in NYHA Functional Class
    - QoL as assessed by change from baseline in the Minnesota Living With Heart Failure (MLHF) questionnaire score
    - QoL as assessed by change from baseline in the EuroQol 5-dimensional Quality of Life (EQ-5D) questionnaire score.

3.2.3 Safety Measures and Endpoints

The safety and tolerability of rexlemestrocel-L in patients with chronic HF due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy will be assessed throughout the study (according to the schedule provided in Table 4 and Table 5 by evaluating adverse events, clinical laboratory test results, vital signs measurements, concomitant medication and therapy usage, ECG, 24–hour Holter monitoring (randomized patients across the US), and physical examination results. In addition, important cardiovascular safety events will be reviewed from CEC-adjudicated data.

The safety variables and endpoints for this study are as follows:

- occurrence of AEs relative to index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 hospitalization hospital discharge for that admission
- occurrence of adverse events
- clinical laboratory tests (serum chemistry and hematology) results
- urinalysis
- vital signs measurements
- ECG findings
- telemetry findings
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- 24-hour Holter monitoring (randomized patients across the US and EU)
- physical examination findings
- review of important cardiovascular safety events from CEC-adjudicated data for all-cause deaths (i.e., including non-cardiac and cardiac death) and hospitalizations for non-fatal decompensated HF, successfully RCD events, pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE, coronary artery revascularization procedure, non-fatal CVA, and non-fatal MI.

3.2.4 [redacted] Pharmacodynamics [redacted]

Blood samples for pharmacodynamic analyses of the biomarkers NT-proBNP and hsCRP will be collected at screening and at Months 3, 6, and 12 (after screening, only from randomized patients who undergo the index cardiac catheterization). Blood samples will be collected every 12 months thereafter during long-term follow-up evaluations until study conclusion.

Blood samples for PGx analyses will be collected, from patients who provide informed consent, are randomized, and undergo the index cardiac catheterization, for possible use in future PGx analyses to determine whether gene variants found in some patients with chronic HF will predict how those patients will respond to therapy with rexlemestrocel-L.

3.2.5 Immunogenicity Measures and Endpoints

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-HLA DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who were randomized and underwent the index cardiac catheterization. All serum samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). [redacted] serum samples [redacted] of rexlemestrocel-L will be analyzed for anti-murine (MIgG) and anti-bovine (BSA) antibodies. The serum samples will be analyzed for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies) [redacted]

- biomarkers as assessed by changes from baseline in NT-proBNP and hsCRP [redacted]
- PGx analyses to determine whether gene variants found in some patients will predict how they respond to rexlemestrocel-L therapy.

3.3 Randomization and Blinding

This is a double-blind study. Patients enrolled in the study will be randomly assigned in a 1:1 ratio to receive active treatment (*i.e.,* intracardiac mapping and transendocardial delivery of rexlemestrocel-L) or control (*i.e.,* a scripted sham cardiac mapping and cell delivery procedure without rexlemestrocel-L), stratified by baseline NYHA Class (Functional Class II versus

Functional Class III), geographic region (US versus ex-US) and presence of epicardial CAD (ischemic versus nonischemic); randomization will not be stratified by site. Patients will be randomly assigned to the treatment groups (approximately 300 patients per group) by means of a computer-generated randomization list after confirmation of all eligibility criteria. The randomization list and treatment group will be assigned via IRT. The IRT will be used to track and monitor the enrollment of women as well as patients with baseline NYHA Class III versus Class II functional status in the study. To ensure that at least 20% of the patient population in the study will be women, frequent discussions with the site staff will take place during the recruitment phase and will include discussion of the current rate of recruitment of women to the study. If there is a large disparity between the number of men and the number of women randomized to the study, the randomization may be limited to women until women represent approximately 20% of the study population.

Patient enrichment and replenishment will be performed such that by the end of the trial, the ratio of enrolled patients with baseline NYHA Class III to baseline NYHA Class II will be approximately 2:1. With this ratio, it is estimated that approximately 600 randomized patients will be needed to achieve a minimum of 531 recurrent non-fatal HF-MACE at the end of the trial. Based on current enrollment projections, at the end of the trial it is estimated that there will be ~200 baseline NYHA Class II patients and ~400 baseline NYHA Class III patients who have undergone the Day 0 index cardiac catheterization resulting in a baseline Class III/Class II ratio of 2:1. In order to achieve this target, an enrollment cap of ~200 baseline NYHA Class II patients will be instituted. It is anticipated that any baseline NYHA Class II patients who are inadvertently screened but not randomized during the suspension of NYHA Class II enrollment will be considered screen failures. The enrollment process will be overseen by the trial's treatment blinded Medical Monitor in conjunction with current computer-generated randomization and interactive response technology (IRT) enrollment methodologies.

Patients will be screened at recruiting HF study centers. The timing of randomization relative to Day 0 will vary based on study drug availability and BDS availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0. Note that any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, and potential primary, key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, **DO**

undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

Hospitalization for index cardiac catheterization (with or without intracardiac mapping and cell delivery) will occur at a cell injection center; the interventional cardiologist performing the catheterization procedure will be unblinded to treatment assignment. Not all HF study centers will be cell injection centers and not all cell injection centers will be HF study centers. However, it is anticipated that the majority of cell injection centers will also be HF study centers. Screening and follow-up evaluations will be performed at HF study sites by study personnel who will be blinded to study treatment for the duration of the study. The interventional cardiologist and the unblinded team performing the study procedure (index cardiac catheterization with or without intracardiac mapping and cell delivery) may participate in screening procedures but will not be involved in follow-up evaluations (follow-up evaluations will be performed by blinded team members only).

During the screening period, all patients (rexlemestrocel-L and control) will undergo cardiac imaging, which will consist, at a minimum, of a 2-D echocardiogram with Doppler. The use of echocardiographic contrast for enhanced LV chamber imaging will be determined by the investigator or designee. If echocardiographic imaging is of insufficient technical quality for LV volume and LV ejection fraction estimation, then a radionuclide ventriculogram (RVG) will be performed to assess LV ejection fraction as part of the patient's screening procedures for inclusion in the trial. All randomized patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo placement of a femoral sheath through which a pigtail catheter will be advanced retrograde to the left ventricle for performance of contrast ventriculography to assess regional wall motion and define chamber anatomy. All patients randomly assigned to the rexlemestrocel-L group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo transendocardial administration of rexlemestrocel-L using the NOGA® /MyoStar™ catheter or CARTO®/MyoStar™ catheter, which use internal cardiac mapping to identify myocardial locations for cell delivery (Appendix 1 and Appendix 3, respectively).

All patients randomly assigned to the control group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted sham cardiac mapping and cell delivery procedure simulating the exact full procedural requirements used for the actual treatment cohort transendocardial delivery of rexlemestrocel-L to the myocardium (Appendix 2). These patients will not undergo placement of the NogaStar® and MyoStar™ catheters. The scripted sham cardiac mapping and cell delivery procedure will not include internal mapping, but will be written to correspond to the operational steps that are used for intracardiac transendocardial delivery of rexlemestrocel-L using the NOGA® /MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System. These patients will not receive treatment with rexlemestrocel-L. This approach to blinding of actual treatment in the cardiac catheterization laboratory (which was used in the Phase 2 HF study with rexlemestrocel-L [Study [redacted]) is essential for a subsequent objective and unbiased assessment of study endpoints.

For all randomized patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization), administration of study treatment (transendocardial delivery of rexlemestrocel-L or scripted sham cardiac mapping and cell delivery procedure) will be performed at a cell injection center by an unblinded interventional cardiology team not involved with review or assessment of subsequent study results. Thus, this separate team is unblinded to study treatment.

Patients, as well as noninterventional investigators and study site personnel at the HF study centers who conduct screening and follow-up evaluations after hospital discharge of patients from the cell injection center, will remain blinded to the study treatment provided at the cell injection center. It is permissible for a physician trained as an interventional cardiologist to take on the role of the blinded HF specialist for this study as long as the physician is adequately experienced to perform this role. In that scenario, another interventional cardiologist at the site must be identified as the (unblinded) interventional cardiologist for this program. Once a physician has been designated as either the blinded or unblinded cardiologist, he/she may not change his/her blinded vs unblinded role within the trial.

An overview of the study personnel blinding is presented in Figure 7.

Figure 7: Study Personnel Blinding

Screening	Hospitalization: Day 0 (Single-treatment study intervention)	Follow-up to 12 months	Long-term Follow-up
• Blinded Heart Failure Specialist, Unblinded Interventional Cardiologist, and Unblinded Team at investigative study center • Consent and all screening assessments	• Unblinded Interventional Cardiologist • Cardiac catheterization center	• Blinded Heart Failure Specialist at investigative study center • Overall management of the patient from hospital discharge from Day 0 study intervention to the study completion	• Blinded Heart Failure Specialist at investigative study center • Overall management of the patient from hospital discharge from Day 0 study intervention to the study completion

NOTE: Unblinded interventional cardiologist and the unblinded team may participate in screening procedures but will not be involved in follow-up evaluations.

Because rexlemestrocel-L is given at a single time point (Day 0) and there is no specific treatment or agent that can reverse the effect of rexlemestrocel-L after administration, it is anticipated that there will be no need to unblind the treatment code to the Sponsor or to the HF study site personnel involved in the follow-up evaluations of the patient. However, for a serious and unexpected adverse event considered related to rexlemestrocel-L or study procedures, the unblinded team (CRO) will have access to unblind the study treatment (on a case-by-case basis) specifically for regulatory reporting purposes (see Section Sponsor Responsibility).

3.4 Study Drugs and Dosage

Study intervention (*i.e.,* a single index cardiac catheterization with or without intracardiac mapping and cell delivery) will be performed during hospitalization on Day 0 only. Duration of treatment is based on the day of the single index cardiac catheterization (with or without intracardiac mapping and cell delivery) to the last day of study participation by the patient.

Rexlemestrocel-L consists of human bone marrow-derived allogeneic MPCs isolated from bone mononuclear cells with anti-STRO 3 antibodies, expanded ex vivo, and cryopreserved. The allogeneic MPCs are cryopreserved [redacted] Rexlemestrocel-L must be thawed before use. Patients randomly assigned to rexlemestrocel-L treatment who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a single index cardiac catheterization involving transendocardial delivery of 150 M completely thawed rexlemestrocel-L, which will be delivered transendocardially into the myocardium, using a specially designed catheter

(MyoStar™ Injection Catheter) that is inserted through a sheath that has been previously inserted into the femoral artery. This catheter is then advanced through the arterial system to the LV. Patients randomly assigned to control treatment who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a single cardiac catheterization involving a scripted sham cardiac mapping and cell delivery procedure without actual intracardiac mapping or transendocardial delivery of rexlemestrocel-L. A more detailed description of administration procedures for both the active and control treatment groups is given in Section 5.1.

During the index cardiac catheterization, contrast left ventriculography as well as evaluations for stable myocardium will be performed. The latter will utilize either the NOGA® or CARTO®. Data will be generated to visualize and map myocardial locations that are potential targets for delivery of rexlemestrocel-L.

Instructions for intracardiac mapping and transendocardial delivery of rexlemestrocel-L and for the scripted sham intracardiac mapping and cell delivery procedure are provided in Appendix 1 (NOGA®), Appendix 3 (CARTO®), and Appendix 2 (scripted sham), respectively.

3.5 Duration of Study/Patient Participation

This is an events-driven study and the study duration will be determined by the number of recurrent non-fatal decompensated HF events. Patients are expected to participate in this study until the required number of recurrent non-fatal HF-MACE occur and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up. Patients who have a minimum of 6 months follow-up at the time the required number of recurrent non-fatal HF-MACE occur will be evaluated as early as possible using the same assessments that are specified for the Month 12 visit. An echocardiogram or RVG will be performed only if more than 6 months have passed since the patient's last echocardiogram or RVG. At least 531 recurrent non-fatal HF-MACE and a minimum of 6 months of follow-up for all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit should be met for study completion.

3.6 Stopping Rules and Discontinuation Criteria

Patients are expected to participate in this study until the required number of recurrent non-fatal HF-MACE occur and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up. The End-of-Study will occur when the two following conditions have been met: 1) at least 531 recurrent non-

fatal HF-MACE have occurred, and 2) all surviving patients without a TCE who remain in the trial have completed a minimum of 6 months of follow-up. However, the Sponsor may discontinue the study due to poor recruitment or other operational issues. During the conduct of the study, SAEs will be reviewed (see Section 7.1.6.3) as they are reported from the investigational sites to identify safety concerns.

The interventional cardiologist may abort the index cardiac catheterization, the cardiac mapping and cell delivery procedure, or the scripted sham cardiac mapping and cell delivery procedure at any time if any acute symptoms develop that may pose an immediate risk to a patient. Guidelines for temporarily halting or terminating the intracardiac mapping and cell delivery procedure or the scripted sham intracardiac mapping and cell delivery procedure are provided in Appendix 1 (NOGA), Appendix 2 (scripted sham), and Appendix 3 (CARTO), respectively.

A patient may discontinue participation in the study at any time for any reason. The investigator and/or Sponsor can withdraw a patient from the study at any time for any reason as discussed in Section 4.3.

3.7 Study Drug Supply and Accountability

3.7.1 Study Drug Storage and Security

Rexlemestrocel-L must be stored in the vapor phase of liquid nitrogen at −140°C to −196°C. Rexlemestrocel-L will be maintained in a monitored freezer with adequate security and an audible alarm and will be appropriately identified and segregated from other products. Additional details regarding the storage and preparation of rexlemestrocel-L are provided in the Pharmacy Manual.

3.7.2 Study Drug Accountability

The cell injection center pharmacist will maintain a record of rexlemestrocel-L received, dispensed, administered, or destroyed. The final disposition of all unused, empty, and partially used cryocyte vials will be handled in accordance with the institutional policy and procedures described in the Pharmacy Manual.

The investigator will complete a record of the cardiac mapping and cell delivery products received, dispensed, administered, or destroyed. If the mapping and/or cell delivery (injection) catheter is defective or malfunctions during a procedure, the catheters should be returned to the medical device manufacturer (Biosense Webster, Inc.) as described in Appendix 4.

3.8 Maintenance of Randomization and Blinding

This is a double-blind study. The randomization code will be maintained by the Sponsor's independent third party provider. At the time of analyses, when treatment codes are revealed, the randomization code will be provided to the statistician assigned to this study. In addition, the randomization code will be provided to the unblinded independent statistician for use in the conduct of the interim analyses and support of the DMC.

The success of this study depends on several factors including: a) the safety of patients enrolled and randomly assigned to treatment; b) demonstration of the potential clinical benefit from transendocardial delivery of rexlemestrocel-L; and c) maintenance of the treatment blind as it relates to clinical follow up and decision making.

This study is designed with 3 distinct time periods relative to knowledge of study treatment:

- **Screening and randomization designation period:** A patient's eligibility to participate in the study will be determined during this period and will be based on the study's inclusion and exclusion criteria for screening. If the patient is deemed eligible to participate in the study, randomization will occur.
- **Study intervention:** For all randomized patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization, study intervention will involve hospitalization for a single index cardiac catheterization with or without intracardiac mapping and cell delivery. For these patients, study intervention will be performed at a cell injection center by an interventional cardiology team not involved with follow-up of patients' safety and efficacy evaluations. Interventional cardiologists and the unblinded team performing the study intervention may participate in screening evaluations (follow-up evaluations will be performed by blinded team members only).
- **Follow-up period:** The follow-up period begins after hospital discharge from the cell injection center and continues until the required number of recurrent non-fatal HF-MACE (*i.e.,* at least 531 recurrent non-fatal HF events or successfully RCD events) is obtained and a minimum follow-up of at least 6 months for all surviving subjects without TCEs is achieved. The follow-up period for patients who were randomized and **DID** undergo index cardiac catheterization includes patients' safety and efficacy evaluations for a minimum of 6 months (assuming the patient has survived for that period of time without a TCE and has not discontinued from the study) and long-term safety and efficacy evaluations after the Month-12 visit (every 6 months) until study conclusion. However, if a patient was randomized but **DID NOT** undergo the index cardiac catheterization, the

patient will be followed for vital status (alive or dead), AEs, potential primary and key secondary endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

The design and maintenance of a blinded follow-up period will help protect the integrity of study data and will help prevent the introduction of physician bias into the clinical decision-making process that could result from knowledge of study treatment. Treatment bias could influence a treating physician's decision to hospitalize a patient for HF. For example, knowledge that a given patient did not receive rexlemestrocel-L could result in a lower threshold for hospitalization because the physician would not expect the sham cardiac mapping and cell delivery procedure to have beneficially affected the patient's long-term clinical state. Maintenance of the blind during follow up is particularly important in this study because a biased decision relating to HF hospitalization would directly impact the study's primary efficacy endpoint. Appropriate blinding over the duration of the follow-up period will also help define the "placebo effect" on subjective measurements including NYHA class, MLHF, and EQ-5D.

Because of the basic study design and the need to minimize inadvertent unblinding to study treatment, this study will be supported by a blinded as well as an unblinded study team. The Blinding Plan includes an independent unblinded statistician who will perform the interim analyses. The following summarizes the roles of these two teams for this study.

- **Unblinded Study Team:** The individuals on the unblinded study team are unblinded to study treatment assignment as prespecified and required. If necessary, they can be unblinded to treatment-specific clinical data. They have the ability to aggregate treatment-specific clinical study information. Any activity associated with the cell injection center is the responsibility of the unblinded study team.
- The unblinded Sponsor Pharmacovigilance team is responsible for the SAEs that occur during the period of Day 0 to hospital discharge for the index cardiac catheterization and may be unblinded to treatment assignment only on a case-by-case basis for a SAE (s) that

is unexpected and considered related to rexlemestrocel-L (see Section 7.8.4 for more information).
- Immunogenicity testing for positive PRA results and for the anti-murine and anti-bovine analysis subsets (see Section 8.3 for more information).

- **Blinded Study Team:** The blinded study team members are blinded to study treatment assignment, the Day 0 index cardiac catheterization procedures, and treatment-specific clinical data. Most activities associated with a HF study site (screening and any follow-up evaluations after the patient has been discharged from the cell injection center after the Day 0 index cardiac catheterization procedures) fall within the scope of the blinded team (an exception is the interventional cardiologist and the unblinded team who may participate in the screening process). Additionally, the following groups will be unblinded to treatment assignment only on a case-by-case basis:
- The blinded Sponsor Pharmacovigilance team is responsible for the SAEs during screening and Day 8 onward but may be unblinded to treatment assignment only on a case-by-case basis for a SAE(s) that is unexpected and considered related to rexlemestrocel-L (see Section 7.8.4 for more information). If this occurs, the study site investigator will remain blinded to treatment but the Sponsor's medical monitor may be unblinded to treatment in order to decide on the action taken as described in Section 3.6.

Patients as well as noninterventional investigators and study site personnel at the HF study centers who conduct follow-up evaluations after hospital discharge of patients from the cell injection center will remain blinded to the study treatment provided at the cell injection center. It is permissible for a physician trained as an interventional cardiologist to take on the role of the blinded HF specialist as long as the physician is adequately experienced to perform this role. In that scenario, another interventional cardiologist at the site will be identified as the (unblinded) interventional cardiologist for this program. Once a physician has been designated as either the blinded or unblinded cardiologist, he/she may not change his/her blinded vs unblinded role within the trial. Further delineation of the responsibilities of the unblinded and blinded individuals can be found in the Blinding Plan.

Because rexlemestrocel-L is given at a single time point (Day 0), and there is no specific treatment or agent that can reverse the effect of rexlemestrocel-L after administration, it is anticipated that there will be no need to unblind the treatment code to the Sponsor or to the study site personnel involved in the long-term follow-up evaluations of the patient. For information about personnel (interventional cardiology team) who may be aware of treatment assignments,

see Section 3.3. These individuals will not be involved in the conduct of any follow-up study procedures or assessment of clinical results.

In the case of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment using IRT after consultation with the Sponsor. In an extreme emergency, if the investigator is unable to contact the Sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. When this occurs, the investigator must contact immediately the individual identified in the clinical study personnel contact information section of this protocol. Proper documentation must be maintained when a treatment code is revealed.

There will be 3 oversight committees: an Executive Steering Committee (ESC), an independent CEC, and an independent DMC. Both the ESC and the CEC will be blinded to study treatment; the DMC will be unblinded. For further details, see Section 7.8.

3.8.1 Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the case report form (CRF). Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the Sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

Data processed from other institutions (*e.g.,* clinical laboratory, central image center, electronic diary data) will be sent to the investigational center, where they will be retained, but not entered into the CRF unless otherwise noted in the protocol. These data may also be sent electronically to the Sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator(s).

The CRFs are filed in the Sponsor's central file.

3.9 Time Schedule

The study started in 2014 and is expected to be completed in 2020. Because this study is endpoint driven, the actual duration of the study will be determined by the time required to achieve a minimum of 531 recurrent non-fatal HF-MACE that have been positively adjudicated

by the CEC, and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up.

Approximately 600 patients with chronic HF due to LV systolic dysfunction of either ischemic or non-ischemic etiology from approximately 80 to 100 study centers are planned to be enrolled in the study.

This study comprises 3 main time periods: 1) screening and randomization designation period period; 2) study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery); and 3) a follow-up period that continues until the required number of recurrent non-fatal HF-MACE (*i.e.,* at least 531 recurrent non-fatal decompensated HF events and/or successfully resuscitated cardiac death events) is obtained and a minimum follow-up of at least 6 months for all surviving subjects without TCEs is achieved. The follow-up period for patients who were randomized and **DID** undergo index cardiac catheterization includes safety and efficacy evaluations for a minimum of 6 months (assuming he/she has survived for that period of time without a TCE and has not discontinued from the study) and long-term safety and efficacy evaluations after the Month-12 visit (every 6 months) until study conclusion. However, if a patient was randomized but **DID NOT** undergo the index cardiac catheterization, the patient will be followed for vital status, AEs, potential primary and key secondary endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, DO undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.
Study procedures and assessments with their timing are summarized in Table 4.

Table 4: Study Procedures and Assessments from Screening through Follow-up Period up to 12 Months

Procedures Assessments	Screening [a]	R [b]	Device Safety Reporting Period (up to 30 days) [c] and Patient Follow-up					Follow-up Period up to 12 Months [d] Month (M) ± days (d) Visit/Telephone Contact (TC)											
			Hospitalization (periprocedural) Day (D) 0			Discharge (DC) and patient follow-up													
	Day -42 to Day -1 [e]	R [b]	Pre-	Mid-	Post-	D1	D10 ±3d	M1 ±3d	M2 ±14d	M3 ±7d	M4 ±14d	M5 ±14d	M6 ±14d	M7 ±14d	M8 ±14d	M9 ±14d	M10 ±14d	M11 ±14d	M12 ±14
	Visit (V) 1		V2.0	V2.1	V2.2	DC	V3	V4	TC1	V5	TC2	TC3	V6	TC4	TC5	TC6	TC7	TC8	V7
Informed consent	X																		
Inclusion and exclusion criteria	X																		
Medical history (including HF)	X																		
Eligibility checklist [f]	X	X [b]																	
Institution-specific informed consent [g]			X																
Full physical examination [h]	X																		X
Body weight measurement [i]	X		X		X	X	X	X		X			X						X
Symptom-directed physical examination			X		X		X	X		X			X						
Prior/concomitant medications/ therapy	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs measurement [j]	X		X		X	X	X	X		X			X						X
Clinical laboratory tests [k]	X				X		X	X		X			X						X
PT, INR, PTT, Fibrinogen	X																		
Urinalysis	X						X	X		X			X						X
Pregnancy test (urine or serum)	X		X																
Immunogenicity testing [l]	X						X	X		X			X						X
2-D echocardiography [m] or RVG, if applicable	X				X [n]					X			X						X
Cardiac enzymes [o]			X		X														
Biomarker testing [p]	X									X			X						X
Index cardiac catheterization				X															

Procedures Assessments	Screening [a]	R [b]	Device Safety Reporting Period (up to 30 days) [c] and Patient Follow-up					Follow-up Period up to 12 Months [d] Month (M) ± days (d) Visit/Telephone Contact (TC)											
			Hospitalization (periprocedural) Day (D) 0			Discharge (DC) and patient follow-up													
	Day -42 to Day -1 [e]	R [b]	Pre-	Mid-	Post-	D1	D10 ±3d	M1 ±3d	M2 ±14d	M3 ±7d	M4 ±14d	M5 ±14d	M6 ±14d	M7 ±14d	M8 ±14d	M9 ±14d	M10 ±14d	M11 ±14d	M12 ±14
	Visit (V) 1		V2.0	V2.1	V2.2	DC	V3	V4	TC1	V5	TC2	TC3	V6	TC4	TC5	TC6	TC7	TC8	V7
Intracardiac [q] mapping/cell delivery or sham procedure				X															
Electrocardiogram (ECG) [r]	X		X		X	X	X	X		X			X						X
ICD device interrogation, if applicable [s]							X	X		X			X						X
Telemetry [t]			X	X	X														
24-hour Holter monitor	X				X		X	X		X									
AE inquiry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical device retention & AE inquiry [u]				X	X	X													
Medical device safety reporting & AE inquiry [v]				X	X	X	X												
HF-MACE evaluation [w]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Overall survival (vital status) [x]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coronary artery revasc, ventricular arrhythmias of interest, CVA, and MI inquiry					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6MWT [y]	X									X			X						X
NYHA classification	X									X			X						X
MLHF questionnaire	X									X			X						X
EQ-5D questionnaire	X									X			X						X
PGx blood sample [z]	X																		

a. A patient's eligibility to participate in the study will be determined during the screening period and will be based on the study's inclusion and exclusion criteria for eligibility as described in Section 3.9.1 and Sections 4.1 and Section 4.2, respectively. Evaluations obtained as part of routine medical care and performed during screening may be used in place of the

protocol specific evaluations. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent. Patients will be screened at recruiting HF study centers. Patients who are screen failures may be re-screened with approval from the medical monitor. Note: Patients who experience an inclusion/exclusion criteria violation after randomization but before the scheduled index cardiac catheterization procedure will be included as part of the ITT analysis and cannot be re-screened. Also, any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including visit clinic times, for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

b. Randomization should occur as close as possible to the scheduled index cardiac catheterization date for potential delivery of study product. The pre-randomization criteria, such as echocardiographic criteria (restrictive, constructive or obstructive physiology, LV wall thickness, mural or arterial thrombus and prosthetic valve) are to be met by all patients and confirmed by both HF referral physician and the interventional cardiologist. Echocardiographic criteria must be confirmed and signed off by interventional cardiologist prior to randomization.
c. The occurrence of AEs during the interval of Day 0 through hospital discharge for the index cardiac catheterization must be reported to the device manufacturer and the unblinded medical monitor.
d. All randomized patients who **DO** undergo index cardiac catheterization will be followed until the minimum required number of recurrent non-fatal HF-MACE (i.e., at least 531 decompensated HF events and/or successfully RCD events) are obtained and minimum follow-up of at least 6 months (assuming the patient has survived that period of time without a TCE and has not discontinued from the study) for efficacy and safety evaluations, as indicated, is achieved. Patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for vital status, AEs, potential primary and key secondary endpoint events, and ICD interrogation at all regularly scheduled study visit times, including visit clinic times, for

the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled study visit times for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization. An echocardiogram (or RVG) will also be performed if more than 6 months have passed since the patient's last echocardiogram or RVG.

e. The 42 days allowed for screening is the maximum allowable time from signing of the informed consent to the Day 0 procedure.

f. After results from all screening assessments and full medical history (including HF) have been obtained, the investigator will assess the patient's eligibility and complete an eligibility checklist that is forwarded to the medical monitor and/or Sponsor for authorization to enroll the patient into the study. Patients who meet all the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) described in Section 3.9.2 will be eligible to participate in the study and will be scheduled for hospitalization at a cell injection center as described in Section 3.9.2. **Important:** The timing of randomization relative to Day 0 will vary based on study drug availability and BDS availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0. Note: Once eligibility has been determined, the results of the following screening assessments will be recorded as baseline values: immunogenicity test, biomarker test, adverse event inquiry, 6MWT (NOTE: 2 tests are required during screening, which are separated by at least 1 calendar day. Patients who complete two 6MWTs during screening with either test [first or second] being a distance > 450 meters will be excluded. The maximum value of 2 eligible 6MWTs [i.e., each a distance < 450 meters] obtained during screening will be used for the baseline 6MWT distance value), RVG (only if 2-D echocardiogram was nonqualifying for LVEF), MLHF questionnaire, EQ-5D questionnaire, 24-hour Holter monitor evaluation (randomized patients across the US and EU), clinical laboratory tests, body weight measurement, urinalysis, and NYHA classification.

g. Prior to the initiation of any procedures on the date of index cardiac catheterization, personnel at the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable.

h. A full physical examination, including measurement of height (to be obtained at the screening visit only) and weight will be performed at baseline. At subsequent visits during the 12-month follow-up period, a symptom-directed physical examination will be performed.
i. Body weight measurement (to be performed when the patient is ambulatory on Day 0 or Day 1 [before hospital discharge] at the discretion of the interventional cardiologist).
j. Vital signs measurements will be assessed up to 24 hours after completion of the Day 0 index cardiac catheterization with or without intracardiac mapping and cell delivery (every 2 hours for 4 hours, then every 4 hours for the next 8 hours, and then at discharge; vital signs are measured while patient is supine).
k. Clinical laboratory tests include serum chemistry and hematology.
l. The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti- human leukocyte antigen (HLA) DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per this Schedule of Assessments (Table 4) for all surviving patients who were randomized and underwent the index cardiac catheterization. All samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA. [redacted] serum samples [redacted] of rexlemestrocel-L will be analyzed for anti-murine and anti-bovine antibodies. The serum samples will be analyzed in batches for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies) [redacted].
m. Two-dimensional (2-D) echocardiographic assessment during screening includes echocardiographic imaging (without or with contrast) and Doppler evaluation. The echocardiograms will be reviewed by the core imaging laboratory and will be used to qualify patients for study enrollment. Subsequent echocardiograms will be conducted as described in Section 3.9.4.

Echocardiograms should be performed prior to or at least 30 minutes after the 6MWT or any other physical exertion. If the non-enhanced image quality is considered inadequate for LVEF calculation, an RVG or echocardiogram with contrast may be performed for LVEF determination. Patients who have an RVG at screening must continue with same scans during the conduct of this study; RVG-qualified patients do not undergo RVG at month 3. Separate serial assessments will be performed for RVGs and echocardiograms, as applicable.

n. For patients who are randomized and **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization), echocardiographic 2-D imaging must be performed immediately following the procedure at Visit 2.2 (Section 3.9.4), and will be read locally for clinical purposes.

o. Cardiac enzyme testing includes troponin I and CK-MB before index cardiac catheterization (either with cardiac mapping and transendocardial delivery of rexlemestrocel-L or a scripted sham cardiac mapping and cell delivery) and 2, 10, and 18 hours after index cardiac catheterization (either with cardiac mapping and transendocardial delivery of rexlemestrocel-L or a scripted sham cardiac mapping and cell delivery).

p. Blood samples for biomarkers (high-sensitivity C-reactive protein [hsCRP] and N terminal pro B type natriuretic peptide [NT-proBNP] will be collected at screening and at specified time points).

q. Includes use of NOGA® /MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System for transendocardial delivery of rexlemestrocel-L. Patients who are randomized to the control treatment group and **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization) will undergo a scripted sham cardiac mapping and cell delivery procedure. Details of the procedures will be recorded, including the number of myocardial locations for cell delivery, arrhythmias, or other complications. In accordance with the process outlined in Appendix 4, the catheters (NOGA® XP or CARTO®3 Cardiac Navigational System in combination with the NogaStar® Mapping Catheter and MyoStar™ Injection Catheter) used in performing cardiac mapping and cell delivery must be placed in a biohazard bag and retained at the cell injection center for up to 7 days following index cardiac catheterization, after which the catheters are to be returned in accordance to the study procedures. However, if the catheters malfunction during intracardiac mapping and cell delivery, the catheters must be returned to the device manufacturer as outlined in Appendix 4. The catheters must also be returned to the device manufacturer if an AE/SAE occurs during the interval of Day 0 through hospital discharge after index cardiac catheterization.

r. The pre- and post-ECG performed on the day of the index cardiac catheterization will be read locally and centrally; the ECG performed on Day 1 post-procedure will be read locally and centrally.
s. For patients with an ICD (or any implantable device capable of defibrillation) who are randomized and treated, rhythm analysis by device interrogation will be conducted at every clinic visit by appropriate site personnel. These episodes will be assessed at each site and captured as AEs or non-fatal HF-MACE as appropriate. When a non-fatal HF-MACE or a TCE is suspected, the rhythm strips obtained by device interrogation and relevant clinical context will be provided to the CEC for their review and adjudication.
t. Telemetry monitoring will commence prior to the index cardiac catheterization procedure for patients who are randomized, **DO NOT** experience an inclusion/exclusion criterion violation after randomization, and undergo index cardiac catheterization and will continue overnight post-procedure.
u. The occurrence of AEs/SAEs during the interval of Day 0 through hospital discharge for the index cardiac catheterization must be reported to the device manufacturer as well as to the unblinded medical monitor.
v. Serious adverse events reported during the prespecified medical device safety reporting period and assessed as related to either mapping or injection catheters used during the index cardiac catheterization will be sent to the medical device manufacturer as well as the Sponsor.
w. Evaluation of HF-MACE includes results of ICD device (or any implantable device capable of defibrillation) interrogation (performed at regularly scheduled intervals). Evaluation of non-fatal HF-MACE will begin on Day 0 as specifically defined in the protocol. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be used for adjustment in the primary analysis using the JFM and will be included in the key secondary analysis (see Section 9.6.4.1).
x. Evaluation of all-cause mortality (i.e., non-cardiac and cardiac death) will begin after randomization. Vital status follow-up is to be conducted via telephone contacts at the regularly scheduled study visit times for the duration of the study. Any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must also be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any

patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

y. Two 6MWTs should be performed during screening, separated by at least 1 calendar day. If the patient is unable to perform the test, the reason for the test not being completed will be noted in the case report form. Patients will be excluded from participation in the study if they cannot perform the 6MWT due to concurrent medical conditions (the exception is those patients with an NT-proBNP >2000 pg/mL [2000 ng/L SI units; 236 pmol/L]) or if they complete two 6MWTs with either test a distance of >450 meters during screening. Note that if on the first 6MWT (or second), the distance is > 450 meters, the patient is ineligible.

z. Blood samples will be collected from patients who provide informed consent for the PGx study and **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization; samples will be collected at the end of screening and stored for future pharmacogenomic analyses. If not available at screening, this sample can be obtained at a subsequent visit, preferably the ensuing one.

2-D=2-dimensional; 6MWT=6-minute walk test; AEs=adverse events; BDS= Biologics Delivery System; ICD= implantable cardioverter defibrillator; CEC=Clinical Endpoints Committee; CK-MB=creatine kinase-myocardial band; CVA=cerebrovascular accident; D=Study Day; d=days; DC=discharge; DSA=donor-specific antibody; ECG=electrocardiogram, electrocardiography; EQ-5D=EuroQoL 5-dimensional Quality of Life Scale; EU=European Union; HF-MACE=heart failure major adverse cardiac events; HLA=human leukocyte antigen; hsCRP=high-sensitivity C-reactive protein; INR=international normalized ratio; LVEDV=left ventricular end diastolic volume; LVEF= left ventricular ejection fraction; LVESV=left ventricular end systolic volume; M=month; MDR=Medical Device Safety reporting; MI=myocardial infarction; MLHF=Minnesota Living With Heart Failure; NT-pro-BNP=N-terminal pro-brain natriuretic protein; NYHA=New York Heart Association; PGx=pharmacogenomic; PRA=panel reactive antibodies; PT=prothrombin time; PTT=partial thromboplastin time; revasc=revascularization; RVG=radionuclide ventriculography; SAE=serious adverse event; TC=telephone contact; TCE=terminal cardiac event; TCEUS=United States; V=visit.

Table 5: Study Procedures and Assessments for Long-term Follow-up Until Study Conclusion

Procedures and Assessments	Long-term Follow-up Until Study Conclusion [a] Months (M) ± days (d) Telephone contact (TC)/ Visit (V)												Until End-of-Study (TC every 2 mo Visit every 6 mo) See Sections 3.9.6.1 and 3.9.6.2, respectively
	M 14 ±14d	M 16 ±14 d	M 18 ±14 d	M 20 ±14 d	M 22 ±14 d	M 24 ±14 d	M 26 ±14 d	M 28 ±14 d	M 30 ±14 d	M 32 ±14 d	M34 ±14 d	M36 ±14 d	
	TC 9	TC 10	V 8	TC 11	TC 12	V9	TC 13	TC 14	V10	TC15	TC 16	V11	
Full physical examination [b]						X						X	
Body weight measurement			X			X			X			X	
Symptom-directed physical examination			X						X				
Prior/concomitant medications and therapy	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs measurement			X			X			X			X	
Clinical laboratory tests [c]			X			X			X			X	
Urinalysis			X			X			X			X	
2-D echocardiography (or RVG, if applicable) [d]						X						X	
Biomarker testing [e]						X						X	
Electrocardiogram (ECG)			X			X			X			X	
ICD device interrogation, if applicable [f]			X			X			X			X	
AE inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X
HF-MACE evaluation [g]	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures and Assessments	Long-term Follow-up Until Study Conclusion [a] Months (M) ± days (d) Telephone contact (TC)/ Visit (V)												Until End-of-Study (TC every 2 mo Visit every 6 mo) See Sections 3.9.6.1 and 3.9.6.2, respectively
	M 14 ±14d	M 16 ±14 d	M 18 ±14 d	M 20 ±14 d	M 22 ±14 d	M 24 ±14 d	M 26 ±14 d	M 28 ±14 d	M 30 ±14 d	M 32 ±14 d	M34 ±14 d	M36 ±14 d	
	TC 9	TC 10	V 8	TC 11	TC 12	V9	TC 13	TC 14	V10	TC15	TC 16	V11	
Overall survival (vital status)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coronary artery revasc, ventricular arrhythmias of interest, CVA, and MI inquiry	X	X	X	X	X	X	X	X	X	X	X	X	
6MWT			X			X			X			X	
NYHA classification						X			X			X	
MLHF questionnaire			X			X			X			X	
EQ-5D questionnaire			X			X			X			X	

a. For the long-term follow-up period (after the month-12 follow-up visit [visit 7]), patients who are randomized and **DO** undergo the index cardiac catheterization will return to the study site approximately every 6 months, as indicated, for follow-up of patients' safety and efficacy evaluations until study conclusion (note that table extends to a 3-year long-term follow-up period). Telephone contact for follow-up inquiries will be made every 2 months between study visits (Months 14, 16, 20, 22, 24, etc.) during the long-term follow-up period. These long-term follow-up visits and telephone contacts will continue until study conclusion. Any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study (see "h"). Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

b. A full physical examination, including measurement of height (to be obtained at the screening visit only) and weight will be performed at screening, Month 12 (Visit 7), and once every 12 months (Visit 9, Visit 11, etc.; long-term follow-up) for randomized patients who **DO** undergo the index cardiac catheterization and thereafter until study conclusion.

c. Clinical laboratory tests include serum chemistry and hematology.

d. Two-dimensional (2-D) echocardiography (in echo-qualifying patients) should always be performed before or at least 30 minutes after the 6MWT or any other physical exertion. Patients whose echocardiographic imaging at screening was of insufficient technical quality for LV volume and LV ejection fraction estimation and who had an RVG performed will continue to have RVG scans for the duration of the study.
e. For patients who are randomized and **DO** undergo index cardiac catheterization, blood samples for analysis of the biomarkers NT-proBNP and hsCRP will be collected will be collected every 12 months during the long-term, follow-up until study conclusion.
f. For patients with an ICD (or any implanted device capable of defibrillation), rhythm analysis by device interrogation will be conducted as indicated. All episodes of firing of ICD will be assessed at each site and captured as AEs or a non-fatal HF-MACE as appropriate. When a non-fatal HF-MACE or a TCE is suspected, the rhythm strips obtained by device interrogation and relevant clinical context will be provided to the CEC for their review and adjudication.
g. Evaluation of HF-MACE includes results of ICD device (or any implanted device capable of defibrillation) interrogation in cases of device firing.
h. Any patients who were screened and discontinued from the study after randomization but before index cardiac catheterization will be contacted by telephone at Months 2, 4, 5, 7, 8, 9, 10, 11, 14, 16, and every 2 months thereafter for the duration of the study to assess vital status, AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study; additional assessments other than vital status, AEs, and endpoint collection will **NOT** be performed. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

2-D=2-dimensional; 6MWT=6-minute walk test; AEs=adverse events; ICD= implantable cardioverter defibrillator; CEC=Clinical Endpoints Committee; CVA=cerebrovascular accident; d=days; ECG=electrocardiogram, electrocardiography; EQ-5D=EuroQoL 5-dimensional Quality of Life Scale; DSA=donor-specific antibody; HF-MACE=heart failure major adverse cardiac events; HLA=human leukocyte antigen; hsCRP=high-sensitivity C-reactive protein; INR=international normalized ratio; LVEF= left ventricular ejection fraction; M=month; MI=myocardial infarction; MLHF=Minnesota Living With Heart Failure; NT-pro-BNP=N-terminal pro-brain natriuretic protein; NYHA=New York Heart Association; PRA=panel reactive antibodies; revasc=revascularization; RVG=radionuclide ventriculography; TC=telephone contact; V=visit.

3.9.1 Procedures for Screening and Enrollment (Day -42 to Day -1 [Visit 1])

A signed and dated institution-specific informed consent form will be obtained for the study before screening procedures commence or any study-specific procedures are performed. A separate written informed consent for an exploratory PGx substudy will be obtained before any PGx-specific procedures are performed. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). A patient will not be excluded from participation in the study if he/she chooses not to provide consent for the additional procedures that are required as part of the exploratory PGx substudy. Some disease-specific assessments performed within a specified time frame before informed consent may be used for the study unless otherwise pre-specified by this protocol. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened and enrolled will be assigned an 8-digit permanent identification number such that all patients from each study site are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the designated country. The next 3 digits of the screening number will be the designated investigator site number, and the last 3 digits will be assigned at the investigator site (*e.g.,* the 3rd patient screened at site 5 would be given the number of [redacted].

A patient who is screened but not randomized because entry criteria are not met or enrollment does not occur within the specified time may be considered for screening again if there is a change in the patient's medical background or a modification of study entry criteria (*e.g.,* a protocol amendment). Re-screening of a patient who is a screen failure requires approval from the medical monitor. If it is determined that a patient requires coronary revascularization, it should be performed at least 2 months before reinitiating any study screening procedures. Randomization should occur as close as possible to the scheduled index cardiac catheterization date for potential delivery of study product. Patients who experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization procedure will be included as part of the ITT analysis and cannot be re-screened.

The procedures for the screening period should be conducted in a prioritized manner that optimizes efficiency and timeliness of the evaluative process. A patient's eligibility to participate in the study will be determined during this period and will be based on the study's inclusion and exclusion criteria. The 42 days allowed for screening is the maximum allowable time for the Day 0 procedure from signing of informed consent. However, if a patient is qualified for

randomization in less time, the site should proceed with the scheduling of the Day 0 hospitalization at the cell injection center for index cardiac catheterization with or without intracardiac mapping and cell delivery. Prior to the initiation of any procedures on Day 0, the study personnel at the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable. Important: The timing of randomization relative to Day 0 will vary based on study drug availability and BDS availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0. Note that any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times (Table 4 and Table 5), for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

After results from all the screening assessments and full medical history have been received and reviewed, the investigator will assess the patient's eligibility and complete an eligibility checklist that is forwarded to the medical monitor and/or Sponsor for authorization to enroll the patient into the study.

Screening eligibility assessments will be completed in a maximum of 42 days prior to the scheduled index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0. All patients will undergo the procedures outlined in the bulleted list below; assessments are performed on separate days as appropriate (*indicates that results of tests will be used to establish baseline values):

- obtain written informed consent, including written informed consent for the PGx substudy. If PGx informed consent is not obtained at screening, informed consent and this sample can be obtained at a subsequent visit, preferably the ensuing one.
- review of inclusion and exclusion criteria
- review medical (including HF) history including recent packed red blood cells transfusion history on all study patients and gravida history on female study patients

- perform full physical examination (including height)
- *body weight measurement.
- review and recording of prior and concomitant medications and therapy including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine
- *obtain vital signs measurements (while patient is supine)
- *clinical laboratory tests (serum chemistry and hematology), including assessment at screening only for hemoglobin A1c (HBA1c), prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen tests
- *urinalysis
- urine or serum pregnancy test for women of childbearing potential
- screening ECG
- *screening 2-D echocardiography with Doppler imaging (2-D echocardiography with contrast should be used if required for LVEF qualification during the screening period; see note below) or RVG (only if echocardiogram is nonqualifying for LVEF; patients with poor quality 2-D echocardiographic imaging at screening will have RVG performed; see note below)
- adverse event inquiry (see Section 7.1)
- *NYHA classification
- *blood sample for immunogenicity testing (test for PRA and antibodies against bovine or murine proteins; if test for PRA is positive, sample will be tested for anti-HLA DSA formation)
- *blood sample for biomarker testing (NT-proBNP and hsCRP)
- *6MWT: two 6MWTs should be performed during screening, separated by at least 1 calendar day (it is preferable to have the same technician perform the 6MWTs for the duration of the study). Patients who complete two 6MWTs with either test a distance >450 meters will be excluded from participation in the study. Patients who cannot perform the 6MWT due to concurrent medical conditions will also be excluded from the study (the exception is those patients with an NT-proBNP >2000 pg/mL [2000 ng/L SI units; 236 pmol/L]). The maximum value of 2 eligible 6MWTs (i.e., each a distance < 450 meters) obtained during screening will be used for the baseline 6MWT distance value.
- *MLHF questionnaire
- *EQ-5D questionnaire
- *24-hour Holter monitor evaluation (randomized patients across the US and EU)

- *blood sample for PGx substudy (only from patients who provided PGx written informed consent).

Note: During screening, all patients will undergo a 2-D echocardiogram with Doppler. The use of echocardiographic contrast for enhanced LV chamber imaging will be determined by the investigator or designee. If the echocardiographic imaging is of insufficient technical quality for LV volume and LV ejection fraction estimation, then a RVG will be performed to assess LV ejection fraction as part of the patient's screening procedures for inclusion in the trial. Patients who have an RVG or echocardiogram with contrast at screening must continue to receive the same scans for the duration of this study. Patients with poor quality 2-D echocardiographic imaging at screening will have an RVG performed.

During the screening period, the HF specialist, interventional cardiologist, or designee will determine if the patient would benefit significantly from an additional coronary revascularization procedure(s). The pre-randomization criteria, such as echocardiographic criteria, including restrictive, constructive or obstructive physiology, LV wall thickness, mural or arterial thrombus and prosthetic valve, are to be met by all patients and confirmed by both the HF referral physician and interventional cardiologist. Echocardiographic criteria must be confirmed and signed off by interventional cardiologist prior to randomization. After all data have been acquired during the screening period, a form summarizing the inclusion and exclusion criteria evaluation will be submitted to the Sponsor/CRO for review and final approval of the patient for randomization into the study.

After the Sponsor accepts the patient for randomization, the study site will be permitted to schedule the index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0. The study site personnel will contact the designated personnel at the study site's predetermined cell injection center to schedule the index cardiac catheterization. To allow for additional time for scheduling purposes, the study site personnel can send a preliminary notice to the cell injection center that pending CRO/Sponsor approval, an index cardiac catheterization needs to be scheduled.

The unblinded interventional cardiologist and other members of his/her team may meet with a patient whose eligibility has already been confirmed by the blinded team prior to Day 0 to become familiar with the patient's medical history. In some cases, the unblinded interventional cardiologist and the unblinded team may have been involved in the screening of patients.

3.9.2 Procedures before Study Intervention (Day 0 [Visit 2.0])

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible to participate in the study and will be scheduled for hospitalization at a cell injection center. Patients will be randomly assigned by the IRT system to receive standard-of-care treatment plus rexlemestrocel-L or standard-of-care treatment without rexlemestrocel-L (control group). The study intervention for patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will occur such that no more than 42 days have passed between the initiation of screening and the planned index cardiac catheterization (*i.e.,* since the patient signed the informed consent form).

Important: The timing of randomization relative to Day 0 will vary based on study drug availability and BDS availability. Guidelines tailored to each site will be provided in order to minimize the time between randomization and Day 0 while allowing sufficient time for operational logistics. Every attempt should be made to minimize the time between randomization and Day 0. Note that any patients who are randomized but DO NOT undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, primary and key secondary potential efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times (Table 4 and Table 5), for the duration of the study. Similarly, any patients who are randomized, DO undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

The IRT system will assign each patient a unique randomization number. Prior to the initiation of any procedures on Day 0, the cell injection center will ensure that an institution-specific informed consent document is obtained. Study intervention (*i.e.,* hospitalization for index cardiac catheterization with or without intracardiac mapping and cell delivery) for these patients will be performed by an interventional cardiologist who is a member of the unblinded team (please see Blinding Plan) not involved with review or assessment of subsequent study results.

All patients who are randomized and **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will be hospitalized at the cell injection center for index cardiac catheterization (with or without

intracardiac mapping and cell delivery) and will remain hospitalized on telemetry for a minimum of one night.

For these patients, the following assessments will be performed at Visit 2.0 before index cardiac catheterization either with intracardiac mapping and transendocardial delivery of rexlemestrocel-L or a scripted sham cardiac mapping and cell delivery procedure:

- institution-specific informed consent (prior to the initiation of any procedures on Day 0, the cell injection center will ensure that an institution-specific informed consent document is obtained.)
- body weight measurement
- symptom-directed physical examination
- review and recording of prior and concomitant medication usage, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine
- vital signs measurement (while patient is supine)
- urine or serum pregnancy test for women of childbearing potential
- cardiac enzymes measurement (troponin I and CK-MB)
- ECG immediately before index cardiac catheterization with or without intracardiac mapping and cell delivery (read locally for clinical purposes and centrally for the database)
- telemetry monitoring
- AE inquiry (see Section 7.1).

3.9.3 Procedures during Study Intervention (Day 0 [Visit 2.1])

3.9.3.1 Index Cardiac Catheterization

The following assessments will be performed at Visit 2.1 during the procedure of the index cardiac catheterization either with cardiac mapping and transendocardial delivery of rexlemestrocel-L or a scripted sham cardiac mapping and cell delivery procedure:

- telemetry monitoring
- adverse event inquiry (see Section 7.1)
- medical device safety reporting and adverse event inquiry:
  - All AEs that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF.

- The occurrence of all AEs on Day 0 through hospital discharge after the index cardiac catheterization must be reported depending on the time interval as follows as shown in Table 6.

Table 6: Reporting of Adverse Events on Day 0 Through Hospital Discharge (for Randomized Patients who Undergo the Index Cardiac Catheterization) (Day 0, Visit 2.1)

Time	Action to be Taken
Day 0 to Hospital Discharge after Index Cardiac Catheterization	Report AE to the unblinded interventional cardiologist
After Hospital Discharge	Report AE to the blinded medical monitor

The interventional cardiologist will inform the unblinded medical monitor of the adverse event.

- Each report of an adverse event on Day 0 through hospital discharge after the index cardiac catheterization must be reported to the device manufacturer as well as to the unblinded medical monitor. For reporting of SAEs, see Section 7.1.6.3.
- Medical device retention and adverse event inquiry: In accordance with prespecified medical device requirements for handling and retention of catheters, cardiac mapping, and cell delivery catheters used during index cardiac catheterization must be retained by the investigational site for 7 days after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with intracardiac mapping and cell delivery). Any device malfunctions during this interval must be documented and reported to the device manufacturer, and the device must be returned to the device manufacturer for further evaluation. If no device malfunctions or adverse events are reported during this interval, the catheters will be disposed in accordance with the study procedures in place at the investigational site. For reporting of SAEs, see Section 7.1.6.3.

All randomized patients (rexlemestrocel-L and control groups) who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo placement of a femoral sheath through which a pigtail catheter will be advanced retrograde to the left ventricle for performance of radiologic contrast ventriculography.

For patients who have atrial fibrillation on the day of the index cardiac catheterization (Day 0 [Visit 2.1]), regularization of ventricular contraction rate should be attempted in the cardiac catheterization laboratory before the start of cardiac mapping and transendocardial delivery of rexlemestrocel-L or performance of the scripted sham cardiac mapping and cell delivery

procedure. This could be accomplished using overdrive pacing with a temporary right ventricular pacemaker or by manipulation of the capabilities of an already present pacing-capable device. In the absence of achieving a regular cardiac rhythm, the interventionalist should use his/her best judgment relating to patient risk prior to proceeding with the cardiac mapping and cell delivery (or sham) procedure. If the interventionalist concludes that the presence of an irregularly irregular cardiac rhythm in a given patient significantly increases the risk of complications (*e.g.,* perforation of the LV wall) then the procedure should be discontinued. Patients who have complete right bundle branch block on the day of the index cardiac catheterization (Day 0 [Visit 2.1]) must have either placement of a temporary pacing wire or precautionary manipulation of the capabilities of an already present pacing-capable device prior to entry of a catheter into the LV chamber. Instructions for intracardiac mapping and transendocardial delivery of rexlemestrocel-L or performance of the scripted sham cardiac mapping and cell delivery procedure are provided in Appendix 1 (NOGA®), and Appendix 2 (scripted sham), and Appendix 3 (CARTO®), respectively.

3.9.3.2 Cardiac Mapping and Cell Delivery

All patients randomly assigned to the active treatment group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will receive rexlemestrocel-L, which will be delivered transendocardially into the myocardium, using a specially designed injection catheter (MyoStar™ Injection Catheter) that is placed through a sheath that has been previously inserted into the femoral artery. This catheter is then advanced through the arterial system to the left ventricle. Transendocardial delivery into the myocardium will require the placement of the catheter needle into the left ventricle wall. During the index cardiac catheterization, contrast left ventriculography as well as evaluations for stable myocardium will be performed. The latter will utilize either the NOGA® or CARTO®. Data will be generated to visualize and map myocardial locations that are potential targets for delivery of rexlemestrocel-L. The cardiac mapping and cell delivery procedure will be performed by appropriately trained interventionalists who have successfully completed the NOGA® System/MyoStar™ Catheter or CARTO® System/MyoStar™ Catheter training program required by BDS. In addition, these individuals must be confirmed as having an active status in the BDS database and are experienced in performing cardiac investigational procedures. Retraining in the use of NOGA® System/MyoStar™ Catheter or CARTO® System/MyoStar™ Catheter must take place if an interventionalist has not performed the NOGA® or CARTO® system procedure in over 1 year. The HF study sites will have the option 1) to perform cardiac mapping and transendocardial delivery of rexlemestrocel-L at their own cardiac catheterization laboratory if the study sites are properly equipped and the staff is trained in the use of the

NOGA®XP/MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System; or 2) to refer patients to a predesignated cell injection center for index cardiac catheterization.

The cardiac mapping and cell delivery process should begin immediately following complete thawing of rexlemestrocel-L so that fully thawed product is delivered within 90 minutes of complete thaw. The total duration of cell delivery must not exceed 90 minutes from time of completion of thaw of rexlemestrocel-L. Instructions for the cardiac mapping and cell delivery procedure using the NOGA® /MyoStar™ and CARTO®/MyoStar™ Cardiac Navigation Systems are presented in Appendix 1 and Appendix 3, respectively.

In the event of procedure-related cardiac arrhythmias, current ACC/AHA/ESC Practice Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented.

If any of the following events/symptoms occur during LV mapping with the NOGA® or CARTO® Cardiac Navigation System or during transendocardial cell delivery with the MyoStar™ Injection Catheter, the procedure should be temporarily halted and the patient should be re-evaluated for suitability to continue with the treatment under investigation:

- Product administration should be discontinued if any of the following occur:
  - persistent complaints of chest pain
  - complaints of cardiac pain associated with injections
  - persistent hypotension
  - complaints of shortness of breath
  - ICD shocks to stop VT
  - direct current (DC) cardioversion or defibrillation for VT
  - any question as to the location of the catheter tip in relation to vasculature or the left ventricle
- The procedure will be terminated in the event that any of the following occur:
  - sustained hypotension not responsive to fluid administration
  - clinical signs and symptoms indicating acute coronary syndrome
  - clinical signs and symptoms indicating a CVA
  - cardiac tamponade is strongly suspected or confirmed
  - hemipericardium requiring pericardiocentesis
  - 2 episodes of sustained VT
  - the patient experiences one episode of VF

- identification of thrombus in the left ventricle or the aorta that was not previously present on echocardiogram or left ventriculogram.

3.9.3.3 Scripted Sham Cardiac Mapping and Cell Delivery

All patients randomly assigned to the control group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted, sham cardiac mapping and cell delivery procedure simulating rexlemestrocel-L delivery to the myocardium. These patients will not undergo placement of the NogaStar®or MyoStar™ catheter nor will they have transendocardial delivery of rexlemestrocel-L. The scripted, sham cardiac mapping and cell delivery procedure to be used for patients in the control group will not include cardiac mapping, but will be written to correspond to the operational steps that are used with the cardiac mapping and transendocardial delivery of rexlemestrocel-L using the NOGA®/ MyoStar™ or CARTO®/MyoStar™ Cardiac Navigation System (see Appendix 2 for instructions for the scripted sham cardiac mapping and cell delivery procedure). The total duration of the cell delivery procedure should range from approximately 1 hour to no more than 2 hours.

3.9.4 Procedures After Study Intervention

3.9.4.1 Day 0 (Visit 2.2)

The patient's post-operative care will be guided by standard practices at the cell injection center. The following are the minimal assessments mandated by protocol and are not intended to replace standard practices. The following assessments will be performed after index cardiac catheterization (with or without intracardiac mapping and cell delivery):

- body weight measurement (to be performed when the patient is ambulatory on Day 0 or Day 1 [before hospital discharge] at the discretion of the interventional cardiologist)
- symptom-directed physical examination
- review and recording of concomitant medications and therapy
- vital signs measurements will be assessed up to 24 hours after completion of index cardiac catheterization (every 2 hours for 4 hours, then every 4 hours for the next 8 hours, and then at hospital discharge; vital signs will be measured while patient is supine)
- clinical laboratory tests (serum chemistry and hematology) to be performed approximately 2 hours after completion of index cardiac catheterization.
- 2-D-echocardiographic imaging with an emphasis on the presence of a new pericardial effusion, new regional wall motion abnormalities, and left ventricular systolic performance. This evaluation should be performed immediately after the index cardiac

catheterization (with or without intracardiac mapping and cell delivery), and will be read and reviewed locally

- cardiac enzymes (troponin I, CK-MB) measured at 2 (±0.5), 10 (±1), and 18 (±1) hours post-procedure
- ECG immediately after index cardiac catheterization with or without intracardiac mapping and cell delivery (locally read) and at 24 hours after index cardiac catheterization with or without intracardiac mapping and cell delivery (read locally for clinical purposes and centrally for the database)
- telemetry monitoring (clinically significant abnormalities identified on telemetry will be reported as adverse events)
- 24-hour Holter monitor (randomized patients across the US and EU) beginning immediately after completion of index cardiac catheterization
- adverse event inquiry (see Section 7.1)
- medical device safety reporting and adverse event inquiry:
  - All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF.
  - All adverse events through hospital discharge after the index cardiac catheterization must be reported by the unblinded interventional cardiologist at the cell injection center. As such, all non-fatal HF-MACE and fatal events (including TCEs) are to be assessed as potential primary and key secondary efficacy endpoints, respectively. The interventional cardiologist will inform the unblinded medical monitor of the adverse event.
- Each report of an AE/SAE on Day 0 through hospital discharge for the index cardiac catheterization that is considered related to the intracardiac mapping or cell delivery catheters must be reported to the device manufacturer as well as to the unblinded medical monitor. For reporting of SAEs, see Section 7.1.6.3.
- Medical device retention and adverse event inquiry. In accordance with prespecified medical-device requirements for handling and retention of catheters, cardiac mapping, and cell delivery catheters used during index cardiac catheterization must be retained by the investigational site for 7 days after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with intracardiac mapping and cell delivery). Any device malfunctions during this interval must be documented and reported to the device manufacturer, and the device must be returned to the device manufacturer for further evaluation. If no device malfunctions or adverse events are reported during this interval, the catheters must be disposed in accordance with procedures in place at the investigational site. For reporting of SAEs, see Section 7.1.6.3.
- HF-MACE evaluation

- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, non-fatal CVA, and non-fatal MI inquiry.

Details regarding the processing and reporting of any SAEs to the Sponsor are provided in Section 7.1.6.3.

3.9.5 Procedures for Follow-up Period

Patients as well as noninterventional investigators and study personnel at the HF study centers who conduct follow-up evaluations after patients have been discharged from the cell injection center will remain blinded to the study treatment provided at the cell injection center.

3.9.5.1 Day 1 Through Hospital Discharge for the Index Cardiac Catheterization

The following procedures/assessments will be performed on the day prior to hospital discharge:

- body weight measurement (to be performed when the patient is ambulatory on Day 0 or Day 1 [before hospital discharge] at the discretion of the interventional cardiologist)
- vital signs measurements (while patient is supine)
- ECG on the day after index cardiac catheterization with or without intracardiac mapping and cell delivery (read locally for clinical purposes and centrally for the database)
- adverse event inquiry (see Section 7.1)
- medical device safety reporting and adverse event inquiry:
- All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF.
- The occurrence of all adverse events through hospital discharge following study intervention, *i.e.,* index cardiac catheterization on Day 0 (with or without intracardiac mapping and cell delivery) must be reported as follows:

Table 7: Reporting of Adverse Events on Day 0 Through Hospital Discharge for Randomized Patients Who DO Undergo the Index Cardiac Catheterization)

Time	Action to be Taken
Day 0 to Discharge after the Index Cardiac Catheterization	Report AE/SAE that is considered related to the intracardiac mapping or cell delivery procedure to the unblinded interventional cardiologist, if possible; if not practical or if the unblinded interventional cardiologist is not available, contact the unblinded medical monitor
After Hospital Discharge	Report AE/SAE to the blinded medical monitor

As such, all non-fatal HF-MACE and fatal events (including TCEs) are to be assessed as potential primary and key secondary efficacy endpoints, respectively. The interventional cardiologist will inform the unblinded medical monitor of the adverse event.

- Each report of an adverse event on Day 0 through hospital discharge that is considered related to the intracardiac mapping or cell delivery procedure must be reported to the device manufacturer as well as to the unblinded medical monitor. For reporting of SAEs, see Section 7.1.6.3.
- medical device retention and adverse event inquiry: According to prespecified medical-device requirements for handling and retention of catheters, cardiac mapping, and cell delivery catheters used during index cardiac catheterization must be retained by the investigational site for 7 days after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with intracardiac mapping and cell delivery). Any device malfunctions during this interval must be documented and reported to the device manufacturer and the unblinded medical monitor, and the device must be returned to the device manufacturer for further evaluation. If no device malfunctions or adverse events are reported during this interval, the catheters must be disposed in accordance with procedures in place at the investigational site. For reporting of SAEs, see Section 7.1.6.3.
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA, and MI inquiry.

3.9.5.2 Day 10±3 Days (Visit 3) and Month 1±3 Days (Visit 4)

The following procedures/assessments will be performed at Day 10±3 days (Visit 3) and Month 1±3 days (Visit 4):

- body weight measurement
- symptom-directed physical examination
- review and recording of concomitant medications and therapy, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine.
- vital signs measurements (while patient is supine)
- clinical laboratory tests (serum chemistry and hematology)
- urinalysis
- blood sample collection for immunogenicity testing (test for PRA and antibodies against bovine or murine proteins; if test for PRA is positive, sample will be tested for DSA formation)

- ECG
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- 24-hour Holter monitor (randomized patients across the US and EU)
- adverse event inquiry (see Section 7.1)
- medical device safety reporting and adverse event inquiry: the occurrence of adverse events on or after Day 8 must be reported to the blinded HF specialist at the HF study site (see Section 7.1.6.3).
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA, and MI inquiry.

3.9.5.3 Months 2, 4, 5, 7, 8, 9, 10, and 11 (±14 days) (Telephone Contact)

Patients will be contacted by telephone at Months 2, 4, 5, 7, 8, 9, 10, and 11 (±14 days) to assess the following:

- review and recording of prior and concomitant medication and therapy, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine.
- adverse events inquiry (see Section 7.1)
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, CVA, and MI inquiry.

3.9.5.4 Month 3±7 Days (Visit 5) and Month 6±14 Days (Visit 6)

The following procedures/assessments will be performed at Month 3±7 days (Visit 5) and Month 6±14 days (Visit 6) unless otherwise stated:

- body weight measurement
- symptom-directed physical examination
- review and recording of concomitant medications and therapy, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine.
- vital signs measurements (while patient is supine)
- clinical laboratory tests (serum chemistry and hematology)
- urinalysis

- blood sample for immunogenicity testing (test for PRA and for antibodies against bovine or murine proteins; if the test for PRA is positive, sample will be tested for anti-HLA DSA formation)
- 2-D echocardiography (echo-qualified patients only); echocardiograms should be performed prior to or at least 30 minutes after the 6MWT or any other physical exertion; RVG is performed in subset of patients who did not achieve LVEF qualification as determined by 2-D echocardiogram during the screening period (note: if echocardiography with contrast is performed during screening, this modality should be used for all follow-up 2-D echocardiography. Patients who have an RVG at screening must continue with RVG scans for the duration of the study). RVG-qualified patients do not undergo RVG at month 3
- blood sample for biomarker evaluation (NT-proBNP and hsCRP)
- ECG
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- 24-hour Holter monitor (randomized patients across the US and EU) (not performed at Month 6)
- adverse event inquiry (see Section 7.1)
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA, and MI inquiry
- 6MWT (it is preferable to have the same technician perform the 6MWTs for the duration of the study)
- NYHA classification
- MLHF questionnaire
- EQ-5D questionnaire.

3.9.5.5 Month 12±14 Days (Visit 7)

The following procedures/assessments will be performed at Month 12±14 days (Visit 7) (Note: Patients who complete or withdraw from the study before or after the Month 12 follow-up visit will be evaluated at the time of study completion/withdrawal, using the same assessments that are specified for the Month-12 visit):

- full physical examination
- body weight measurement

- review and recording of concomitant medication and therapy, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine.
- vital signs measurement (while patient is supine)
- clinical laboratory (serum chemistry and hematology) tests
- urinalysis
- blood sample collection for immunogenicity testing (test for PRA and antibodies against bovine or murine proteins; if test for PRA is positive, the sample will be tested for anti-HLA DSA formation)
- 2-D echocardiography (echo-qualifying patients only); echocardiograms should be performed prior to or at least 30 minutes after the 6MWT or any other physical exertion; RVG is performed in the subset of patients who did not achieve LVEF qualification by 2-D echocardiography during the screening period (note: if echocardiography with contrast is performed during screening, this modality should be used for all follow-up 2-D echocardiography. Patients who have an RVG at screening must continue with RVG scans for the duration of the study)
- blood sample for biomarker evaluation (hsCRP and NT-proBNP)
- ECG
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- adverse events inquiry (see Section 7.1)
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA and MI inquiry
- 6MWT (it is preferable to have the same technician perform the 6MWTs for the duration of the study)
- NYHA classification
- MLHF questionnaire
- EQ-5D questionnaire.

3.9.6 Procedures for Long-term Follow-up

After the Month-12 visit, patients who are randomized and **DO** undergo index cardiac catheterization will have safety and efficacy evaluations performed every 6 months until study conclusion, as described in the sections below and Table 5. Note that text in the sections below is

carried through Month 60; however, the study will continue until the required minimum number of events has occurred.) Telephone contact will be made every 2 months between visits during the long-term follow-up period (at Months 14, 16, 20, 22, 26, 28, 32, 36, 38, 40 and every 2 months through Month 60).These long-term follow-up visits and telephone contacts will continue until study conclusion. Any patients who are randomized but **DO NOT** undergo the index cardiac catheterization must also be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times, for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

3.9.6.1 Months 14, 16, 20, 22, 26, 28, 32, 34 (±14 days) (Telephone Contact)

Patients will be contacted by telephone at Months 14, 16, 20, 22, 26, 28, 32, 34, 36, 38, 40 and every 2 months through Month 60 (±14 days) to assess the following:

- review and recording of prior and concomitant medication and therapy, including recent immunization and / or vaccines, for example: flu vaccine, pneumonia vaccine, shingles vaccine
- adverse events inquiry (see Section 7.1)
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted] CVA, and MI inquiry.

3.9.6.2 Evaluations at 18, 30, 42, 54 Months ±14 Days (Visits 8, 10, 12, and 14)

After Month 12, the following assessments will be performed every 12 months starting at Month 18 until the study concludes:

- body weight measurement
- symptom-directed physical examination
- review and recording of concomitant medication and therapy
- vital signs measurements (while patient is supine)
- clinical laboratory tests (serum chemistry and hematology)

- urinalysis
- ECG
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- adverse event inquiry (see Section 7.1)
- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA and MI inquiry
- 6MWT (it is preferable to have the same technician perform the 6MWTs for the duration of the study)
- MLHF questionnaire
- EQ-5D questionnaire.

3.9.6.3 Evaluations at 24,36, 48, 60 Months ±14 Days (Visits 9, 11, 13, 15)

The following assessments will be performed every 12 months from Month 12 (Visit 7) until the study concludes:

- full physical examination
- body weight measurements
- review and recording of concomitant medication and therapy
- vital signs measurements (while patient is supine)
- clinical laboratory tests (serum chemistry and hematology)
- urinalysis
- 2-D echocardiography in echo-qualifying patients; echocardiograms should always be performed prior to or at least 30 minutes after the 6MWT or any other physical exertion; RVG is performed in the subset of patients who did not achieve LVEF qualification as determined by 2-D echocardiography during the screening period (note: if echocardiography with contrast is performed during screening, this modality should be used for all follow-up 2-D echocardiography. Patients who have an RVG at screening must continue with RVG scans for the duration of the study).
- blood sample for biomarker evaluation (NT-proBNP and hsCRP)
- ECG
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- adverse event inquiry (see Section 7.1)

- HF-MACE evaluation
- overall survival assessment (alive or dead)
- coronary artery revascularization procedure, [redacted], CVA and MI inquiry
- 6MWT (it is preferable to have the same technician perform the 6MWTs for the duration of the study)
- NYHA classification
- MLHF questionnaire
- EQ-5D questionnaire.

Patients who complete the study or withdraw before or after the Month 12 visit will undergo final evaluations at the time of study completion or withdrawal or as soon as possible thereafter, using the same assessments that are specified for the Month 12 visit. An echocardiogram or RVG will also be performed if more than 6 months have passed since the patient's last echocardiogram or RVG. Procedures for patients who withdraw prematurely from the study are described in Section 4.3.

If a patient withdraws from the study during the treatment period, the reason must be determined and recorded on the patient's CRF (see Section 4.3). For patients who withdraw consent, every attempt will be made to determine the reason. Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.3, respectively.

3.9.7 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as other data obtained (*e.g.,* adverse events, concomitant medications and treatments, and results from procedures or tests).

4. SELECTION AND WIITHDRAWAL OF PATIENTS

4.1 Patient Inclusion Criteria

NOTE: Current entry criteria are included in the synopsis and main text of the protocol. In the trial, replaced and/or deleted entry criteria from the time the 1st patient was enrolled through the final amendment to this protocol are included in Section 17.

Patients may be included in the study only if they meet all of the following criteria:

a. The patient is 18 to 80 years of age, inclusive; both men and women will be enrolled.

b. **Inclusion criterion b was replaced by b1**
(b1) The patient has a diagnosis of chronic HF of ischemic or nonischemic etiology for at least 6 months before the initiation of screening procedures, with NYHA Functional Class II or Functional Class III symptoms. Chronic HF of ischemic etiology includes epicardial CAD, defined as documented stenosis of at least 50% in one or more major epicardial coronary arteries, documented prior coronary artery revascularization, and/or documented prior MI.

c. The patient is on stable, optimally tolerated dosages of HF therapies including beta-blockers (approved for country-specific usage), ACE inhibitors or angiotensin-receptor blockers (ARBs), and/or aldosterone antagonists and/or neprilysin inhibitor, without change in dose for at least 1 month prior to study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Details regarding HF therapies are provided in Section 5.3.

d. **Inclusion criterion d was replaced by d1**
(d1) The patient is on a stable, outpatient, oral diuretic dosing regimen in which the patient remains clinically stable during the screening period. Flexible diuretic dosing that allows the patient to titrate the dose or add a dose of a second diuretic during screening is permitted, provided that the dosing regimen is not further altered and the patient remains stable during this period) or the patient is not on a regular dose of diuretics but takes diuretics as needed based on daily weight or the appearance of symptoms.

e. The patient is not a candidate for either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery as determined by the Principal Investigator (or designee) during screening.

f. **Inclusion criterion f was replaced by f1**
(f1) The patient may be on the cardiac transplant list. However, he/she must have low priority status with low probability of having a transplant procedure performed over the next 12 months (*i.e.,* cannot be UNOS status 1A or 1B).

g. The patient has a LVEF as assessed by the Core Cardiac Imaging Laboratory of 40% or less as measured by 2-D echocardiogram, or 35% or less as measured by RVG within 42 days prior to study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Additional information about the assessment of baseline of LVEF is provided in Section 3.9.1.

h. **Inclusion criterion h was replaced by h1**
(h1) The patient has 1 or more of the following:
   - at least 1 HF hospitalization more than 1 month, but 9 months or less before initiation of screening procedures
   - at least 1 outpatient visit requiring IV diuretic, vasodilator, and/or positive inotropic therapy more than 1 month, but 9 months or less before initiation of screening procedures
   - plasma levels of NT-pro-BNP as measured by the central laboratory of greater than 1000 pg/mL (1000 ng/L SI units; 118 pmol/L) or 1200 pg/mL (1200 ng/L SI units; 141.6 pmol/L) for patients with atrial fibrillation

i. **Inclusion criterion i was replaced by i1**
(i1) If the patient has an ICD (or any implanted device capable of defibrillation) in place, the procedure must have occurred at least 1 month before initiation of screening procedures.

j. If the patient has had CRT, the procedure must have occurred at least 3 months before screening.

k. The patient has an LV end-diastolic wall thickness of at least 8 mm at the potential myocardial target site for cell injection.

l. Women must be surgically sterile, 1 year post-menopausal, or must have a negative urine or serum pregnancy test at screening.

m. **Inclusion criterion m1 was replaced by m2**
(m2) Women must be surgically sterile, 1 year post-menopausal, or, if of childbearing potential, currently using a medically accepted method of contraception, and must agree to continue to use this method of contraception after initiation of screening procedures and for 6 months after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Acceptable methods of contraception include barrier method with spermicide, abstinence, intrauterine device (IUD) (known to have a failure rate of less than 1% per year), or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. Men must be surgically sterile, or, if capable of producing offspring, currently using a medically accepted method of contraception and must agree to continue to use this method of contraception after initiation of screening and for 16 weeks after study intervention. Acceptable methods of contraception include abstinence, female partner's use of steroidal contraceptive (oral, implanted or injected) in conjunction with a barrier method, female partner's use of an IUD (known to have a failure rate of less than 1% per year), or if female

partner is surgically sterile or 1 year post-menopausal. In addition, men may not donate sperm for 16 weeks after study intervention.

n. The patient must be willing to return for required follow-up visits.
o. Written informed consent is obtained for the study before any study-specific procedures are performed. A separate written informed consent for the exploratory PGx substudy is obtained before any PGx-specific procedures are performed. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). A patient will not be excluded from participation in the study if he/she chooses not to provide consent for the additional procedures that are required as part of the exploratory PGx substudy.
p. Prior to the initiation of any procedures on Day 0, the cell injection center will ensure that an institution-specific informed consent document is obtained, if applicable.
q. The patient must be able to receive systemic anticoagulant therapy.

4.2 Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has NYHA Functional Class I or Functional Class IV symptoms.
b. The patient has had an acute MI within 1 month before initiation of the screening procedures.
c. The patient has unstable angina pectoris within 1 month before initiation of screening procedures; unstable angina is defined as the occurrence of chest pain more frequently than usual, pain at rest or upon minimal exertion, or protracted episodes of pain without any discernible trigger, and/or chest pain that persists despite use of vasodilatory therapy (*e.g.,* nitroglycerin) and or aggravation of stable angina or new onset angina.
d. The patient has peri-/postpartum cardiomyopathy.
e. The patient has ischemic or hemorrhagic stroke as diagnosed by CT or MRI within 3 months prior to study enrollment.
f. The patient has had coronary arterial or peripheral arterial revascularization procedure within 2 months before initiation of screening procedures.
g. The patient has had IV therapy with diuretic, vasodilator, and/or positive inotropes or aquapheresis within 1 month before initiation of screening procedures, and/or during the screening period.
h. **Exclusion criterion h was replaced by h1**

(h1) The patient, who in the absence of an ICD (or any implanted device capable of defibrillation), has a history of malignant ventricular arrhythmia or sustained ventricular tachycardia (VT), with sustained VT demonstrated by QRS complexes wider than 120 milliseconds, lasting more than 30 seconds, and with a rate of more than 100 beats per minute on screening ECG or other data supporting this diagnosis.

i. The patient has restrictive, obstructive, or infiltrative CM, pericardial constriction, amyloidosis, or uncorrected thyroid disease.

j. The patient has moderate to severe aortic stenosis as determined by the Core Cardiac Imaging Laboratory echocardiography-Doppler assessment with a valve area less than 1.0 cm^2.

k. The patient requires valve or other cardiac (*e.g.,* pericardectomy) surgery.

l. The patient has had LV reduction surgery, implanted LVAD, cardiac transplantation or artificial heart placement. The patient may be on the cardiac transplant list, but must have low probability of having a transplant procedure over the next 12 months.

m. The patient has an LV thrombus diagnosed by echocardiography, left ventriculogram, or other cardiac imaging.

n. The patient has cardiogenic shock that is dependent upon mechanical or inotropic support at the time of study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery), as defined by Killip Class IV physiology indicative of cardiogenic shock and/or requirement of intra-aortic balloon pump or IV inotropic support for the maintenance of mean arterial blood pressure at least 60 mmHg.

o. The patient is known to have unprotected left main coronary artery disease (CAD) greater than 50%.

p. **Exclusion criterion p1 was replaced by p2**
(p2) The patient has known hypersensitivity to radiocontrast media or dimethyl sulfoxide (DMSO), murine, and/or bovine products, with the exception of patients with mild hypersensitivity to radiocontrast media, who may be pretreated with corticosteroids and/or antihistamines.

q. The patient has a known active malignancy within the past 3 years except for localized prostate cancer, cervical carcinoma in situ, breast cancer in situ, or non-melanoma skin cancer that has been definitively treated.

r. **Exclusion criterion r was replaced by r1**
(r1) The patient has acute bacterial or viral infectious disease, or acute exacerbation of a chronic infectious disease at the time that Day 0 intervention is planned. However, patients with an upper respiratory infection diagnosed at screening that is

cleared by Day 0 (maximum of 42 days from signing of informed consent form) may undergo the procedure.

s. **Exclusion criterion s was replaced by s1**
(s1) Patients with severe chronic obstructive pulmonary disease (COPD) or patients who require home oxygen for any kind of pulmonary disease; home oxygen use as part of CPAP (continuous positive airway pressure) for the indication of sleep apnea in patients living at high altitude is permitted, and as-needed home oxygen use solely as therapy for HF is permitted. A patient with moderate COPD without severe RV dilatation and dysfunction on echocardiogram may be included in the study if they have a documented HF history that meets qualifying HF criteria. A patient who has a forced expiratory volume (FEV_1) in one second of less than 1.0 L will be excluded. A given patient will be excluded from serial echocardiographic imaging assessments if his/her heart is difficult to image adequately using standard precordial echocardiographic techniques. In that case, RVG estimations of LVEF will be used for screening inclusion criteria as well as for serial changes in overall cardiac performance after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Patients with clinically meaningful COPD will be excluded from serial 6MWT evaluations if their exercise limitation is thought to be due predominantly to their intrinsic pulmonary disease rather than from the patient's HF state.

t. The patient has a bleeding diathesis disorder such as abnormal coagulation profile, precluding study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

u. **Exclusion criterion u was replaced by u1**
(u1) The patient has 1 or more clinical laboratory test value(s) performed by the Central Clinical Laboratory that are outside the range for 1 or more of the tests specified below, or any other clinically significant abnormality as determined by the investigator or medical monitor as follows (note: repeat of suspected spurious lab abnormalities may be permitted after consultation with the medical monitor):
   - aspartate aminotransferase (AST/SGOT)/alanine aminotransferase (ALT/SGPT) greater than 3 times ULN range
   - total bilirubin greater than 1.5 times ULN
   - eGFR less than 30 mL/min/1.73 m^2 (calculated by the central clinical Laboratory using the MDRD formula); measures to minimize the risk of contrast-induced nephropathy will be taken at the discretion of the investigator
   - hemoglobin less than 9 g/dL

- platelets consistently less than $100 \times 10^3/mm^3$
- HbA1c of 10% or greater

v. The patient has any concurrent disease or condition that in the opinion of the investigator would make the patient unsuitable for participation in the study.

w. The patient has previously participated in any stem cell or regenerative medicine study, in which he/she received active agent.

x. The patient has received hematopoietic growth factors within 12 months preceding study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

y. **Exclusion criterion y was replaced by y1.**
(y1) The patient has had treatment and/or an uncompleted follow-up treatment of any investigational therapy within 6 months before study intervention and/or intends to participate in any other investigational drug or cell therapy study in the 3 years after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

z. The patient has hemodynamically compromised, complex congenital heart disease.

aa. **Exclusion criterion aa1 was replaced by aa2.**
(aa2) A patient with an ICD (or any implanted device capable of defibrillation) in place who has had a device firing within 1 month of Day 0.

bb. A patient has had angina on the average of more than 3 times per week.

cc. **New exclusion criterion.**
The patient completes two 6MWTs with either test a distance >450 meters during screening.

dd. **New exclusion criterion.**
The patient is unable to perform the 6MWT due to concurrent medical conditions; the exception is those patients with NT-proBNP >2000 pg/mL (2000 ng/L SI units; 236 pmol/L).

ee. **New exclusion criterion.**
The patient has an aortic valve prosthesis.

4.3 Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki, a patient may withdraw from the study at any time at his/her own request or at the discretion of the investigator or the Sponsor for safety, behavioral or administrative reasons. In addition, a patient may be withdrawn from the study as described in Section 3.6 and Section 5.4.

A patient reaching a primary non-fatal HF-MACE endpoint would not, by itself, be grounds for withdrawing a patient from the study as long as safety and efficacy can continue to be assessed and a reasonable comparison made to baseline. The Sponsor may terminate the study at any time, and for any reason, including by the recommendation of the DMC.

Patients are expected to participate in this study until the required number of recurrent non-fatal HF-MACE occur and all surviving patients without a TCE and without study discontinuation prior to the Month 6 visit have completed a minimum of 6 months of follow-up. The End-of-Study will occur when the two following conditions have been met: 1) at least 531 recurrent non-fatal HF-MACE have occurred, and 2) all surviving patients without a TCE who remain in the trial have completed a minimum of 6 months of follow-up.

Every effort should be made to contact a patient who does not return for a scheduled visit. In any circumstance, every effort should be made to document patient outcome (vital status), at a minimum, and reason for withdrawal from the study, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, and follow-up with the patient regarding any unresolved adverse event. The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to rexlemestrocel-L, the catheters used in index cardiac catheterization, or study procedure is made. The specific event or test result(s) must be recorded on the source documentation and transcribed onto the CRF.

Investigators should have a conversation with the patient regarding vital status follow-up, requesting that he/she continue to participate in the telephone contacts at the regularly scheduled study visit times for the duration of the study; it is important that this conversation be documented in the medical record. In the unusual circumstances of a patient withdrawing from the study and being lost to follow-up, the study site should make every possible effort to assess ongoing survival (i.e., vital status), at a minimum, at the time of study completion.

Should a patient decide to withdraw after administration of rexlemestrocel-L, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

If the patient withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected as part of the study. The Sponsor will retain and use any data collected before withdrawal of consent.

5. TREATMENT OF PATIENTS

5.1 Study Drug Administered

Following the screening procedures, patients who meet all entry requirements will be randomly assigned to receive active treatment (*i.e.,* intracardiac mapping and transendocardial delivery of rexlemestrocel-L) or control treatment (*i.e.,* a scripted sham cardiac mapping and cell delivery procedure without rexlemestrocel-L). Patients randomly assigned to the active treatment group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will receive 150 M transendocardially delivered rexlemestrocel-L during a single index cardiac catheterization by means of a specially designed injection catheter (MyoStar™ Injection Catheter) that is placed through a sheath that has been previously inserted into the femoral artery. This catheter is then advanced through the arterial system to the left ventricle. Transendocardial delivery into the myocardium will require the placement of the injection catheter needle into the left ventricular wall.

During the index cardiac catheterization, contrast left ventriculography as well as evaluations for stable myocardium will be performed. The latter will utilize either the NOGA® or CARTO®. Data will be generated to visualize and map myocardial locations that are potential targets for delivery of rexlemestrocel-L. After the completion of the mapping procedure, 15 to 20 appropriate myocardial sites will be identified (20 sites is ideal). The injection sites will be captured by NOGA® or CARTO® and transcribed into EDC. Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to the imaging identified myocardial locations; the total volume of study product administered should not exceed 4.0 mL. The total duration of the transendocardial delivery procedure must not exceed 90 minutes from the completion of thaw of rexlemestrocel-L. The cell delivery process should begin immediately after complete thaw of rexlemestrocel-L so that delivery is completed within 90 minutes of complete thaw. Additional details regarding the preparation and administration of rexlemestrocel-L are provided in the Pharmacy Manual and in Appendix 1 (NOGA®) and Appendix 3 (CARTO®).

A more detailed description of rexlemestrocel-L is given in Section 3.4.

Patients randomly assigned to the control group who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will undergo a scripted sham cardiac mapping and cell delivery procedure that includes index cardiac catheterization with left ventriculography. The sham cardiac mapping and cell delivery procedure will be staged to script and will not include actual cardiac mapping or transendocardial delivery of rexlemestrocel-L. Additional details regarding the scripted sham cardiac mapping and cell delivery procedure are provided in Appendix 2.

5.2 Restrictions

There are no restrictions in this study. The investigator should monitor patient during the course of the study and optimize HF therapy per clinical judgment.

5.3 Prior and Concomitant Therapy or Medication

All patients enrolled in this study will be on and maintain stable, optimally tolerated dosages of HF therapies including beta blockers (approved for country-specific usage), angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and/or aldosterone antagonists, without change in dose for at least 1 month before study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). The exception is use of diuretic therapy. The patient will be on a stable, outpatient, oral diuretic dosing regimen in which the patient remains clinically stable during the screening period. Flexible diuretic dosing that allows the patient to titrate the dose during this period is permitted, provided that the dosing regimen is not further altered and the patient remains stable during this period. Intermittent diuretic dosing for patients who are not on a regular stable dose of diuretic but who take diuretics as-needed based on daily weight or the appearance of symptoms is permitted, provided the patient fulfills all other study entry criteria. Beta blocker use at baseline must be consistent with local country treatment guidelines and in accordance with local regulatory approval for beta blocker and dose for the treatment of HF (Section 4.1).

Patients receiving systemic anticoagulation with either warfarin or a novel oral anticoagulant (NOAC) should have their systemic anticoagulation stopped for study product injection procedures. Local guidelines regarding management of periprocedural anticoagulation with or without bridging should be followed and documented.

Any prior or concomitant therapy or medication given to a patient from the initiation of screening procedures up to and including index cardiac catheterization on Day 0 will be

documented on the CRF. All concomitant therapy, medication, or therapy administered during the study will also be indicated on the CRF. Dosage and generic name or trade name will be indicated. The Sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug). Additionally, all patients enrolled in this study will be encouraged to remain on their cardiac rehabilitation program.
At each clinic visit after the screening visit, and at the Day 0 index cardiac catheterization, the investigator will ask the patient whether any medications, including over-the-counter medications, were taken since the previous visit, and any prior and concomitant medications reported will be recorded, including recent immunization and / or vaccinations such as the flu vaccine.

5.4 Procedures for Monitoring Patient Compliance

Each investigator will be responsible for monitoring patient compliance with study procedures.

5.5 Total Blood Volume

The timing of blood draws for clinical laboratory tests, immunogenicity testing, cardiac enzymes, and biomarker testing is provided in Table 4 and Table 5. In general, the total amount of blood volume drawn to perform these assessments will be 15 to 20 mL per visit (through the Month 12 visit) except for screening, when approximately 42.5 mL of blood volume will be drawn ([redacted]). For patients who complete the minimum follow-up per protocol (*i.e.,* 6 months), the total amount of blood volume drawn will be at least 110 mL. Patients who are followed beyond 12 months will have at least 10 to15 mL of blood drawn every 6 months until the study is completed.

6. ASSESSMENT OF EFFICACY

6.1 Primary Efficacy Variable

The primary efficacy measure and endpoint for this study is time from Day 0-to recurrent non-fatal HF-MACE, which consists of recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully resuscitated cardiac death events. The primary endpoint only considers HF-MACE that occur prior to the first TCE. However, all recurrent and terminal HF-MACE following non-fatal TCEs will be collected and adjudicated for sensitivity analysis based on different definitions of recurrent and TCEs. Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be

analyzed jointly with recurrent non-fatal HF-MACE within the JFM analysis. The following definitions apply to the TWO components of the primary endpoint:

- **Non-fatal decompensated HF event** will be adjudicated when the diagnosis of a non-fatal decompensated HF event demonstrates the presence of signs and symptoms consistent with clinical decompensation of the patient's HF state requiring an in-hospital stay or intravenous (IV) diuretic therapy or aquapheresis during an urgent care outpatient HF visit;
- **Successfully resuscitated cardiac death (RCD)** will be adjudicated when a subject experiences sudden death or cardiac death and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness or syncope and receive a successful appropriate shock from an implantable cardioverter-defibrillator with meaningful recovery will also be designated as RCD.

NOTE: Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be analyzed jointly with recurrent non-fatal HF-MACE within the Joint Frailty Model analysis. It is the intent that a "terminal cardiac event" occurs when the left ventricle (LV) is no longer functioning as an independent viable pumping chamber that provides pulsatile blood flow to the systemic circulation. Time from Day 0-to-first TCE is also a key secondary endpoint that will be evaluated using only TCEs. This analysis, which will be performed utilizing a proportional hazards model, will help assure that any improvement in recurrent non-fatal HF-MACE is not associated with worsening in time-to-terminal event for the Cell Therapy vs. Control (Sham) group. This analysis will provide assurance that any beneficial difference in recurrent non-fatal HF-MACE for the Cell Therapy vs Sham groups is not due to disproportionate early and/or late TCE rate for the Cell Therapy group.

Cardiac events that occur beginning on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths after time of randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

Adjudication of all potential non-fatal HF-MACE or TCEs will be performed by an independent, blinded CEC. Once the first TCE has occurred for a patient, subsequent TCEs and/or non-fatal HF-MACE for that patient will be excluded from the primary JFM analysis. All recurrent non-fatal HF-MACE and TCEs will be collected and adjudicated through end-of-study or patient's death for safety and sensitivity efficacy analysis purposes. (For details on the role and responsibilities of the CEC, please see the CEC Manual of Operations.)

Transendocardial delivery of rexlemestrocel-L into the myocardium will require the placement of the injection catheter needle into the left ventricle wall. In order to accomplish this procedure, there will be significant catheter manipulation within the LV chamber. This normally causes premature ventricular contractions (PVCs) and multiple brief episodes of nonsustained VT during the cardiac mapping and cell delivery procedure. These arrhythmias are usually self-terminated. Sustained ventricular arrhythmias such as VT or ventricular fibrillation (VF) may occasionally be triggered even in the normal heart. Because of the underlying pathology in patients who will be enrolled in this study (which specifies significant LV systolic dysfunction of either ischemic or non-ischemic etiology as an inclusion criterion), ventricular arrhythmias may be more pronounced and occur more often than in less ill patients. Because of the close association between ventricular arrhythmias due to LV catheter manipulation and the cell delivery procedure, the occurrence of sustained ventricular arrhythmias that may require cardioversion or defibrillation during index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 is expected and will not be considered a non-fatal HF–MACE. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

6.2 Secondary Efficacy Variables

6.2.1 Key Secondary Efficacy Variable

Time-to-first TCE will be evaluated as the single key secondary efficacy endpoint to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-TCE for the Cell Therapy vs. Control (Sham) group.

The key secondary endpoint relating to TCEs is as follows:

- Time from Day 0-to-first TCE (cardiac death, LVAD placement, heart transplant, or artificial heart implantation), whichever occurs first.

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control.

6.2.2 Secondary Efficacy Variables

Secondary efficacy variables of the study comprise the following:

- time-to-hospital admissions for decompensated HF events beginning on Day 1
- time-to-urgent care outpatient HF visits beginning on Day 1
- time-to-successfully RCD events beginning on Day 1
- total length of in-hospital stay in intensive care unit for decompensated HF events beginning on Day 1
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated HF, urgent care outpatient HF visits, and successfully RCD events
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated HF, urgent care outpatient HF visits, successfully RCD events, or TCE
- time-to-cardiac death
- time-to-all-cause death
- time-to-non-fatal MI, non-fatal CVA, or coronary artery revascularization, whichever comes first.

6.2.3 Other Secondary Efficacy Variables

Other secondary efficacy variables for this study relating to LV remodeling, functional exercise capacity, functional status, and QoL, and comprise the following:

- LV remodeling as assessed by change from baseline in left ventricular end-systolic volume (LVESV) as determined by 2-dimensional (2-D) echocardiography (echo-qualifying patients only).

Sensitivity analyses would, at a minimum, include the following:

  - Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE)
  - Correlations between baseline LVESV ≤100 mL and LVESV >100 mL and change in month 6 - baseline LVESV (increase or no change vs. decrease) and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE).

- LV remodeling as assessed by change from baseline in left ventricular end-diastolic volume (LVEDV) as determined by 2-D echocardiography (echo-qualifying patients only)
- LV systolic performance as assessed by change from baseline in left ventricular ejection fraction (LVEF)

- functional exercise capacity as assessed by change from baseline in distance covered during the 6-minute walk test (6MWT)
- functional status as assessed by change in New York Heart Association (NYHA) functional class
- QoL as assessed by change from baseline in the Minnesota Living With Heart Failure (MLHF) questionnaire score
- QoL as assessed by change from baseline in the EuroQol 5-dimensional Quality of Life (EQ-5D) questionnaire score.

6.2.3.1 Left Ventricular End-Systolic Volume

LVESV will be measured using 2-D-echocardiographic imaging without or with contrast enhancement in all patients who had echocardiographic qualification for LVEF inclusion criterion during screening. Sequential echocardiograms will be used to assess response to therapy. If required, patients will receive a suitable, IV echocardiographic contrast agent for optimal endocardial border definition; in cases where echocardiogram with contrast is performed to qualify the patient during screening, echocardiogram with contrast should be performed for sequential echocardiograms. Patients who are difficult to image or for whom a high quality echocardiogram is not possible to obtain at screening will not be considered as participants in long-term echocardiographic evaluations.

A highly experienced core echocardiography laboratory will be used to develop a standard echocardiography acquisition protocol, certify the technician at each site and provide standardized data analyses. At each site, it is preferable to have the same technician performing all echocardiograms for the duration of the study. For a given patient, echocardiography should be performed at approximately the same time of the day throughout the study, if possible. Please see the core cardiac imaging and echocardiography laboratory manual for more detailed information.

Follow-up echocardiograms will be performed for patients who are randomized and undergo the index cardiac catheterization as indicated in Table 4 and Table 5. Echocardiograms should be performed prior to or at least 30 minutes after the 6MWT or other significant physical exertion.

6.2.3.2 Left Ventricular End-Diastolic Volume

LVEDV will be measured using 2-D-echocardiographic imaging with or without contrast enhancement in all patients who had echocardiographic qualification for LVEF inclusion criterion. Sequential echocardiograms will be used to assess response to therapy.

6.2.3.3 Left Ventricular Systolic Performance as Assessed by Change from Baseline in Left Ventricular Ejection Fraction

Serial assessment of LVEF will be performed in selected patients using either echocardiographic imaging or RVG, depending upon which technique was used to qualify the patient during screening (Section 3.9.1) (note that while echocardiograms will be performed at the Month 3 Visit, RVGs are not performed until the month 6 visit during the follow-up period). Separate serial assessments will be performed for RVG and echocardiograms, as applicable. For RVG, LV end-diastolic and LV end-systolic counts will be determined in regions of interest. From these data, LVEF will be calculated as the difference in counts (*i.e.,* LVED counts minus LVES counts divided by LVED counts). The RVGs will be performed according to specified acquisition procedures agreed upon by the Sponsor and the designated core imaging laboratory. In order to maintain consistency across all sites, the equipment at each site will be qualified to ensure that the data are of sufficient quality for comparison. Qualified personnel who are blinded to the patient's specific clinical situation and method of treatment will read the images. All RVG-determined LVEF data will be analyzed and quantified by a highly experienced nuclear medicine core laboratory.

6.2.3.4 6-minute Walk Test

The distance covered during the 6MWT is the primary measurement. In order to ensure consistency across all investigative sites, a standardized procedure will be provided to each study site, with a standard methodology for performing the 6MWT for every patient (see Appendix 4 for 6MWT procedure). Patients will undergo the 6MWT twice during the screening period. Completion of these tests should be separated by at least 1 calendar day. At follow-up study visits, patients will undergo one 6MWT. The maximum value obtained during screening will be used for the baseline 6MWT distance value. At each study site, it is preferable to have the same assessor performing all 6MWTs on all patients for the duration of the study. If the patient is unable to perform the test, the reason for the test not being completed will be noted on the case report form. Note: Patients who complete two 6MWTs with either test a distance >450 meters during screening will be excluded from participation in the study. Also, patients who cannot perform the 6MWT due to concurrent medical conditions will be excluded (the exception is those patients with NT-proBNP >2000 pg/mL [2000 ng/L SI units; 236 pmol/L]).

6.2.3.5 New York Heart Association Functional Class

Patients with NYHA Classification of Functional Class II or III are characterized as presented in Table 8.

Table 8: New York Heart Association Functional Class

Class	Physician (or Designee) assessment of how the patient feels
I	No limitation of activity; no symptoms from ordinary activities.
II	Slight, mild limitation of activity, comfortable with rest or with mild exertion.
III	Marked limitation of activity, comfortable only at rest.
IV	Any physical activity brings on discomfort and symptoms occur at rest.

Source: Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th Ed. The Criteria Committee of the New York Heart Association. Boston, Mass: Little Brown, 1964.

6.2.3.6 Quality of Life as Assessed by Minnesota Living With Heart Failure Questionnaire

QoL will be measured using the MLHF questionnaire that will be completed by the patient.

The MLHF was originally designed in 1984 to measure the effects of HF and treatments on HF on an individual's QoL.[77] It is a populously applied disease specific instrument with its contents selected to be representative of the ways HF and treatments can affect the key physical, emotional, social and mental dimensions of life quality.

It detected beneficial effects on the daily life of patients treated with medications, devices disease management, rehabilitation as well as other types of interventions efficiently and reliably on most frequent and important aspects of quality of life impacted by HF, including physical and emotional influences.

This systematical and comprehensive tool has gained very high reputation in clinical trials and research studies in terms of reproducibility, internal consistency, content, and construct validity, responsiveness to changes, interpretability, precision, acceptability and feasibility.[77]

MLHF has strong correlations with NYHA classes and 6-minute walks as well as depression and anxiety, fatigue, patient and physician global assessments.[77]

To measure the effects of symptoms, functional limitations, psychological distress on an individual's quality of life, the MLHF questionnaire evaluates a total of 21 facets in questions using a 6-point Likert scale, ranging from 0 to 5, with 0 indicating 'No', 1 'Very Little' and 5 'Very Much' impact. The assessment can be administered via telephone or paper-pencil format very quickly, just 5 to 10 minutes.[78]

The questionnaire can be scored by summing the responses to all 21 questions, ranging from 0 to 105. The total score should be taken as the best measure of how HF and treatments impact an individual's life quality. In addition, a physical dimension score from 8 highly inter-related questions and emotional dimension score from another 5 inter-related domain questions have been identified by factor analysis and simple summation of the responses to these subgroups of questions may be applied for descriptive purpose.[77]

The MLHF, combined with EQ-5D, provide complementary evidence of heart status of patients with HF, which was more efficient in large scale population studies. See Appendix 5 for an example of the MLHF questionnaire.

The minimum important difference (MID) is a score point indicating the lowest clinically meaningful point in outcome measurement. The MID has been defined as the smallest change in a patient reported outcome (PRO) measure that is perceived by patients as beneficial or that would result in a change in treatment. An improvement of 5 points in the MLHF score was detected to be sufficient in clinical trials.[78]

The cut-off points of MLHF for QoL measurement were examined with high accuracy (91%).[79] A score of <24 on the MLHF represents a good QoL, a score between 24 and 45 represents a moderate QoL, and a score >45 represents a poor QoL. The indication of three levels of MLHF was recommended in clinical decision making.[79]

6.2.3.7 General Health Outcome as Assessed by EQ-5D Questionnaire

The general health status will be assessed by the EQ-5D questionnaire at Day 0 and at predefined time points during the study. The EQ-5D questionnaire is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the questionnaire provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care and population health surveys. The EQ-5D questionnaire has been specially designed to complement other patient reported outcomes measures, including disease-specific measures such as the MLHF questionnaire. The EQ-5D questionnaire is designed for self-completion by patients and is ideally suited for use in postal surveys, in clinics, and face-to-face interviews. In this study the instrument will be self-administrated during the predefined visits. It is cognitively simple, taking less than 5 minutes to complete. Instructions to respondents are included in the questionnaire. The EQ-5D questionnaire is specifically included to address concerns regarding the health economic impact

of HF and treatments for HF, which have been considered in cost effectiveness arguments. See Appendix 6 for the EQ-5D questionnaire.

A systematic review of literatures revealed a median MID in health utility from the EQ-5D of approximately 0.08. [80] Patients' health descriptive scores greater than this point are regarded as sizable improvement and clinically meaningful.

[redacted]

- biomarkers as assessed by changes from baseline in NT-proBNP and hsCRP

[redacted]

- PGx analyses to determine whether gene variants found in some patients will predict how they respond to rexlemestrocel-L therapy.

6.4 Methods and Timing of Assessing, Recording, and Analyzing Efficacy Data

Methods and timing of assessing efficacy data are discussed in Section 3.9. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.6.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by evaluating adverse events, clinical laboratory test results, vital signs measurements, concomitant medication and therapy usage, ECG, 24-hour Holter monitoring (randomized patients across the US and EU), echocardiographic, and physical examination results. In addition, important cardiovascular safety events will be reviewed from CEC-adjudicated data for all-cause death (including cardiac death) and hospitalizations for non-fatal decompensated HF, successfully RCD events, pre-specified ventricular arrhythmic events that do not fulfil criteria for positively adjudicated HF-MACE, non-fatal CVA, and non-fatal MI. Device interrogation will be performed for patients who have an ICD or any implanted device capable of defibrillation (device interrogation will be performed at regularly scheduled intervals by appropriate site personnel; see Table 4 and Table 5).

The Sponsor Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities. Additionally, an ESC, an independent CEC, and an independent DMC will be formed. For details, see Section 7.8.

For CEC details, please see the CEC Manual of Operations. For DMC details, please see the DMC Charter.

7.1 Adverse Events

7.1.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to rexlemestrocel-L, catheters used in index cardiac catheterization and cell delivery, or study procedures.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent document (including the informed consent form for the PGx substudy and the institution-specific informed consent document) should be processed and reported as an adverse event. As participation in the pharmacogenomics substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible), adverse event reporting will not be contingent on this consent. An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or any concurrent disease, whether or not considered related to rexlemestrocel-L, medical device, or study intervention. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as HF) that are present prior to study entry and do not worsen during the study will not be considered adverse events.

Accordingly, an adverse event could include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition, recorded as pre-existing, that is intermittently symptomatic [*e.g.,* headache] and which occurs during the study should be recorded as an adverse event.)

- drug interactions
- events occurring during diagnostic procedures or any washout phase of the study
- laboratory or diagnostic test abnormalities occurring after the start of the study (*i.e.,* after screening and once confirmed by repeat testing) that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant. **Note:** Abnormal laboratory test results during the screening period that preclude a patient from entering the study or from receiving study treatment are not considered adverse events, but will be recorded to monitor data from patients who do not meet screening criteria.

The only exception will be any serious event deemed related to the study medication by the investigator, which will be evaluated by the Sponsor Pharmacovigilance team as a potential suspected unexpected severe adverse reaction (SUSAR), even if it is potentially one of the above endpoints events.

7.1.2 Recording and Reporting Adverse Events

For the purpose of processing and reporting adverse events, the study period is defined as that time period from signature of the informed consent form (including the informed consent form for the PGx substudy and the institution-specific informed consent document) through the duration of the study. Enrollment in this study will end at or before the time that a minimum number of pre-specified recurrent non-fatal HF-MACE have been positively adjudicated and all surviving patients without a TCE and without study discontinuation have completed a minimum of 6 months of follow-up.

7.1.2.1 Investigational Product

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the investigational product. For SAEs, the Serious Adverse Event Form must also be completed, and the SAE must be reported immediately (see Section 7.1.6). The investigator does not need to actively monitor patients for adverse events once the study follow-up period has ended. If the investigator becomes aware of serious and related adverse events occurring after the study follow-up period should be reported to the Sponsor within 24 hours if the investigator becomes aware of them, following the procedures described in Section 7.1.6.3.

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or

medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the Serious Adverse Event Form and on the CRF.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to rexlemestrocel-L or study procedure is made. The onset and end dates, duration (in case of adverse event duration less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF. The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.2.2 Prespecified Medical Device Adverse Event Reporting Requirements

The medical devices used in this study (*i.e.,* NOGA® XP and the MyoStar™ Injection Catheter or CARTO® and the MyoStar™ Injection Catheter) have predefined safety-reporting requirements. In the event an AE/SAE has been assessed as related to one of the catheters used in the cardiac mapping and cell delivery procedure, Mesoblast Safety will forward the related AE/SAE to Biosense Webster within 30 calendar days from the event awareness date.

7.1.3 Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild	No limitation of usual activities
Moderate	Some limitation of usual activities
Severe	Inability to carry out usual activities

7.1.4 Relationship of an Adverse Event to the Investigational Product

The relationship of an adverse event to rexlemestrocel-L is characterized as follows:

Table 9: Definition of Adverse Event Relationship to Investigational Product

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to rexlemestrocel-L.	The relationship of an adverse event to rexlemestrocel-L may be considered to have no reasonable possibility if it is clearly due to extraneous cause(s) such as: • it does not follow a reasonable temporal sequence from the administration of rexlemestrocel-L. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
Reasonable possibility (related)	This category applies to those adverse events for which there is evidence to suggest a causal relationship between the drug and the adverse even after careful medical consideration at the time they are evaluated, a connection with rexlemestrocel-L administration was felt with a high degree of certainty to be related to rexlemestrocel-L.	The relationship of an adverse event to rexlemestrocel-L may be considered reasonable possibility related if: • it follows a reasonable temporal sequence from administration of rexlemestrocel-L and/or • convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

7.1.5 Relationship of an Adverse Event to the Medical Specialty Device

The occurrence of each adverse event must be assessed relative to the medical specialty device as follows:

Table 10: Definition of Adverse Event Relationship to Medical Specialty Device

Relationship of Adverse Event	Assessment	
Causal relationship to NogaStar® Mapping Catheter	No reasonable possibility (not related)	Reasonable possibility (related)
Causal relationship to MyoStar™ Injection Catheter	No reasonable possibility (not related)	Reasonable possibility (related)
Causal relationship to the pigtail catheter	No reasonable possibility (not related)	Reasonable possibility (related)
Causal relationship to specific catheter unknown	No reasonable possibility (not related)	Reasonable possibility (related)
Causal relationship to cardiac mapping procedure	No reasonable possibility (not related)	Reasonable possibility (related)
Causal relationship to cell delivery procedure	No reasonable possibility (not related)	Reasonable possibility (related)

Note: Catheter-specific relationship pertains to the unblinded AE form only.

7.1.6 Serious Adverse Events

7.1.6.1 Definition of a Serious Adverse Event

A SAE is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (*i.e.,* the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- in-patient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that inpatient hospitalization and/or prolongation of existing hospital stay occurred as a consequence of the adverse event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered SAEs (e.g., battery or generator replacement of an ICD device; social admission [i.e., patient has no place to sleep])
- a persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition; examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.
  Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

Serious criteria pertaining to hospitalization should include the following:

- Any formal inpatient admission (even if less than 24 hours).
- Chronic or long-term inpatient admission: transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit)

Serious criteria pertaining to hospitalization should NOT include the following:

- Emergency Room visits
- Outpatient/same-day/ambulatory procedures and observation/short- stay units
- Hospice facilities and Respite care (e.g., caregiver relief)
- Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities.

The study period for the purposes of serious advent event reporting is defined as the period from when the patient provides written informed consent to participate in the study (including the informed consent for the PGx substudy and the institution-specific informed consent document) until the patient completes the end of the follow-up period or withdraws from the study.

7.1.6.2 Expectedness

A SAE that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the rexlemestrocel-L Investigator Brochure.

For the most complete safety information, refer to the NogaStar® or CARTO® Mapping Catheter IFU and user manual.

The Sponsor Pharmacovigilance team will determine the expectedness for all SAEs.

7.1.6.3 Reporting a Serious Adverse Event

Investigator Responsibility

To satisfy regulatory requirements, all SAEs (as defined in Section 7.1.6.1) that occur during the study (including the protocol-defined follow-up period), regardless of judged relationship to treatment with rexlemestrocel-L, must be reported to the Sponsor by the investigator within 24 hours of when the investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day. To report the SAE, the investigator or designee will complete the SAE information electronically in the eCRF. When it is completed, Mesoblast Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible to access the eCRF, the investigator or designee should complete the backup paper SAE form and e-mail it at [redacted] to Mesoblast Safety with 24 hours of awareness. In case of difficulty transmitting the form, contact the Sponsor study personnel identified in the front of this protocol for further instruction. Following this process and reporting the event must not be

delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious and related adverse events that occur after the patient has completed or withdrawn from the study should be reported to the Sponsor if the investigator becomes aware of them.

For clinically important events that must be sent for adjudication, see Section 7.1.6.4.

The following information should be provided to record the event accurately and completely:

- study number MSB=MPC-CHF001
- investigator and study site identification
- patient number
- patient initials
- SAE(s)
- investigator's assessment of the relationship of the SAE to the study drug (no reasonable possibility or reasonable possibility)
- Additional information may include the following:
- age and sex of patient
- date of study drug administration
- date and amount of administered dose of study product
- onset date and end date of SAE
- description of clinical course of SAE
- action taken
- outcome if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory test data, or other diagnostic test data
- medical history
- if the adverse event results in death
  - cause of death (whether or not the death was related to study product)
  - autopsy findings (if available).

In the US, the investigator must ensure that the IRB is also informed of the event in accordance with local regulations.

In the European Union, the sponsor or its designee must ensure that the IEC is also informed of the event in accordance with local regulations.

Each report of a SAE will be reviewed and evaluated to assess the nature of the event and the relationship of the event to rexlemestrocel-L, study procedures, and to underlying disease. This will be done by the investigator and the Sponsor.

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the investigator or designee to the Sponsor Pharmacovigilance team by means of completing the information electronically in the eCRF within 24 hours of the information becoming available and following the same process as described above. When the eCRF is completed, Mesoblast Safety personnel will be notified electronically. If it is not possible to access the eCRF, the investigator or designee should complete the backup paper SAE form and e-mail it at [redacted] to Mesoblast Safety with 24 hours of awareness. In non-EU countries, SAEs should be reported by the Sponsor to investigators. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures.

Note: Although pregnancy is not a SAE, the process for reporting a pregnancy is the same as that for reporting a SAE, but using the pregnancy form.

Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to rexlemestrocel-L or the mapping/injection catheters, the Sponsor will take appropriate steps to determine and notify all investigators participating in sponsored clinical studies of rexlemestrocel-L and the appropriate regulatory authorities, if required.
In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing informed consent form and informing current study participants of new findings
- modifying listings of adverse drug reactions to include adverse events newly identified as related to rexlemestrocel-L
- The blinding will be maintained for the people who are involved directly in the study and will only receive blinded reports. In case of a SUSAR, only the unblinded team will have access to unblind the study treatment.

For a serious and unexpected adverse event considered related to rexlemestrocel-L or study procedures, the unblinded team will have access to unblind the study treatment (on a case by-

case basis) specifically for regulatory reporting purposes. If the treatment code is revealed for this reason, the blinded committees and study team (*e.g.,* the HF study site investigator, clinical scientists, CEC personnel, blinded CRO and Sponsor blinded Pharmacovigilance team), will remain blinded to treatment. In the case of an emergency, if it is necessary to know what treatment a patient has received, the investigator may determine the patient's treatment using IRT after consultation with the Sponsor. In an extreme emergency, if the investigator is unable to contact the Sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. For such an occurrence, the investigator must contact the individual identified in the clinical study personnel contact information section of this protocol immediately. Proper documentation must be maintained when a treatment code is revealed.

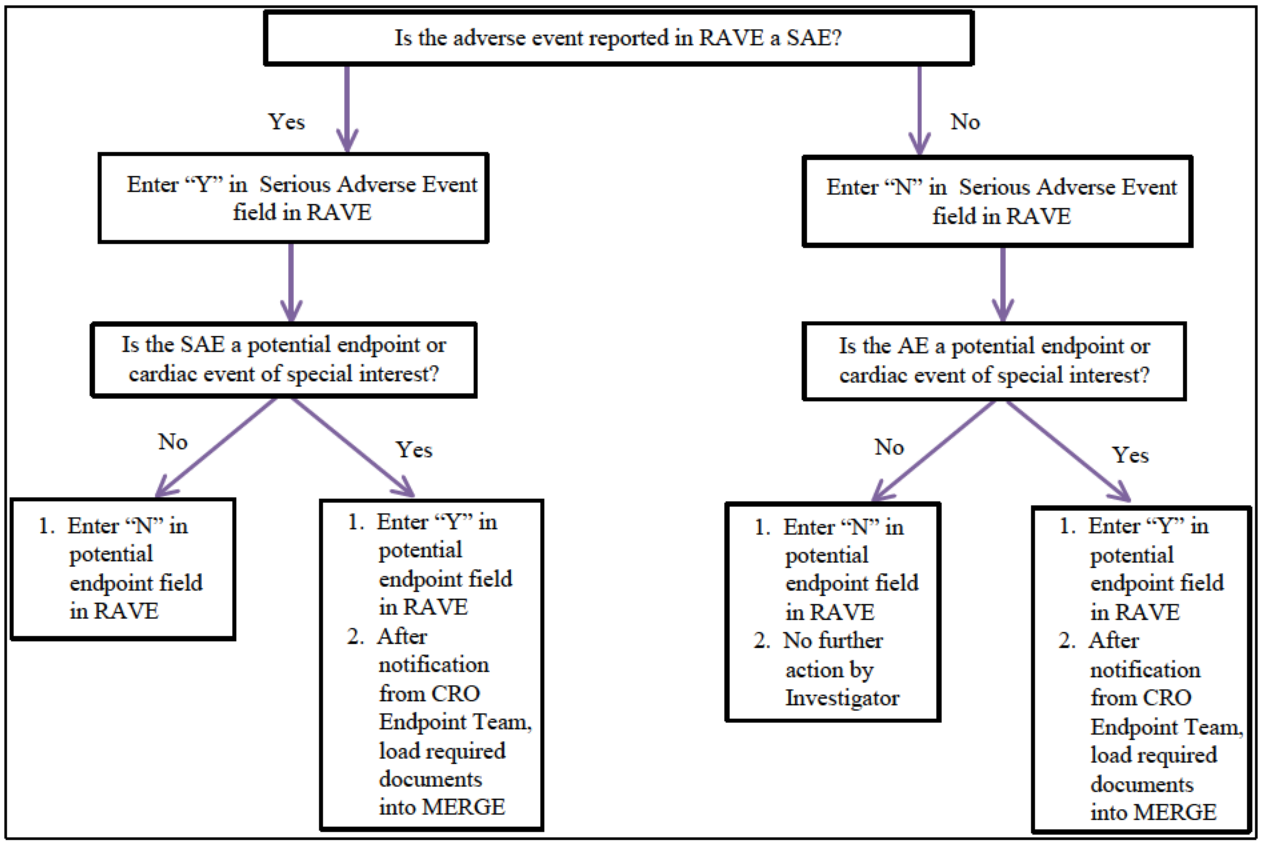
7.1.6.4 Reporting Events that are "Potential Endpoints"

Serious Adverse Event and Potential Endpoint Reporting by the Investigator

For the purposes of investigator reporting of AEs, the study period is defined as that time period from signature of the informed consent form through the duration of the study (Section 7.1.2). All events that meet the definition of a SAE (regardless of whether or not they are potential endpoints) are subject to SAE reporting at the time they are determined to be an adverse event by the investigator (Figure 8). If any cardiac event meets SAE criteria, the investigator must report the SAE to the Sponsor Pharmacovigilance team using the same process as described in Section 7.1.6.3 within 24 hours of when the investigator learns about the event or, if the event occurs on a weekend or national holiday, on the next working day.

In parallel, all events that are potential non-fatal HF-MACE, TCEs, or cardiac events of interest interest (regardless of whether they are serious or nonserious) are to be considered by the investigator as events for adjudication. All cardiac events after time of randomization onward that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system (Figure 8). Upon notification of the confirmation of the potential endpoint or cardiac event of special interest by the CRO Endpoint Team, the investigator uploads the required documents detailing the event into the MERGE system. The CEC will periodically review and positively or negatively adjudicate events in the MERGE system.

Figure 8: Investigator AE/SAE and Potential Endpoint Reporting



CRO=contract research organization.

Consideration of events as potential efficacy endpoints and SAEs by the investigator depends on the study time period (Table 11).

Table 11: Serious Adverse Event and Potential Endpoint Reporting by Study Period

Time Period	SAE Reporting by the Site to Mesoblast[a]	Send for Adjudication
Informed consent to Screening	Yes	No
Screening to randomization	Yes	No
Randomization to Day 0[a]	Yes	Yes
Day 0 (index cardiac catheterization)	Yes	Yes
Day 1 and throughout study	Yes	Yes

[a] SAE reporting by the site into RAVE and the eCRF as described in Section 7.1.6.3.

Note that any patients who are randomized but **Do NOT** undergo the index cardiac catheterization must be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at all regularly scheduled study visit times, including clinic visit times

(Table 4 and Table 5), for the duration of the study. Similarly, any patients who are randomized, **DO** undergo index cardiac catheterization procedure but discontinue the study after Day 0 will be followed for determination of vital status (alive or dead), AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points for the duration of the study. Every attempt should also be made to obtain, at a minimum, vital status from patients who withdraw consent to participate in the study after randomization.

Cardiac events that occur on Day 0 will be included in the primary efficacy endpoint if they meet the study's definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac deaths after the time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

In addition, a sensitivity analyses will be performed including: 1) all recurrent non-fatal HF-MACE and TCE from the time of randomization; 2) successfully RCD events as TCEs; 3) the primary efficacy analysis based on the full analysis set (FAS); and 4) recurrent non-fatal HF-MACE that occurred before and after the adaptation for enrichment and replenishment of baseline NYHA Class III patients (Section 9.6.4.1). Additional sensitivity analyses are detailed in the Statistical Analysis Plan (SAP) Version (V) 5.0.

If the cardiac event meets SAE criteria and is positively adjudicated as an efficacy endpoint by the CEC (i.e., either positively adjudicated as a recurrent non-fatal HF-MACE [the trial's primary efficacy endpoint] or positively adjudicated as a TCE [the trial's critical secondary endpoint]), the event is **NOT** captured as a SAE in the final clinical study report (Table 12). Cardiac events of special interest that are positively adjudicated by the CEC are not efficacy endpoints; all cardiac events of special interest meeting SAE criteria are to be captured as SAEs in the final clinical study report.

Summary of Cardiac Events and Process Flow After CEC Adjudication

Table 12 is a summary of potential non-fatal HF-MACE, TCEs, and cardiac events of special interest and classification of positively adjudicated events as SAEs or not in the final clinical study report.

Cardiac events of special interest are as follows:

- non-fatal myocardial infarction (MI)
- non-fatal cerebrovascular accident (CVA)/stroke
- coronary artery revascularization

[redacted]

Table 12: Summary of Cardiac Events for CEC Adjudication and Subsequent Process Flow

	Event Categories	Endpoint Event Categorizations	Cardiac Events for Adjudication by the Clinical Endpoints Adjudication Committee (CEC)	Following Positive Adjudication, is the Event a SAE in the Final Clinical Study Report?
Primary Efficacy Endpoints	**Non-FatalHF-MACE**[a]	Decompensated HF (Admitted to Hospital)	Yes	No
		Decompensated HF (Not Hospitalized/ Urgent Care Heart Failure Visit)	Yes	No
		Successfully Resuscitated Cardiac Death (RCD)	Yes 1. Successful Cardiopulmonary Resuscitation (CPR) 2. Appropriate ICD firing for VF 3. Appropriate ICD firing for VT associated with LOC/Syncope	No
Other Clinical Endpoints	**Terminal Cardiac Events (Key Secondary Endpoints)**[a]	Cardiac Death	Yes	No
		Cardiac Transplant	Yes	No
		Left Ventricular Assist Device (LVAD) Placed	Yes	No
		Artificial Heart Placement	Yes	No
	Events of Special Interest	Non-Fatal Myocardial Infarction (MI)[b]	Yes	Yes[e]
		Non-Fatal Cerebrovascular Accident (CVA)/Stroke[c]	Yes	Yes[e]
		Coronary Revascularization Procedure	Yes	Yes[e]
		[redacted]	Yes	Yes[e]

a. Joint Frailty Model Components for Recurrent Events Analysis (Non-fatal HF-MACE and TCEs); TCEs are considered critical secondary endpoints and therefore are NOT captured as SAEs in the final clinical study report. Non-fatal HF-MACE include recurrent non-fatal decompensated HF events and/or successfully resuscitated cardiac death (RCD) events. Terminal cardiac events include cardiac death, LVAD placement, heart transplant, or artificial heart implantation.
b. Episodes of Unstable Angina are adjudicated by the CEC but are not considered Events of Special Interest. They are considered SAEs if they meet SAE criteria.
c. Transient Ischemic Attacks (TIA) are adjudicated by the CEC but are not considered Events of Special Interest. They are considered SAEs if they meet SAE criteria.

[redacted]

e. Note that both positively and negatively adjudicated cardiac events of special interest are considered SAEs if they meet SAE criteria; they are NOT primary or secondary efficacy endpoints.

Definitions:

VF: Ventricular Fibrillation or Flutter rate greater than 250 beats/min with disorganized ventricular activity (or as set up by treating physician); VT: Ventricular Tachycardia with rate between 180 beats/min up to 250 beats/min (or as set up by treating physician); ICD: Implantable cardiac defibrillator; LOC: Loss of consciousness; SAE: Serious Adverse Event.

Note: Unstable angina will be adjudicated by the CEC but will not be counted as a cardiac event of special interest.

Sustained ventricular arrhythmias such as VT or VF may occasionally be triggered even in the normal heart by the procedures that will occur on Day 0. Because of the underlying pathology in patients enrolled in this study (which specifies significant LV systolic dysfunction of either ischemic or non-ischemic etiology as an inclusion criterion), ventricular arrhythmias may be more pronounced and occur more often than in less ill patients. Because of the close association between ventricular arrhythmias due to LV catheter manipulation and transendocardial delivery of rexlemestrocel-L, the occurrence of sustained ventricular arrhythmias that may require cardioversion or defibrillation during index cardiac catheterization on Day 0 is expected and will not be considered a non-fatal HF-MACE and, therefore, will be classified as serious adverse events. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart

transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary analysis and included in the key secondary analysis.

In accordance with Health Canada guidance 13-108409-403, serious adverse reactions that also represent primary efficacy endpoint events (*i.e.,* are positively adjudicated by the CEC) will not be subject to expedited reporting.

7.1.7 Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time. The patient will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the patient is referred to the care of a local health care professional. The investigator must inform the CRO as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event.

7.1.8 Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study product, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the Sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.8.

7.1.9 Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment for the emergency to protect patient safety has been administered, the investigator or other physician in attendance in such an emergency must contact the individual identified in the clinical study personnel

contact information section of this protocol, as soon as possible to discuss the circumstances of the emergency. The investigator, in consultation with the Sponsor, will decide whether the patient should continue to participate in the study. Any protocol deviation related to adverse events must be noted on the CRF and in source documents along with the reason for such deviations.

7.2 Pregnancy

Pregnancies that occur during the study are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the Sponsor Pharmacovigilance team with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.6.3).

All patients who become pregnant, and all female partners of male patients who become pregnant within 16 weeks of study intervention (Day 0), will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the Sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

All pregnancies that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the Sponsor, by facsimile, with a signed pregnancy tracking form. All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications will be reported to the Sponsor. Any complication of pregnancy will be reported as an adverse event or serious

adverse event, as appropriate. Because of potential unknown side effects of MPCs on the fetus, all female patients of childbearing potential must have a negative urine pregnancy test prior to study entry. In addition, women of childbearing potential are only included in study participation if they are willing to use adequate contraception (*e.g.,* barrier method with spermicide, abstinence, IUD, or steroidal contraceptive in conjunction with a barrier method) for a minimum of 6 months following study intervention.

7.3 Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator using the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening.

A laboratory test result that has significantly worsened (according to medical judgment) compared with the baseline result will be recorded on the CRF as an adverse event and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study or requires medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry and hematology) will be performed at screening, Days 0, 10, and Months 1, 3, 6, and 12, and every 6 months thereafter until study conclusion for long-term safety evaluations (for randomized patients who **DO** undergo the index cardiac catheterization). Clinical laboratory tests will be performed using the central core laboratory identified in the front matter of this protocol (and in the Laboratory Procedures Manual provided in the study file documents). Specific laboratory tests to be performed are listed in the following sub-sections.

7.3.1 Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- potassium
- chloride

- bicarbonate or carbon dioxide
- glucose
- HbA1c (at screening visit only)
- blood urea nitrogen (BUN)
- creatinine
- cholesterol
- uric acid
- ALT
- AST
- lactic dehydrogenase (LDH)
- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase
- creatine phosphokinase
- total protein
- albumin
- total bilirubin
- direct bilirubin.

In addition, cardiac enzyme assessments (troponin I, CK-MB0) will be performed at Day 0.

7.3.2 Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- platelet count
- white blood cell (WBC) count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils
  - monocytes
  - basophils.

In addition, PT, INR, PTT, and fibrinogen will be assessed at screening only.

7.3.3 Urinalysis

Urinalysis will be performed at screening and at all clinic follow-up visits thereafter until study conclusion. Urinalysis will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity.

If the urinalysis results are positive, then the following will be evaluated:

- microscopic bacteria
- RBCs
- WBCs
- casts
- crystals.

7.3.4 Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients.

7.3.4.1 N-terminal-pro B-type Natriuretic Peptide

N-terminal-pro-B-type natriuretic peptide (NT-proBNP) will be assessed at screening and postprocedure (Months 3, 6, and 12 and every 12 months thereafter for duration of the study) and used as a cardiac biomarker for changes in severity of HF.

7.3.4.2 High-sensitivity C-reactive Protein

Serial measurements of high-sensitivity C-reactive protein (hsCRP) will be assessed at screening and postprocedure as a nonspecific biomarker of inflammation.

7.3.4.3 Human Chorionic Gonadotrophin Tests

Urine or serum pregnancy tests will be performed for all women of childbearing potential at screening (Visit 1), on Day 0 (pre-procedure), and if clinically indicated thereafter.

7.4 Vital Signs

Vital signs will be measured as described in Table 4 and Table 5 Vital signs include the following:

- pulse
- supine blood pressure
- body temperature
- respiratory rate.

Before pulse and blood pressure are measured, the patient must be supine and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.5 Electrocardiography

Electrocardiography (including telemetry, rhythm analysis by 12-lead tracing, 24-hour Holter monitor [randomized patients across the US and EU], and device interrogation for patients who have an ICD or any implanted device capable of defibrillation [device interrogation will be performed at regularly scheduled intervals by appropriate site personnel]) will be performed as described in Table 4 and Table 5.

7.5.1 Telemetry

All randomized patients who **DO NOT** experience an inclusion/exclusion criterion violation after randomization but before the scheduled index cardiac catheterization will be hospitalized at the cell injection center for index cardiac catheterization (with or without intracardiac mapping and cell delivery) and will remain hospitalized on telemetry for a minimum of 1 night. Telemetry monitoring is both implied and standard of care. In the event of procedure-related cardiac arrhythmias, current ACC/AHA/ESC Practice Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented. Any telemetry finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.5.2 Electrocardiograms

A12-lead electrocardiogram will be performed, as described in Table 4 and Table 5, to evaluate QT and QTc (corrected) intervals using Fridericia (QTcF) and Bazett (QTcB) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QTcB, QT, QRS complex, PR interval, and heart rate) and waveforms (T waves) will be evaluated. The Day 0 pre-procedure and post-procedure ECGs will be read locally for clinical purposes and centrally for the database. A central diagnostic center identified in the front matter of this protocol will be responsible for providing interpretation of the ECG. Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.5.3 Holter Monitor Assessment

A 24-hour Holter monitor will be used to assess arrhythmias in patients enrolled at US and EU sites, as described in Table 4. The DMC will evaluate the data. For monitoring variables, see Table 13.

7.5.3.1 Ventricular Ectopy

Ventricular arrhythmias will be assessed in a subset of patients using a 24-hour Holter monitor. Patients will be monitored immediately after the index cardiac catheterization (Day 0) and then on Day 10 and Months 1 and 3. For monitoring variables, see Table 13.

7.5.4 Implantable Cardioverter Defibrillator

For patients with an ICD or any implanted device capable of defibrillation, rhythm analysis by device interrogation (performed at regularly scheduled intervals by appropriate site personnel; see Table 4 and Table 5) will be conducted. These episodes will be assessed at each site and captured as adverse events or non-fatal HF-MACE as appropriate. When a non-fatal HF-MACE or a TCE is suspected, the rhythm strips obtained by device interrogation and relevant clinical context will be provided to the CEC for their review and adjudication.

7.6 Physical Examinations

Full physical examinations (including height to be obtained at the screening visit only) and symptom-directed physical examinations will be performed as described in Table 4 and Table 5. Physical examination findings will be classified using standard categories as listed on the CRFs. Any physical examination finding that is judged by the investigator as a clinically significant

change (worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.6.1 Body Weight

Measurement of body weight will be performed at all clinic visits.

7.7 Other Safety Measures and Variables

7.7.1 Cardiovascular Safety Events

All serious cardiovascular safety events will be sent to the CEC for review and adjudication for the following:

- all-cause death
- non-fatal decompensated HF-MACE (hospitalized or not hospitalized)
- urgent care outpatient HF visit
- successfully RCD event
- TCEs (cardiac death, cardiac transplant, LVAD placement)
- non-fatal MI
- non-fatal CVA/stroke
- hospitalization for unstable angina
- coronary artery revascularization
- [redacted]

For details on the adjudication process, refer to Section 7.1.6.4 and the CEC charter.

7.7.2 Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored and recorded throughout the study as discussed in Section 5.3.

7.8 Methods and Timing of Assessing, Recording, and Analyzing Safety Data

Methods and timing of assessing safety data are discussed in Section 3.9. Procedures for recording safety data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.7.

Furthermore, all adverse events will be reviewed on a periodic basis (*e.g.,* scheduled safety reviews for study drug) as interim/preliminary safety databases become available (see Section 7).

7.8.1 Executive Steering Committee

The ESC, which is blinded to study treatment, will provide oversight for the operation of the study, including working with national leaders and local HF study site investigators to achieve goals for enrollment of patients into the study, reviewing recommendations from the project team for study conduct, and reviewing recommendations from the DMC for patient safety, and making a go/no-go decision based on recommendations presented by the independent and unblinded interim analysis statistician performing the planned IA2. This individual reviewed the results and informed the Sponsor, the DMC, and the trial's ESC of its findings relating to pre-defined HR thresholds. Throughout the IA2 process, the Sponsor remained blinded to the quantitative results and was informed only if the pre-defined HR thresholds were achieved. The IA2 output did not include an analysis for superiority or any other early stopping of the trial for success. Details regarding these interim analyses are available in the SAP V5.0 for this clinical study (Section 9.10).

7.8.2 Clinical Endpoints Committee

The independent **Clinical Endpoints Committee (CEC)**, which will be blinded to study treatment, will adjudicate all potential clinical events and survival in accordance with pre-specified criteria. The events for adjudication include all-cause deaths (i.e., including non-cardiac and cardiac death), LVAD placement, heart transplant, artificial heart implantation, hospitalization for non-fatal decompensated HF, urgent care outpatient HF visit, successfully RCD events, non-fatal MI, hospitalization for unstable angina, non-fatal CVA, coronary artery revascularization, and [redacted]

7.8.3 Data Monitoring Committee

The **Data Monitoring Committee (DMC)**, which will be unblinded to study treatment, will oversee the study with primary responsibility for ensuring patient safety. Specific goals and responsibilities of the DMC are outlined in the Data Monitoring Committee Manual of Operations. The DMC will review on a regular predefined basis the occurrence of adverse events including TCEs (cardiac death, LVAD placement, heart transplant, or artificial heart implantation), non-fatal HF-MACE (*i.e.,* decompensated HF events and/or successfully RCD events), overall survival, non-fatal CVA, non-fatal MI, and other [redacted]. The DMC will perform prespecified serial assessments of patient safety and monitor treatment effects to assess whether the objectives of the ongoing study can be met. Periodically, the DMC will conduct unblinded analyses of clinical events that have been adjudicated by the independent

CEC. Additionally, the DMC may formulate recommendations to the unblinded sponsor study team regarding the conduct and execution of the protocol as issues arise (see Blinding Plan for more information). The DMC will also review the results of IA2.

The independent DMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, including a statistician. The DMC will receive safety data periodically and will have the right to recommend discontinuation of the study for safety reasons, and will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

DMC sessions can be open or closed. During open sessions, representatives of the Sponsor and the ESC may be present, and blinded aggregate data will be provided. During closed sessions, the only participants are members of the DMC and the designated unblinded statistician (if approved to be present).

The DMC chairperson will communicate with the Sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The Sponsor will work closely with the DMC to provide any necessary data for review by the DMC.

Should the DMC identify any clinically important safety concerns, it will consider making recommendations relating to these findings to the health authorities, investigators, and IRBs.

As noted above in Section 7.8.1, for IA1 the DMC will make a recommendation to the ESC at each meeting of the DMC that occurs during the conduct of the trial to:

- continue with the study or
- terminate the study for futility or overwhelming efficacy.

As described in Section 7.8.1, the IA2 output will not include an analysis for superiority or any other early stopping of the trial for success.
Information about the planned interim analyses is provided in detail in Section 9.10.

7.8.4 Sponsor Pharmacovigilance Team

The Sponsor Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities. During the course of the study, SAEs and pregnancies will be

entered into a pharmacovigilance safety database, which will be separate from the clinical database. The pharmacovigilance safety database has restricted user access and is controlled.

For a serious adverse event considered related to rexlemestrocel-L or study intervention and unexpected per the IB, the Sponsor Pharmacovigilance team may request the unblinded PV team (CRO) to independently retrieve the treatment code (on a case-by-case basis) specifically for regulatory reporting purposes. If the treatment code is revealed for this reason, the blinded committees and study team (*e.g.,* the HF study site investigator, clinical scientists, CEC personnel) personnel will remain blinded to treatment.

8. [redacted]/PHARMACODYNAMICS/[redacted]

[redacted]

8.2 Pharmacodynamics

8.2.1 Cardiac Biomarkers

N-terminal-pro B-type Natriuretic Peptide

NT-proBNP will be assessed at screening and postprocedure (Months 3, 6, and 12 and every 12 months thereafter for duration of the study) and used as a cardiac biomarker for changes in severity of HF. [redacted]

8.2.2 Nonspecific Biomarkers

High-sensitivity C-reactive Protein

Serial measurements of hsCRP will be assessed at screening and postprocedure as a nonspecific biomarker of inflammation.

8.3 Immunogenicity

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-HLA DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who were randomized and underwent the index cardiac catheterization. All serum samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). serum samples of rexlemestrocel-L will be analyzed for anti-murine (MIgG) and anti-bovine (BSA) antibodies. The serum samples will be analyzed for the presence of antibodies (PRA, DSA, anti-murine antibodies, or anti-bovine antibodies) .

8.3.1 Panel-reactive Antibodies

The immunogenic potential of rexlemestrocel-L will be assessed by testing for the development of PRA. Blood serum samples to test for PRA will be collected during the screening period, on Day 10, at Months 1, 3, 6, and 12.

8.3.2 Anti-human Leukocyte Antigen Donor-specific Antibody Formation

If the test for PRA is positive, blood serum samples will be tested for the development of anti-HLA DSA formation.

8.3.3 Anti-murine and Anti-bovine Antibodies

Blood serum samples will be tested for anti-bovine and anti-murine antibodies (*i.e.,* BSA and MIgG).

8.4 Pharmacogenomics

The PGx study is voluntary for the patient and patients will have to give a separate consent to the sampling and storage. Refusal of patients to consent for this component does not exclude them from participation in the core clinical study. **However, submission of the PGx informed consent forms by participating sites to IEC/IRB is mandatory**. PGx assessment will be performed using blood samples taken at the screening visit (preferably) or any other visit following screening.

[redacted]

[redacted]

9. STATISTICS

9.1 Study Design and Randomization

This is a multicenter, double-blind, randomized, scripted sham-procedure-controlled, parallel-group study to evaluate the efficacy and safety of rexlemestrocel-L in patients with advanced chronic HF due to LV systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy. Patients will be randomly assigned to active or control groups in an 1:1 ratio, stratified by baseline NYHA Class (Functional Class II versus Functional Class III), geographic region (US versus ex-US) and presence of epicardial CAD (ischemic versus nonischemic); randomization will not be stratified by site.

Patient enrichment and replenishment will be performed such that by the end of the trial, the ratio of enrolled patients with baseline NYHA Class III to baseline NYHA Class II will be approximately 2:1. With this ratio, it is estimated that approximately 600 randomized patients will be needed to achieve a minimum of 531 recurrent non-fatal HF-MACE at the end of the trial. Based on current enrollment projections, at the end of the trial it is estimated that there will be ~200 baseline NYHA Class II patients and ~400 baseline NYHA Class III patients who have undergone the Day 0 index cardiac catheterization resulting in a baseline Class III/Class II ratio of 2:1. In order to achieve this target, an enrollment cap of ~200 baseline NYHA Class II patients will be instituted. It is anticipated that any baseline NYHA Class II patients who are inadvertently screened but not randomized during the suspension of NYHA Class II enrollment will be considered screen failures. The enrollment process will be overseen by the trial's

treatment blinded Medical Monitor in conjunction with current computer-generated randomization and interactive response technology (IRT) enrollment methodologies.

The enrichment for enrollment of patients with baseline NYHA Functional Class III status will have no effect on the pre-specified statistical methodologies for the primary efficacy analysis, secondary efficacy analyses, sensitivity analyses, or subgroup analyses**, which will all be conducted as planned**.

9.2 Sample Size and Power Considerations

This is an events-driven study. The sample size is based on Monte-Carlo simulations: 600 patients with an estimated total of at least 531 recurrent non-fatal HF-MACE defined as non-fatal decompensated HF events and/or successfully RCD events adjusted for TCEs. These non-fatal HF-MACE will provide approximately 93.5% power (with 91.4% for the low limit of 95% CI for the powers from all the simulations) at the 0.05 two-sided (0.025 one-sided) significance level to detect at least a 40% risk reduction (hazard ratio of 0.6) in recurrent non-fatal HF-MACE adjusted for TCEs. The simulations to determine the sample size were based on the following assumptions:

- overall recurrent event rate of 1.06 (based on the Phase 2 study data)
- median follow-up period of at least 2 years (patients who were enrolled early in the study and followed for recurrent non-fatal HF-MACE through to the end-of-study would have a follow-up period substantially longer than 2 years, unless they experience a TCE.

The assumption regarding terminal event rate was based on data from the Phase 2 (Study [redacted] and the ESSENTIAL study (which evaluated patients with entry criteria similar to the current study).[1] It was assumed that the TCE rate would be between 25% and 31% based on an approximate 2-year median follow-up (27% was used in the simulation for the sample size in the current study). This sample size of 600 patients also considers and includes the potential 4% patient drop-out rate during the study.

Two planned interim analyses were completed (Section 9.10).

9.3 Analysis Sets / Populations

9.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all patients randomly assigned to treatment (active or sham). In this population, treatment will be based on the treatment to which patients were randomly assigned regardless of which treatment they actually received.

9.3.2 Safety Population

The safety population will include all patients in the ITT population who underwent Day 0 index cardiac catheterization and in whom the interventional cardiologist was able to advance the pigtail catheter across the aortic valve and into the LV chamber. In this population, treatment (active or sham) will be based on the treatment patients actually received regardless of the treatment to which they were randomly assigned.

9.3.3 Full Analysis Set

The definition of the full analysis set (FAS) is the same as that for the safety population.

9.3.3.1 Echo-Qualifying Patients

The echo-qualifying patients are those in FAS who have a baseline 2-D echocardiography assessment.

[redacted]

9.4 Data Handling Conventions

Details of censoring rules and event-recording conventions for time-to-recurrent event analyses are provided in the SAP V5.0.

The details for data imputation rules (missing data) are also described in the SAP V5.0 as appropriate.

9.5 Study Population

The ITT population (see Section 9.3) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group (active or sham) and for all patients.

9.5.1 Patient Disposition

The number of patients screened as well as the number of patients screened but not randomized (screen failures with reason) will be summarized in total.

Data from patients who are randomized (ITT), randomized but not treated, randomized and undergo an incomplete index cardiac catheterization, randomized and discontinue the study and/or withdraw consent, patients in the safety population, patients in the FAS, patients in other sensitivity analysis sets, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

By-subject disposition listings will be provided for all patients in the ITT population, patients who were randomized but did not receive treatment, and patients who were randomized but did not complete the index cardiac catheterization.

9.5.2 Demographic and Baseline Characteristics

Demographics including age, age group (< 65, ≥65), race as collected, race group (white, black and others including missing race), ethnicity, gender, and geographic region (US or ex-US), diagnosis of diabetes mellitus at baseline, weight, height, and BMI will be summarized using descriptive statistics. The summary will be presented for all analysis set/populations [ITT and safety populations, FAS, echo-qualifying patients, and [redacted]

Baseline characteristics including baseline NYHA, substance usages (alcohol and tobacco), and current menopausal status will be summarized using descriptive statistics.
Missing categories will be presented if necessary.

9.5.3 Cardiovascular History and Surgery

Cardiovascular history data including cardiomyopathy etiology (ischemic or non-ischemic), past MI, number of MIs, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), discharge of subject's implantable cardioverter defibrillator (ICD) within 28 days of study

procedure, ventricular tachycardia, and ventricular fibrillation will be summarized using descriptive statistics.

Year(s) of each CABG procedure, year(s) of each intervention, and years of ventricular fibrillation event(s) will be listed.

Number of patients with surgery/transplant will be summarized using descriptive statistics.

9.5.4 General Medical History

Patients with a general medical history assessment, patients with at least 1 abnormal finding, and abnormal findings for each category will be summarized using descriptive statistics.

9.5.5 Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug Dictionary Version March 2013). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug treatment.

9.5.6 Protocol Violations

Patients with at least 1 protocol violation for each category will be summarized using descriptive statistics.

9.5.7 Childbearing Potential

For female patients information related to childbearing potential, contraception, and menopause will be collected during the screening period of the trial. The data will be listed.

9.6 Efficacy Analysis

Efficacy analyses will be performed on the ITT population unless otherwise indicated. Summaries will be presented by treatment group as randomized/assigned unless otherwise specified.

Day 0 Definition: Day 0 for all time-to-event analyses is defined as follows:

1. For patients who are randomized but **DO NOT** undergo the index cardiac catheterization as the date of the disqualifying event (*i.e.,* violation of at least one inclusion/exclusion criteria);
2. For patients who are randomized and **DO** undergo the index cardiac catheterization as the date of index cardiac catheterization.

9.6.1 Primary Efficacy Endpoint

The primary efficacy measure and endpoint for this study is time-to recurrent non-fatal HF-MACE, which consists of recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully resuscitated cardiac death events. The primary endpoint only considers non-fatal HF-MACE that occur prior to the first TCE. However, all recurrent and terminal HF-MACE following non-fatal TCEs (e.g., LVAD implantation) will be collected and adjudicated for sensitivity analysis based on different definitions of recurrent and TCEs. The following definitions apply to the TWO components of the primary endpoint:

- **Non-fatal decompensated HF event** will be adjudicated when the diagnosis of a recurrent non-fatal decompensated HF event demonstrates the presence of signs and symptoms consistent with clinical decompensation of the patient's HF state requiring an in-hospital stay or intravenous (IV) diuretic therapy or aquapheresis during an urgent care outpatient HF visit;
- **Successfully resuscitated cardiac death (RCD)** events will be adjudicated when a subject experiences sudden death or cardiac death and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness (LOC) or syncope and receive a successful appropriate shock from an implantable cardioverter-defibrillator with meaningful recovery will also be designated as successful RCD event. These events will be considered recurrent (non-terminal) events for the purpose of the primary efficacy analysis, and will be considered terminal events in sensitivity analyses.

NOTE: Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be analyzed jointly with recurrent non-fatal HF-MACE within the Joint Frailty Model analysis. It is the intent that a "terminal cardiac event" occurs when the left ventricle (LV) is no longer functioning as an independent viable pumping chamber that provides pulsatile blood flow to the systemic circulation. Time from Day 0-to-first TCE is

also a key secondary endpoint that will be evaluated using only TCEs. This analysis, which will be performed utilizing a proportional hazards model, will help assure that any improvement in recurrent non-fatal HF-MACE is not associated with worsening in time-to-terminal event for the Cell Therapy vs. Control (Sham) group. This analysis will provide assurance that any beneficial difference in recurrent non-fatal HF-MACE for the Cell Therapy vs Sham groups is not due to disproportionate early and/or late TCE rate for the Cell Therapy group.

Cardiac events that occur on Day 0 will be included in the primary endpoint if they meet the definition of a recurrent non-fatal HF-MACE and are positively adjudicated as per the Cardiac Adjudication Manual. Cardiac deaths that occur on Day 0 will be considered as a TCE. All cardiac events after time of randomization that are deemed potential endpoints by the investigator will be reported by the investigator in the RAVE system. All cardiac deaths post randomization are considered a TCE. The first TCE (cardiac death, LVAD implantation, heart transplant, artificial heart placement) for a patient that occurs after randomization will be adjusted for in the primary efficacy analysis and included in the key secondary analysis.

Adjudication of all potential non-fatal HF-MACE will be performed by an independent, blinded CEC. Once the first TCE has occurred for a patient, subsequent TCEs and/or non-fatal HF-MACE for that patient will be excluded from the primary efficacy analysis. All recurrent non-fatal HF-MACE and TCEs will be collected and adjudicated through end-of-study or patient's death for safety and sensitivity efficacy analysis purposes. (For details on the role and responsibilities of the CEC, please see the CEC Manual of Operations.)

The details of the primary efficacy analysis are presented in Section 9.6.4.1.

9.6.2 Secondary Efficacy Endpoints

9.6.2.1 Key Secondary Efficacy Endpoint Relating to Terminal Cardiac Events

Time from Day 0 (defined in Section 9.6)-to-first TCE will be evaluated to assure that any improvement in recurrent non-fatal HF-MACE is not associated with the worsening in time-to-TCE for the Cell Therapy vs. Control (Sham) group.

The key secondary endpoint relating to TCEs is as follows:

- Time from Day 0-to-first TCE (cardiac death, LVAD placement, heart transplant, or artificial heart implantation), whichever occurs first.

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control.

9.6.2.2 Secondary Efficacy Endpoints

Additional secondary efficacy endpoints of the study comprise the following:

- time-to-hospital admissions for non-fatal decompensated HF events beginning on Day 1
- time-to-urgent care outpatient HF visits beginning on Day 1
- time-to-successfully RCD events beginning on Day 1
- total length of in-hospital stay in intensive care unit for decompensated HF events beginning on Day 1
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated HF, urgent care outpatient HF visits, and successfully RCD events
- time-to-first major cardiac event defined as a composite of hospital admissions for decompensated heart failure, urgent care outpatient HF visits, successfully RCD events or TCE
- time-to-cardiac death
- time-to-all-cause death (overall survival)
- time-to-non-fatal MI, non-fatal CVA, or coronary artery revascularization, whichever comes first.

9.6.2.3 Other Secondary Efficacy Endpoints (e.g, LV Remodeling, Functional Exercise Capacity, Functional Status, QoL)

Other secondary efficacy variables relate to LV remodeling, functional exercise capacity, functional status, and QoL, and include the following:

- LV remodeling as assessed by change from baseline in LVESV as determined by 2-D echocardiography (echo-qualifying patients only) at Months 3, 6, and 12 and every 12 months thereafter until study conclusion.

Other endpoint analyses would include the following:

- Association between baseline LVESV ≤100 mL and LVESV >100 mL and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE)
- Association between baseline LVESV ≤100 mL and LVESV >100 mL and change in month 6 - baseline LVESV (increase or no change vs. decrease) and clinical outcomes (including recurrent non-fatal HF-MACE and/or TCE).
    - LV remodeling as assessed by change from baseline in LVEDV as determined by 2-D echocardiography (echo-qualifying patients only) at Months 3, 6, and 12 and every 12 months thereafter until study conclusion
    - LV systolic performance as assessed by change from baseline in LVEF at Months 3, 6, and 12 and every 12 months thereafter until study conclusion

- functional exercise capacity as assessed by change from baseline in distance covered during the 6MWT at Months 3, 6, and 12 and every 6 months thereafter until study conclusion
- functional status as assessed by change from baseline in NYHA Functional Class at Months 3, 6, and 12 and every 12 months thereafter until study conclusion
- QoL as assessed by change from baseline in the MLHF questionnaire score at Months 3, 6, and 12 and every 6 months thereafter until study conclusion
- QoL as assessed by change from baseline in the EQ-5D questionnaire score at Months 3, 6, and 12 and every 6 months thereafter until study conclusion.

[redacted]

- biomarkers as assessed by changes from baseline in NT-proBNP and hsCRP

[redacted]

- PGx analyses to determine whether gene variants found in some patients will predict how they respond to rexlemestrocel-L therapy.

9.6.4 Planned Method of Analysis

9.6.4.1 Primary Efficacy Analysis

The primary efficacy endpoint for this study is time from Day 0-to-recurrent non-fatal HF-MACE, which consists of recurrent (multiple events per patient) non-fatal decompensated HF events and/or successfully resuscitated cardiac death events. Day 0 is defined in Section 9.6. The primary endpoint only considers non-fatal HF-MACE that occur prior to the first TCE. However, all recurrent and recurrent and terminal HF-MACE following non-fatal TCEs (e.g., LVAD implantation) will be collected and adjudicated through end-of-study or patient's death for safety and sensitivity efficacy analysis purposes. Terminal cardiac events (defined as a composite of cardiac death, LVAD placement, heart transplant, or artificial heart implantation) are not a direct component of the primary efficacy endpoint. Rather, they will be analyzed jointly with recurrent non-fatal HF-MACE within the Joint Frailty Model (JFM) analysis.

The primary efficacy analysis will be based on ITT population. As a supportive sensitivity analysis, the primary efficacy analysis will also be performed based on the FAS (see Section 9.3.3 for definition of FAS). The details of all sensitivity analyses of the primary efficacy endpoint are described in the SAP V5.0, Section 8.4.6. All will use methods similar to that described for the primary analysis, unless otherwise stated.

The key sensitivity analysis will be performed for baseline NYHA Class III only patients. The statistical methodology for this sensitivity analysis will be exactly the same as for the primary analysis.

Adjustment for baseline NYHA Class (Functional Class II versus Class III), geographic region (US versus ex US), presence of epicardial CAD (ischemic versus nonischemic), use of ICD (any type), and use of CRT/CRT-D as covariates in the model may be utilized for sensitivity analysis purposes. The JFM provides two related quantified measures of comparison between treatment groups (two hazard ratios, one for recurrent non-fatal HF-MACE and one for TCEs, respectively) taking into account the risk of recurrent clinical events confounded by the competing risk of terminal events.

The treatment effect estimate (hazard ratio [active versus control] for recurrent non-fatal HF-MACE), its 95% confidence interval, and p-value will be calculated using the Joint Frailty Model.

Censoring indicator rules for recurrent non-fatal HF-MACE or TCEs are described in the SAP V5.0, Section 8.2.1. Only the first TCE for a patient is accounted for in the JFM; for example, if a patient had an LVAD implanted followed by a heart transplant or an artificial heart implantation during the study, only the LVAD procedure will be considered a TCE for the purpose of the primary analysis. Patients lost to follow-up before experiencing any non-fatal HF-MACE will be censored at the time of last assessment/contact. For all recurrent non-fatal HF-MACE and TCEs, inclusion in the analyses begins at randomization.

The null hypothesis is defined as no difference between active treatment and placebo in risk of recurrent non-fatal HF-MACE, HR=1. The alternative hypothesis is that there is such a difference, HR $\neq$1. The null hypothesis H0 will be rejected at the final analysis if 2-sided p-value obtained at the final analysis is less than the pre-specified two-sided of 0.05.

To graphically illustrate the primary endpoint analysis, the mean cumulative rate (MCR) for recurrent non-fatal HF-MACE including decompensated HF events (hospitalizations and urgent care HF visits) and successfully RCD over time, adjusted for TCEs, will be estimated and plotted by treatment group, i.e., rexlemestrocel-L and control. Details are provided in the SAP V5.0, Section 8.4.4.

Subgroup analyses will be performed for the primary endpoint in the manner analogous to the primary analysis:

- Baseline NYHA class (Functional Class II versus Functional Class III); Baseline Functional Class III analysis is the key sensitivity analysis for the primary endpoint
- Gender (male, female)
- Race (white, black, other)
- Ethnicity (depending on the outcome of a blinded data review)
- Geographic region (US versus ex-US)
- Presence of epicardial coronary artery disease (CAD; ischemic versus non-ischemic)
- Baseline diagnosis of diabetes mellitus (yes; no)
- Subjects with ICD (any type) vs. those without ICD
- Subjects with CRT/CRT-D vs. subjects without CRT/CRT-D.

The analyses will be based on both ITT (primary) and FAS (sensitivity) populations.

9.6.4.2 Key Secondary Efficacy Analysis

The key secondary efficacy analyses will be performed on the ITT and FAS populations. The time from Day 0-to-first TCE analysis will be performed using the proportional hazards model to compare treatment groups. The Kaplan-Meier curves by treatment group will be generated. The patients without TCEs will be censored at the end-of-study (censoring indicator=0).

One sensitivity analysis will be performed with baseline NYHA Class, baseline NT-proBNP and baseline ESV as covariates. Covariate by treatment interactions will be explored. Another sensitivity analysis using Cox proportional hazards regression model with treatment as the main effect adjusting for NYHA Class (Functional Class II versus Class III), geographic region (US versus ex US), presence of epicardial CAD (ischemic versus nonischemic), use of ICD (any type), and use of CRT/CRT-D as covariates in the model will also be performed.

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control. Details of this analysis are provided in the SAP V5.0, Section 8.5.3.

9.6.4.3 Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the ITT Population.

Analysis of Time-to-Hospital Admissions for Non-Fatal Decompensated HF Events after Day 1

Multiple hospital admissions for non-fatal decompensated HF beginning on Day 1 are considered as recurrent events. The index hospitalization will be excluded from this analysis. This analysis will be performed using the Joint Frailty Model in a manner analogous with the methods described in Section 9.6.4.1, with the hospital admissions considered recurrent events; the TCEs are defined identically to that in the primary analysis.

Analysis of Time-to-Urgent Care Outpatient HF Visits After Day 1

Multiple hospital admissions or urgent care outpatient HF visits are considered as recurrent events. Total hospital admissions or urgent care outpatient HF visits beginning on Day 1 will be analyzed in a manner analogous with the methods described in Section 9.6.4.1. The index hospitalization will be excluded from this analysis.

Analysis of Time-to-Successfully Resuscitated Cardiac Death Events

The time from Day 0-to-first RCD analysis will be performed using the proportional hazards model to compare treatment groups. The Kaplan-Meier curves by treatment group will be generated. Any patients without RCD will be censored at the end-of-study.

Analysis of Total Length of In-Hospital Stay in Intensive Care Unit for Decompensated HF

The total length of in-hospital stay in intensive care unit for non-fatal decompensated HF beginning on Day 1 will be calculated in days from each stay. Multiple admissions per patients will be accounted for. The data will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect adjusting for baseline NYHA Class (Functional Class II versus Class III), geographic region (US versus ex-US), presence of epicardial CAD (ischemic versus nonischemic), use of ICD (any type), and use of CRT/CRT-D as covariates in the model.

Time-to-First Major Cardiac Event

Time-to-first major cardiac event (each of the secondary composite endpoints in Section 9.6.2.2) will be analyzed using a Cox proportional hazards regression model with treatment as the main effect. Adjustment for baseline NYHA Class (Functional Class II versus Class III), geographic region (US versus ex US), presence of epicardial CAD (ischemic versus nonischemic), use of ICD (any type), and use of CRT/CRT-D will be performed using these covariates in the model. The time to-event will be presented graphically by Kaplan-Meier curves stratified by treatment group. For patients with no clinically important major cardiac event, their time-to-event will be censored at their last follow up date.

[redacted]

Analysis of Total Successfully Resuscitated Cardiac Death Events

Total successfully resuscitated cardiac deaths will be analyzed as a categorical variable with patient counts and percentages provided. The Cochran-Mantel-Haenszel test stratified by NYHA class at Baseline will be utilized to compare treatment groups.

Analysis of Time-to-Non-fatal MI, Non-fatal CVA, or Coronary Artery Revascularization

This is a time-to-first event analysis with the event defined as a composite of non-fatal MI, non-fatal CVA, coronary artery revascularization, whichever occurs first, and that occur beginning on Day 1. Data will be analysed in the manner analogous to the analysis described in above for time-to-first major cardiac event.

For patients who do not experience any of the above-listed events at the time of analysis, their time to event will be censored at the date of their last follow-up/contact.

9.6.4.4 Analyses of Other Secondary Efficacy Endpoints

All continuous secondary variables of change from baseline at Months 3, 6, and 12 and every 6 or 12 months thereafter until study conclusion will be analyzed using a mixed model for repeated measures (MMRM) including treatment, visit, and treatment-by-visit as fixed factors, and patient as a random factor. The covariates to the model will be baseline value for the endpoint being analyzed, NYHA Class (Functional Class II versus Functional Class III), geographic region (US versus ex-US), presence of epicardial CAD (ischemic versus nonischemic), use of ICD (any type), and use of CRT/CRT-D. An unstructured covariance matrix will be used for the within-patient correlation. Treatment comparison at each visit will be made using appropriate contrast statement under this model. Data collected after Month 60 will be summarized descriptively only. Baseline is defined as the data value obtained at screening.

The potential association between TCEs and LVESV, LVEDV, LVEF, 6MWT, and [redacted] will be evaluated using proportional hazards model, with these variables utilized as covariates.

Details of the analyses for specific secondary variables including analysis of LVESV, LVEDV, LVEF, and 6MWT; change from baseline in NYHA Functional Class status; MLHF questionnaire; and EQ-5D questionnaire are provided in the SAP.

[redacted]

[redacted]

[redacted]

9.7 Multiple Comparisons and Multiplicity

Starting in the latter part of 2017, only patients with NYHA Class III at baseline will be enrolled in this study. The motivation, details, and statistical approach to this population enrichment/adaptation are described in Appendix 1 of the SAP V5.0.

There is a single primary efficacy endpoint, therefore no respective alpha-level adjustment is required. There is only one key secondary endpoint (i.e., time from Day 0-to-TCE), therefore no respective alpha-level adjustment will be performed.

A fixed sequence step-down multiplicity procedure will be implemented to test the secondary endpoints (in the order specified in Section 9.6.2.2) while controlling the overall Type I error rate at 5% (2-sided alpha of 0.05).

Additional details for multiplicity are outlined in the SAP V5.0.

9.8 Safety Variables and Analyses

The safety population (see Section 9.3) will be used for all safety analyses.

9.8.1 Safety Variables

The safety and tolerability of rexlemestrocel-L will be assessed throughout the study by evaluating the following: adverse events, clinical laboratory test results, vital signs measurements, concomitant medication and therapy usage, ECG, 24-hour Holter monitoring (randomized patients across the US and EU), echocardiographic, and physical examination results. In addition, important cardiovascular safety events will be reviewed from CEC-adjudicated data for all-cause death (i.e., including non-cardiac and cardiac death) and hospitalizations for non-fatal decompensated HF, RCD events, pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE, non-fatal CVA, and non-fatal MI.

Safety measures and endpoints will include the following:

- occurrence of adverse events relative to index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 hospitalization through discharge for that hospitalization
- occurrence of adverse events
- clinical laboratory tests (serum chemistry and hematology) results
- urinalysis
- vital signs measurements
- ECG findings
- telemetry findings
- rhythm analysis by ICD device (or any implanted device capable of defibrillation) interrogation, if applicable
- 24-hour Holter monitoring (randomized patients across the US and EU)
- physical examination findings
- review of important cardiovascular safety events from CEC-adjudicated data for all-cause death (i.e., including non-cardiac and cardiac death) and hospitalizations for non-fatal decompensated HF, successfully RCD events, pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE, coronary revascularization procedure, non-fatal CVA, and non-fatal MI.

9.8.2 Safety Analysis

For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of

SAEs, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

9.8.2.1 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to rexlemestrocel-L/medical device/cardiac mapping procedure/cell delivery procedure (*i.e.,* reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), SAEs, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of SAEs and adverse events leading to withdrawal will be presented.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

9.8.2.2 Efficacy Endpoint Events

All endpoint events used in efficacy analyses will be summarized using descriptive statistics.

Important cardiovascular safety events from CEC adjudicated data for all-cause death (including cardiac death) and hospitalizations for non-fatal decompensated HF, urgent care outpatient HF visits for non-fatal decompensated HF event, successfully RCD events, overall survival, coronary artery revascularization procedure, pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE, non-fatal CVA, and non-fatal MI will be summarized using descriptive statistics.

9.8.2.3 Deaths

If any patient dies during the study, all relevant information will be discussed in the patient's narrative and included in CSR. A summary table and by-patient listing will be provided for all deaths during the study.

9.8.2.4 Clinical Laboratory Evaluations

Changes in laboratory measurement data will be summarized descriptively. All changes will be compared with prespecified boundaries to identify potentially clinically significant changes. Criteria for clinically significant laboratory values are provided in the SAP V5.0, Section 9.6.

9.8.2.5 Vital Signs

Changes in vital signs measurement data will be summarized descriptively. All changes will be compared with prespecified boundaries to identify potentially clinically significant changes. Criteria for clinically significant vital signs values are provided in the SAP V5.0, Section 9.7.

9.8.2.6 Concomitant Medications

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

9.8.2.7 Electrocardiography

Electrocardiography includes the following: telemetry, electrocardiograms, Holter monitoring, and ICD or any implanted device capable of defibrillation.

Telemetry

Telemetry monitoring will commence prior to the procedure (the index cardiac catheterization) and continue overnight post-procedure.

During and after the single-treatment procedure, clinically significant arrhythmias will be listed and tabulated by treatment group.

Electrocardiograms

Individual 12-lead ECGs will be extracted at specified timepoints and will be evaluated by a core electrocardiography laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia (QTcF) and Bazett (QTcB) correction methods. The primary QTc parameter will be QTcF. Secondary parameters (QTcB, QT, QRS complex, and HR) and waveforms (T waves) will be evaluated. Summary statistics (n, mean, SD, SE, median, minimum and maximum) will be provided for actual values and changes from baseline by treatment and

visit. The number and percentage of patients in each treatment group having specific abnormal interpretive statements which represent an appearance after baseline will be tabulated by visit.

Holter Monitor

For each patient in the Holter monitor substudy (randomized patients across the US and EU), baseline values of numeric variables will be the mean of the pre-dose Holter monitoring numerical data variables. There will be a baseline tabulation of abnormal interpretive statements present in any of the baseline Holter monitoring periods for that patient. The Holter analysis will determine the mean change from the preprocedure baseline measurement in each of the numeric parameters at each post-procedure observation by treatment group.

Summary statistics (n, mean, SD, SE, median, minimum and maximum) will be provided for actual values and changes from baseline by treatment and visit. The number and percentage of patients in each treatment group having specific abnormal interpretive statements, which represent an appearance after baseline will be tabulated by visit.

Holter monitor parameters are presented in Table 13.

Table 13: Holter Monitor Numeric Parameters

Variable	Units
Heart Rate	bpm
Longest/Fastest Tachycardia Duration	h:mm:ss
Longest/Fastest Tachycardia Rate	bpm
Longest/Slowest Bradycardia Duration	h:mm:ss
Longest/Slowest Bradycardia Rate	bpm
Atrial Fibrillation Average Rate	bpm
Supraventricular Ectopy Singles/Couplets/Runs/Total	Count/24 hours
Ventricular Ectopy Singles/Couplets/R on T/Total	Count/24 hours
Non-sustained Ventricular Tachycardia Episodes	Count/24 hours
Sustained Ventricular Tachycardia Episodes	Count/24 hours
Longest Pauses RR Duration	ss
Total Pauses	Count/24 hours

Bpm=beats per minute; h=hour; mm=minutes; ss=seconds

Ventricular Ectopy

All patients who undergo the index cardiac catheterization will be hospitalized on Day 0 at the cell injection center for index cardiac catheterization (with or without intracardiac mapping and cell delivery) and will remain hospitalized on telemetry after the index cardiac catheterization for a minimum of 1 night or until hospital discharge is clinically indicated. Ventricular arrhythmias will be assessed in a subset of patients (randomized patients across the US and EU) using a

24-hour Holter monitor. Patients will be monitored immediately after the index cardiac catheterization (Day 0) and then on Day 10 and at Months 1 and 3.

Patients who have an ICD will have their device interrogated at regularly scheduled intervals (see Table 4 and Table 5) for ventricular and other arrhythmias associated with episodes of firing of the device.

Automated Implantable Cardioverter Defibrillator

For patients who have an ICD or any implanted device capable of defibrillation, ventricular arrhythmias (arrhythmias obtained by device interrogation) will be listed and tabulated by treatment group.

9.8.2.8 Physical Examinations

Newly occurring abnormalities in the physical examinations will be identified and listed. Body weight measurement will be listed as changes from baseline.

9.9 Immunogenicity Variables and Analysis

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-HLA DSA formation. Blood serum samples for immunogenicity analyses will be collected during the screening period, and on Day 10, at Months 1, 3, 6, and 12 from randomized patients who do not experience a disqualifying event after randomization but before the scheduled index cardiac catheterization; immunogenicity testing will continue per the Schedule of Assessments (Table 4) for all surviving patients who were randomized and underwent the index cardiac catheterization. All serum samples from each patient will be tested for PRA, but only samples that test positive for PRA will be tested for DSA (anti-HLA). [redacted] serum samples [redacted] of rexlemestrocel-L will be analyzed for anti-murine (MIgG) and anti-bovine (BSA) antibodies. Immunogenicity data will be summarized for samples collected at screening, on Day 10, at Months 1, 3, 6, and 12 using descriptive statistics.

9.10 Planned Interim Analyses

Two pre-specified interim analyses were conducted during the study.

Both interim analyses were performed by the independent interim analysis statistician, who was fully unblinded to treatment assignment. The investigators, study participants, and the Sponsor (and its designees) remained blinded to the results of both interim analyses. For IA1, the independent unblinded statistician (outside of the DMC) was to inform the Sponsor and ESC directly if the predefined thresholds were met. For IA2, the independent and unblinded interim analysis statistician reviewed the results and informed the Sponsor, the DMC, and the trial's ESC of its findings relating to pre-defined HR thresholds. Throughout the IA2 process, the Sponsor remained blinded to the quantitative results and was informed only if the pre-defined HR thresholds were achieved. The IA2 output did not include an analysis for superiority or any other early stopping of the trial for success. Details regarding these interim analyses are available in the SAP V5.0 for this clinical study.

9.11 Reporting Deviations From the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (*e.g.,* medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

Each investigator must maintain, at all times, the primary records (*i.e.,* source documents) of each patient's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source (see Section 3.8.1).

Each investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Protocol Amendments and Protocol Deviations and Violations

11.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. The Principal Investigator and the Sponsor will sign the protocol amendment.

11.1.2 Protocol Deviations

A **protocol deviation** is nonadherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A **protocol violation** is any significant divergence from the protocol, *i.e.,* nonadherence on the part of the patient, the investigator, or the Sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by the study site personnel, on the CRF.

As a matter of policy, the Sponsor will not grant **exceptions** to protocol-specific entry criteria to allow patients to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular patient, prior approval from the Sponsor and the responsible IEC/IRB, in accordance with the SOP, is required before the patient will be allowed to enter the study. If investigative site personnel learn that a patient who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the Sponsor. Such patients will be discontinued from the study, except in a rare instance following review and written approval by the Sponsor and the responsible IEC/IRB, according to the applicable SOP.

11.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the practical performance of the study and during the course of the study (*e.g.,* when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members

must be listed on the study site authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The investigator is responsible for explaining the protocol to all study staff, including sub investigators, and for ensuring their compliance with the protocol, and training of site staff. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3 Study Monitoring

To ensure compliance with GCP, the study monitor or representative is responsible for ensuring that the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the Sponsor and each investigator. The main responsibilities of the study monitors are to visit each investigator before, during, and after the study to ensure adherence to the protocol, so that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before their participation in the study (including the informed consent form for the PGx substudy and the institution-specific informed consent document).

The study monitors will contact each investigator and visit the study site at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.8.1]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic case report forms (eCRFs) are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the eCRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other Sponsor personnel may, on request, accompany the study monitor on visits to the study site. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

11.4 Audit and Inspection

The Sponsor may audit the study sites and the cell injection centers to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The Sponsor quality assurance unit, independent of the Clinical Research Department, is responsible for determining the need for (and timing of) a study center audit.

Each investigator must accept that regulatory authorities and Sponsor representatives may conduct inspections to verify compliance of the study with GCPs.

12. ETHICS

12.1 Informed Consent

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. Additionally, the cell injection center will ensure that an institution-specific informed consent document is obtained before any protocol procedures are performed on Day 0. The patient's willingness to participate in the study will be documented in writing in an informed consent form, which will be signed by the patient with the date of that signature indicated. The investigator will keep the original informed consent forms, and signed copies will be given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the patient will be given to all patients.

A separate informed consent will also be obtained from each patient for permission to obtain DNA for PGx analysis. Participation in the PGx substudy is optional and consent may be collected at a later stage than screening (though preferred as early as possible). [redacted] Entry into the study is not dependent on this separate consent.

12.2 Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given site before the

IEC/IRB and health authority (where applicable) for the site is given written approval or a favorable opinion to commence.

12.3 Confidentiality Regarding Study Patients

Each investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, patients will be identified not by their names, but by an identification code (*e.g.,* initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

12.4 Declaration of the End of the Clinical Study

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10©; for other countries, local regulations will be followed.

12.5 Registration of the Clinical Study

This study is registered on the applicable clinical trial websites.

13. DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING

13.1 Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient screened according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be

verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (*e.g.,* central laboratory, bioanalytical laboratory, central image center, electronic diary data), the results will be sent to the investigational center, where they will be retained, but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the Sponsor (or organization performing data management) for direct entry into the clinical database. Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigator(s).

For patients who enter a study but do not meet screening criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.1.1 Data Collected by Contract Research Organizations

The CRO BioTelemetry Research is responsible for the processing and quality control of the echocardiogram, 24-hour Holter monitor, RVG, and ECG data as described in their standard operating procedures (SOPs). The Sponsor is responsible to ensure that the collection and evaluation of data by vendors adheres to protocol specifications. Electronic data from Cardiocore will be archived by the Sponsor.

The CRO inVentiv Health Clinical, LLC is responsible for the processing and quality control of the adjudicated data and database as described in their SOPs. The Sponsor is responsible for ensuring that the collection and evaluation of data by vendors adheres to protocol specifications. Electronic data from inVentiv Health Clinical, LLC will be archived by the Sponsor.

13.2 Data Quality Assurance

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data-management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3 Archiving of Case Report Forms and Source Documents

13.3.1 Investigator Responsibilities

All records related to the study (*i.e.,* source data, source documents, CRFs [see Section 3.8.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the Sponsor notifies the institution, in writing, that records may be destroyed.

If the Sponsor has not provided written notification of records destruction after 10 years (or in accordance with local regulations, whichever is greater) from study completion (or earlier in the case of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the Sponsor at least 60 days before the planned disposition of the study records; [redacted] No study document or image (*e.g.,* scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the Sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the Sponsor.

13.3.2 Sponsor Responsibilities

The Sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the Sponsor's SOPs for clinical studies.

If data management and filing for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the Sponsor prior to the start of data management and filing activities.

The original CRFs will be archived by the Sponsor for the lifetime of the product. If eCRFs are used in the study, electronic images will be archived by the Sponsor for the lifetime of the product. Site-specific eCRF images will be sent to the study site for archiving.

14. FINANCING AND INSURANCE

The study is covered under a liability insurance policy. The certificate of insurance and essential information about the insurance coverage can be provided upon request.

For this covered clinical study (see 21CFR54), the investigator will provide the Sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the Sponsor of any relevant changes during the conduct of the study and for one (1) year after the study has been completed.

This clinical study is insured in accordance with the corresponding local legal provisions. The policy coverage is patient to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease which would have occurred or continued if the patient had not taken part in the clinical study.

15. REPORTING AND PUBLICATION OF RESULTS

The Sponsor is responsible for the preparation of a clinical study report, in cooperation with the Principal/Coordinating Investigator. The final report is signed by the Sponsor and, if applicable, by the Principal/Coordinating Investigator.

When the Sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator when required by local regulatory agencies.

All unpublished information given to the investigator by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor. The primary publication from this study will report the results of the study in accordance with the current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, analysis, and manuscript preparation. The publications committee established by ESC will oversee this process. Additional publications may follow the first. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application(s) based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of Mesoblast, Inc.

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17. PATIENT ENTRY CRITERIA NO LONGER IN EFFECT

17.1 Patient Inclusion Criteria No Longer In Effect

The following inclusion criterion was replaced or deleted as a result of Amendment 02:
d. The patient is on a stable, outpatient, oral diuretic dosing regimen in which the patient clinically stable during the screening period. Flexible diuretic dosing that allows the patient to titrate the dose or add a dose of a second diuretic during screening is permitted, provided that the dosing regimen is not further altered and the patient remains stable during this period. **This inclusion criterion was replaced by (d1).**

The following inclusion criterion was replaced or deleted as a result of Amendment 02:
h. The patient has 1 or more of the following:

- at least 1 HF hospitalization more than 1 month, but 9 months or less before initiation of screening procedures
- at least 1 outpatient visit requiring IV diuretic, vasodilator, and/or positive inotropic therapy more than 1 month, but 9 months or less before initiation of screening procedures
- plasma levels of NT-pro-BNP greater than 1000 pg/mL or 1200 pg/mL (for patients with atrial fibrillation

This inclusion criterion was replaced by (h1).

The following inclusion criterion was replaced or deleted as a result of Amendment 02:
i. If the patient has an AICD in place, the procedure must have occurred at least 1 month before initiation of screening procedures. **This inclusion criterion was replaced by (i1).**

The following inclusion criterion was replaced or deleted as a result of Amendment 02:
m1. Women must be surgically sterile, 2 years post-menopausal, or, if of childbearing potential, currently using a medically accepted method of contraception, and must agree to continue to use this method of contraception after initiation of screening procedures and for 6 months after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). Acceptable methods of contraception include barrier method with spermicide, abstinence, intrauterine device (IUD) (known to have a failure rate of less than 1% per year), or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. Men must be surgically sterile, or, if capable of producing offspring, currently using a medically accepted method of contraception and must agree to continue to use this method of contraception after initiation of screening and for 16 weeks after study intervention. Acceptable methods of contraception include abstinence, female partner's use of steroidal contraceptive (oral, implanted or injected) in conjunction with a barrier method,

female partner's use of an IUD (known to have a failure rate of less than 1% per year), or if female partner is surgically sterile or 2 years post-menopausal. In addition, men may not donate sperm for 16 weeks after study intervention. **This inclusion criterion was replaced by (m2).**

The following inclusion criterion was replaced and/or deleted as a result of Amendment 01:
b. The patient has a diagnosis of chronic HF of ischemic or nonischemic etiology for at least 6 months before the initiation of screening procedures, with NYHA Functional Class II or Functional Class III symptoms. **This inclusion criterion was replaced by (b1).**

The following inclusion criterion was replaced and/or deleted as a result of Amendment 01:
f. The patient may be on the cardiac transplant list. However, he/she must have low priority status (*i.e.,* no greater than status 2) with low probability of having a transplant procedure performed over the next 12 months. **This inclusion criterion was replaced by (f1).**

The following inclusion criterion was replaced and/or deleted as a result of Amendment 01:
m. If the patient or female partner is of childbearing potential, the patient or female partner must be willing to use acceptable methods of contraception after initiation of screening procedures and for 16 weeks after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without cardiac mapping and cell delivery). Acceptable methods of contraception include barrier method with spermicide, abstinence, IUD, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. **This criterion was replaced by (m1).**

17.2 Patient Exclusion Criteria No Longer In Effect

The following exclusion criterion was replaced and/or deleted as a result of Amendment 03
p1. The patient has known hypersensitivity to radiocontrast media or dimethyl sulfoxide (DMSO), murine, and/or bovine products, with the exception of patients with mild hypersensitivity to radiocontrast media or DMSO, who may be pre-treated with corticosteroids and/or antihistamines. **This exclusion criterion was replaced by p2.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 02:
h. The patient, who in the absence of an AICD, has a history of malignant ventricular arrhythmia or sustained ventricular tachycardia (VT), with sustained VT demonstrated by QRS complexes wider than 120 milliseconds, lasting more than 30 seconds, and with a rate of more than 100 beats per minute on screening ECG or other data supporting this diagnosis. **This exclusion criterion was replaced by h1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 02:
aa1. A patient with an AICD in place who has had an AICD firing within 1 month of Day 0. **This exclusion criterion was replaced by aa2.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
p. The patient has known hypersensitivity to radiocontrast media or DMSO, murine, and/or bovine products. **This exclusion criterion was replaced by p1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
r. The patient has acute bacterial or viral infectious disease, or acute exacerbation of a chronic infectious disease. **This exclusion criterion was replaced by r1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
s. Patients with severe chronic obstructive pulmonary disease (COPD) or requires home oxygen. A patient with moderate COPD without severe RV dilatation and dysfunction on echocardiogram may be included in the study if they have a documented HF history that meets qualifying HF criteria. A patient who has a forced expiratory volume (FEV_1) in one second of less than 1.0 L will be excluded. A given patient will be excluded from serial echocardiographic imaging assessments if his/her heart is difficult to image adequately using standard precordial echocardiographic techniques. In that case, RVG estimations of LVEF will be used for screening inclusion criteria as well as for serial changes in overall cardiac performance after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without cardiac mapping and cell delivery). Patients with clinically meaningful COPD will be excluded from serial 6MWT evaluations if their exercise limitation is thought to be due predominantly to their intrinsic pulmonary disease rather than from the patient's HF state. **This exclusion criterion was replaced by s1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
u. The patient has 1 or more clinical laboratory test value(s) outside the range for 1 or more of the tests specified below, or any other clinically significant abnormality as determined by the investigator or medical monitor as follows

- aspartate aminotransferase (AST/SGOT)/alanine aminotransferase (ALT/SGPT) greater than 3 times ULN range
- total bilirubin greater than 1.5 times ULN

- eGFR less than 30 mL/min/1.73 m^2 (calculated by the central clinical Laboratory using the MDRD formula); measures to minimize the risk of contrast-induced nephropathy will be taken at the discretion of the investigator
- hemoglobin less than 9 g/dL
- platelets consistently less than 100 × $10^3/mm^3$
- hemoglobin A1c of 10% or greater.

This exclusion criterion was replaced by u1.

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
y. The patient has had treatment and/or an uncompleted follow-up treatment of any investigational therapy within 6 months before study intervention and intends to participate in any other investigational drug or cell therapy study in the 3 years after study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery). **This exclusion criterion was replaced by y1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 01:
aa. A patient with an AICD in place who has had an AICD firing within the past 1 month. **This exclusion criterion was replaced by aa1.**

The following exclusion criterion was replaced and/or deleted as a result of Amendment 06:
ff. The patient cannot receive anticoagulant therapy. This exclusion criterion was deleted due to confusion over wording and was replaced with an inclusion criterion that states: The patient must be able to receive systemic anticoagulant therapy.

The following exclusion criterion was deleted as a result of Amendment 07:
u1. total bilirubin greater than 1.5 times ULN

Appendix 1: Instructions for Cardiac Mapping and Transendocardial Delivery of Investigational Product with NOGA® XP/MyoStar™ Cardiac Navigation System and Myostar™ Catheter

Overview

Patients will be hospitalized at the cell injection center on the day of the index cardiac catheterization (with or without intracardiac mapping and cell delivery). They will remain hospitalized in the cardiac step-down or coronary care unit with telemetry monitoring for a minimum of 1 night following study intervention (*i.e.,* hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

Procedure-related cardiac arrhythmias will be handled according to the current American College of Cardiology/American Heart Association/European Society of Cardiology Practice Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

For patients with atrial fibrillation on Day 0 during the index cardiac catheterization (with or without intracardiac mapping and cell delivery), attempts should be made in the cardiac catheterization laboratory for regularization of ventricular contraction rate prior to cell delivery. Regularization could be accomplished using overdrive pacing with a temporary right ventricular pacemaker or by manipulation of the capabilities of an already present pacing-capable device. Patients who have complete right bundle branch block on the day of the index cardiac catheterization (Day 0) must have either placement of a temporary pacing wire or precautionary manipulation of the capabilities of an already present pacing-capable device prior to entry of a catheter into the left ventricle chamber.

Heparin Administration in the Cardiac Catheterization Laboratory

Patient care will be guided by the personnel at the cell injection center. The following suggestions for use of heparin are the minimal assessment mandated by the protocol and are not intended to replace standard practices.

Heparin 5000 units as an intravenous bolus will be administered to each patient immediately following vascular access procedure for cardiac mapping and cell delivery. Activated clotting time (ACT) will be monitored for 5 minutes following administration of heparin. Target value for ACT is 200 seconds. Once therapeutic ACT is reached, ACT monitoring will continue every 30 to 60 minutes during index cardiac catheterization. If ACT is nontherapeutic (<200 seconds),

additional heparin 1000 units as an IV bolus will be administered followed by ACT check 5 minutes after administration of heparin until therapeutic target is obtained. The sheath will be removed when the ACT reading is <130 seconds or acceptable ACT reading as per standard practice at the regional cell injection center.

If the patient is taking therapeutic heparin before the index cardiac catheterization, no bolus of heparin will be administered and the ACT target of 200 seconds will be maintained for the duration of the cardiac catheterization. In patients with a known intolerance to heparin (*e.g.,* have a history of heparin-induced thrombocytopenia), the alternative anti-coagulant bivalirudin may be used at the discretion of the interventional cardiologist.

Cardiac Mapping with the NOGA® XP Cardiac Navigation System and Targeting of Myocardial Sites for Cell Delivery

An electromechanical map of the left ventricle will be performed with the NOGA®XP Cardiac Navigation System (Biosense Webster, Inc.; also referred to as NOGA®XP) to locate the target myocardial area(s) for cell delivery. Ideally, the target myocardial area should display points that show electrical viability, as defined as a unipolar voltage of ≥ 6.9 mV, thus representing viable myocardial tissue. Therefore, cell delivery will be avoided in areas of transmural infarction in ischemic patients and cell delivery will be made in areas of higher unipolar voltage (less fibrosis) in nonischemic patients.

The target myocardial region will be defined at the time of NOGA®XP cardiac mapping. It will include areas of unipolar voltage ≥6.9 mV (as delineated above) and ideally will include areas of low linear local shortening (LLS) <12%. If there are no areas of low LLS noted on the LV map, information regarding the presence of potentially viable myocardium should be integrated from prior echocardiographic or other imaging data that may be available. This will further inform the choice of the target area for cell delivery in the NOGA®XP-defined viable myocardium.

Patients with chronic HF due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy will receive cell delivery in myocardial territories as identified by the operator. The targeted cell delivery in these territories will be ideally delivered in a homogeneous pattern approximately 0.5 to 1 cm apart. Please refer to "Techniques for the NOGA®XP Cardiac Navigation System Left Ventricular Mapping and Transendocardial Injection" (provided by Biosense Webster, Inc.) for a detailed description of electromechanical mapping and transendocardial cell delivery techniques.

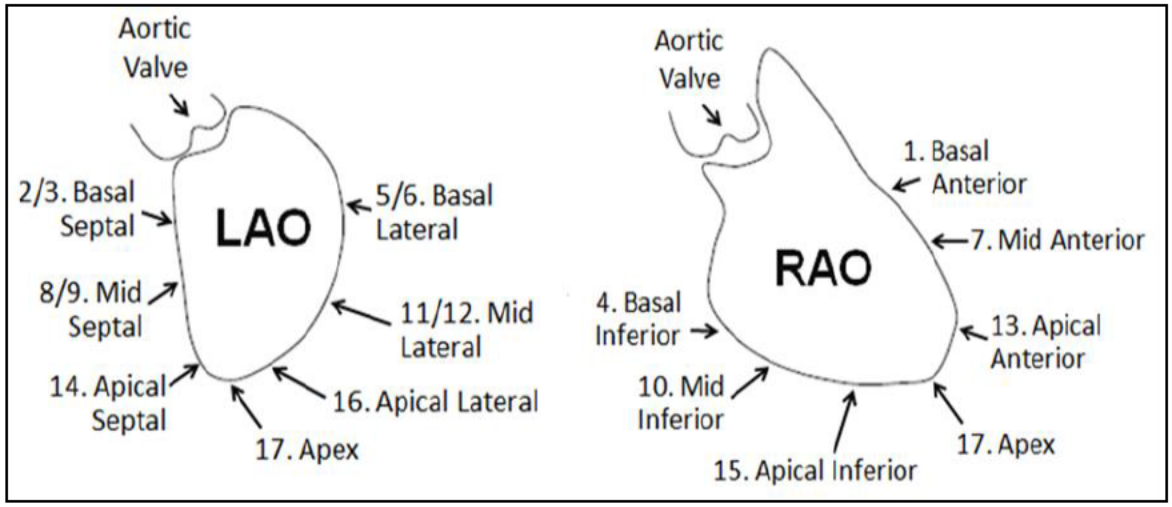
Preparation of the Cryopreserved Investigational Product

The cryopreserved rexlemestrocel-L is removed from the liquid nitrogen container within the cardiac catheterization laboratory to the area designated for thawing of rexlemestrocel-L. The vial containing the cryopreserved rexlemestrocel-L will be placed in a ziplock bag and immersed into a 37°C water bath that should either be on a permanent bench top or a portable cart. With gentle agitation (cells are not to be shaken), the cells should be thawed after approximately 4 to 6 minutes of submersion and just before the last crystal of ice has fully melted. Using an 18-gauge needle, the thawed rexlemestrocel-L should be aspirated into a 10-mL syringe, yielding a volume of approximately 4 mL. During any downtime or delay in the procedure, the syringe should be gently hand-rocked in order to prevent clumping. Additional details regarding the storage and preparation of rexlemestrocel-L are contained in the Pharmacy Manual.

Cardiac Mapping and Transendocardial Delivery of Investigational Product

An 8F femoral artery sheath will be inserted and a pigtail catheter advanced retrograde to the left ventricle for performance of contrast ventriculography using left anterior oblique (LAO) and right anterior oblique (RAO) views (Figure A- 1).

Figure A- 1: Diagrammatic Representation of Left Anterior Oblique and Right Anterior Oblique Views of the Left Ventricle Obtained During Contrast Angiography



Abbreviations: LAO=left anterior oblique; RAO=right anterior oblique.
Note: The regional assignments and numbers correspond to the traditional 17-segment "bull's eye map" of the left ventricle.

The orthogonal LV images will be used as references for the subsequent intracardiac mapping performed with the NOGA®XP.

The MyoStar™ injection catheter used with NOGA® XP will be prepared by adjusting the needle extension at 0° and 90° flex and 0.1 cc of rexlemestrocel-L to fill the needle dead space. To ensure safety and limit the potential for extracardiac administration of the injectate, the needle extension/wall thickness ratio will be ≤ 0.5 at all times.

The maximum needle extension permitted will be 6 mm. Needle movement is controlled by moving a piston on a second handle, the injection handle, located proximal to the deflection handle. Pushing and holding the thumb knob forward on the injection handle extends the needle. Rotating the thumb knob adjusts the length of needle extension.

Following insertion through the 8F femoral artery sheath, the injection catheter will be advanced under fluoroscopic guidance to the aortic valve. In a retrograde fashion, the catheter will cross the aortic valve into the left ventricle, and the catheter tip will be placed against the endocardium at the target area. In the event the catheter cannot be advanced, such as due to atherosclerotic disease precluding insertion, the cell delivery procedure will be aborted. Long femoral sheaths are recommended in patients with peripheral arterial disease. Each targeted myocardial site will be carefully evaluated prior to cell delivery to enhance safety and ensure transendocardial delivery of rexlemestrocel-L. The following represent the ideal criteria for mapping sites: perpendicular position of the catheter to the left ventricle wall; loop stability <3 mm; underlying voltage ≥6.9 mV; and presence of a premature ventricular contraction on extension of the needle into the myocardium.

Patients randomly assigned to active treatment will receive a single index cardiac catheterization involving the administration of 150 M transendocardially delivered rexlemestrocel-L in 4 mL of cell media. The cell delivery process should begin immediately following complete thawing of rexlemestrocel-L, so that fully thawed rexlemestrocel-L is transendocardially delivered within 90 minutes of complete thaw. After the completion of the mapping procedure, 15 to 20 appropriate myocardial sites will be identified (20 sites is ideal) for transendocardial delivery of rexlemestrocel-L. The injection sites will be captured by NOGA® XP and transcribed into electronic data capture (EDC). Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to the imaging identified myocardial locations; the total volume of rexlemestrocel-L administered must not exceed 4.0 mL. The total duration of the transendocardial delivery procedure must not exceed 90 minutes from the time of complete thaw of rexlemestrocel-L. During index cardiac catheterization, patients will be sedated and, if available, provided with headsets with music.

Stopping Rules for Cardiac Mapping and Cell Delivery Procedure

Circumstances may occur either during cardiac mapping with the NOGA®XP/MyoStar™ System or during transendocardial delivery of rexlemestrocel-L with the MyoStar™ Injection Catheter that could indicate serious deterioration of the patient's clinical condition.

- If any of the following events/symptoms occur, the cardiac mapping and cell delivery procedure should be **temporarily halted** and the patient should be reevaluated for suitability to continue with the treatment under investigation: administration of rexlemestrocel-L should be discontinued.
  - persistent complaints of chest pain
  - complaints of cardiac pain associated with injections
  - persistent hypotension
  - complaints of shortness of breath
  - implantable cardioverter defibrillator (ICD or any implanted device capable of defibrillation) shocks to stop ventricular tachycardia (VT)
  - direct current (DC) cardioversion or defibrillation for VT
  - there is any question as to the location of the catheter tip in relation to vasculature or the left ventricle.
- The cardiac mapping and cell delivery procedure will be **terminated** if any of the following events occurs:
  - sustained hypotension not responsive to fluid administration
  - clinical signs and symptoms indicating acute coronary syndrome
  - clinical signs and symptoms indicating a cerebrovascular accident
  - cardiac tamponade is strongly suspected or confirmed
  - hemopericardium requiring pericardiocentesis
  - 2 episodes of sustained ventricular tachycardia
  - the patient experiences one episode of ventricular fibrillation (VF)
  - identification of thrombus in the left ventricle or the aorta that was not previously present on echocardiogram or left ventriculogram.

Appendix 2: Instructions for Scripted Sham-cardiac Mapping and Cell delivery Procedure with NOGA®XP or CARTO®3 Cardiac Navigation System and MyoStar™ Catheter

Overview

Patients will be hospitalized on the day of the procedure for left ventriculography and scripted sham cardiac mapping and cell delivery procedure. They will remain hospitalized in the cardiac step down or coronary care unit with telemetry monitoring for a minimum of 1 night following study intervention and until patient discharge is clinically indicated.

Patients randomly assigned to the control group will receive standard-of-care treatment and will undergo a scripted sham cardiac mapping and cell delivery procedure that includes index cardiac catheterization with left ventriculography. The sham procedure will be staged to script and will not include actual cardiac mapping or delivery of rexlemestrocel-L.

Patients enrolled in the study with atrial fibrillation on the day of the procedure (Day 0), should have attempts made in the cardiac catheterization laboratory for regularization of ventricular contraction rate prior to the conduct of the scripted sham procedure. This could be accomplished using overdrive pacing with a temporary right ventricular pacemaker or by manipulation of the capabilities of an already present pacing-capable device. Patients who have complete right bundle branch block on the day of the procedure (Day 0) must have either placement of a temporary pacing wire or precautionary manipulation of the capabilities of an already present pacing-capable device prior to entry of a catheter into the LV chamber.

Heparin Administration in the Cardiac Catheterization Laboratory

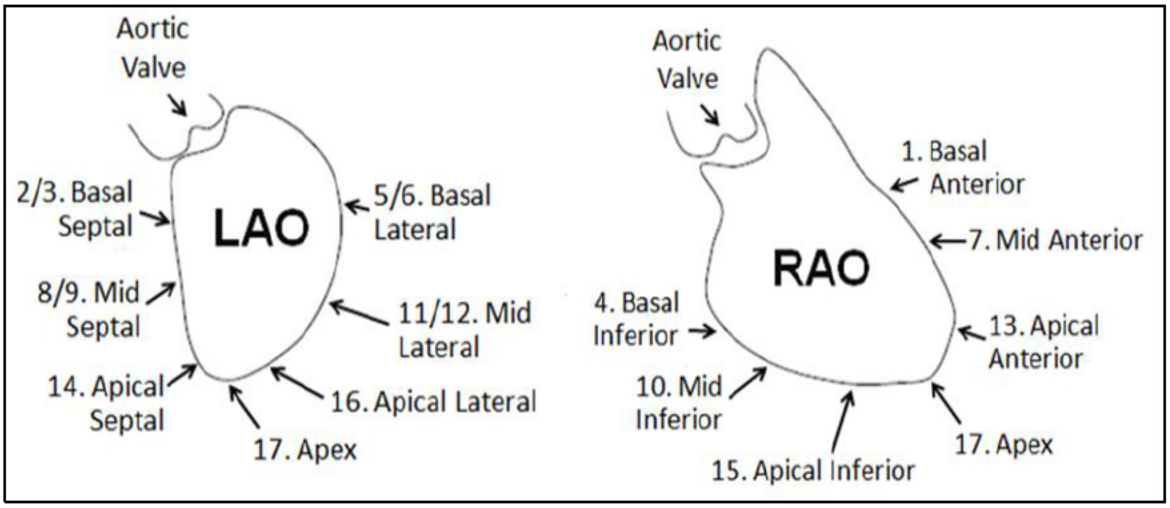
Patient care will be guided by the regional cell injection center personnel. The administration of heparin will be performed according to the regional cell injection center's guidelines for heparin administration for diagnostic cardiac catheterization. In patients with a known intolerance to heparin, (*e.g.,* have a history of heparin-induced thrombocytopenia), the alternative anti-coagulant bivalirudin may be used at the discretion of the interventional cardiologist.

Cardiac Catheterization and Scripted Sham Cardiac Mapping and Cell Delivery Procedure

During the index cardiac catheterization, patients will be sedated and provided, if available, headsets with music.

A femoral artery sheath will be inserted and a pigtail catheter advanced retrograde to the left ventricle for performance of contrast ventriculography using left anterior oblique (LAO) and right anterior oblique (RAO) views (Figure A- 2).

Figure A- 2: Diagrammatic Representation of Left Anterior Oblique and Right Anterior Oblique Views of the Left Ventricle Obtained During Contrast Angiography



LAO=left anterior oblique; RAO=right anterior oblique.
Note: The regional assignments and numbers correspond to the traditional 17-segment "bull's eye map" of the left ventricle.

The interventional cardiologist will announce "Let's begin the mapping procedure" and will recite, "that's a good mapping point" after 20 mock mapping sites are identified, pausing between each repetition in order to simulate delivery of rexlemestrocel-L.

The interventional cardiologist will then announce "That concludes the mapping procedure". At the start of the sham cardiac mapping and cell delivery procedure, the interventional cardiologist will ask "Are the cells ready for delivery?" upon which the assistant will announce "Yes, the cells are here and ready for delivery". The usual script of "needle out, PVC (premature ventricular contraction), inject, needle in" will be recited for 20 mock injections, pausing between each mock injection. "Cell delivery completed" will be announced to signal the end of the scripted sham cardiac mapping and cell delivery procedure. It is imperative that the total duration of the sham cardiac mapping and cell delivery procedure should range from approximately 1 hour to no more than 2 hours in order to maintain the treatment blind for patients in the control group.

Appendix 3: Instructions for Cardiac Mapping and Transendocardial Delivery of Investigational Product with CARTO®3/MyoStar™ Cardiac Navigation System and MyoStar™ Catheter

Overview

Patients will be hospitalized at the cell injection center on the day of the index cardiac catheterization (with or without intracardiac mapping and cell delivery). They will remain hospitalized in the cardiac step-down or coronary care unit with telemetry monitoring for a minimum of 1 night following study intervention (i.e., hospitalization on Day 0 for index cardiac catheterization with or without intracardiac mapping and cell delivery).

Procedure-related cardiac arrhythmias will be handled according to the current American College of Cardiology/American Heart Association/European Society of Cardiology Practice Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

For patients with atrial fibrillation on Day 0 during the index cardiac catheterization (with or without intracardiac mapping and cell delivery), attempts should be made in the cardiac catheterization laboratory for regularization of ventricular contraction rate prior to cell delivery. Regularization could be accomplished using overdrive pacing with a temporary right ventricular pacemaker or by manipulation of the capabilities of an already present pacing-capable device. Patients who have complete right bundle branch block on the day of the index cardiac catheterization (Day 0) must have either placement of a temporary pacing wire or precautionary manipulation of the capabilities of an already present pacing-capable device prior to entry of a catheter into the left ventricle chamber.

Heparin Administration in the Cardiac Catheterization Laboratory

Patient care will be guided by the personnel at the cell injection center. The following suggestions for use of heparin are the minimal assessment mandated by the protocol and are not intended to replace standard practices.

Heparin 5000 units as an intravenous bolus will be administered to each patient immediately following vascular access procedure for cardiac mapping and cell delivery. Activated clotting time (ACT) will be monitored for 5 minutes following administration of heparin. Target value for ACT is 200 seconds. Once therapeutic ACT is reached, ACT monitoring will continue every 30 to 60 minutes during index cardiac catheterization. If ACT is nontherapeutic (<200 seconds),

additional heparin 1000 units as an IV bolus will be administered followed by ACT check 5 minutes after administration of heparin until therapeutic target is obtained. The sheath will be removed when the ACT reading is <130 seconds or acceptable ACT reading as per standard practice at the regional cell injection center.

If the patient is taking therapeutic heparin before the index cardiac catheterization, no bolus of heparin will be administered and the ACT target of 200 seconds will be maintained for the duration of the cardiac catheterization. In patients with a known intolerance to heparin (e.g., have a history of heparin-induced thrombocytopenia), the alternative anti-coagulant bivalirudin may be used at the discretion of the interventional cardiologist.

Cardiac Mapping with the CARTO®3 Cardiac Navigation System and Targeting of Myocardial Sites for Cell Delivery

An electrical map of the left ventricle will be performed with the CARTO®3 Cardiac Navigation System (Biosense Webster, Inc.; also referred to as CARTO®) to locate the target myocardial area(s) for cell delivery. Ideally, the target myocardial area should display points that show electrical viability, as defined as a unipolar voltage of ≥ 6.9 mV, thus representing viable myocardial tissue. Therefore, cell delivery will be avoided in areas of transmural infarction in ischemic patients and cell delivery will be made in areas of higher unipolar voltage (less fibrosis) in nonischemic patients.

The target myocardial region will be defined at the time of CARTO® cardiac mapping. It will include areas of unipolar voltage ≥6.9 mV (as delineated above). Information regarding the presence of potentially viable myocardium should be integrated from prior echocardiographic or other imaging data that may be available. This will further inform the choice of the target area for cell delivery in the CARTO®-defined viable myocardium.

Patients with chronic HF due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy will receive cell delivery in myocardial territories as identified by the operator. The targeted cell delivery in these territories will be ideally delivered in a homogeneous pattern approximately 0.5 to 1 cm apart. Please refer to "Techniques for the CARTO®3 Cardiac Navigation System Left Ventricular Mapping and Transendocardial Injection" (provided by Biosense Webster, Inc.) for a detailed description of electrical mapping and transendocardial cell delivery techniques. Techniques utilized for mapping and cell delivery with the CARTO® are highly similar to those delineated for NOGA®.

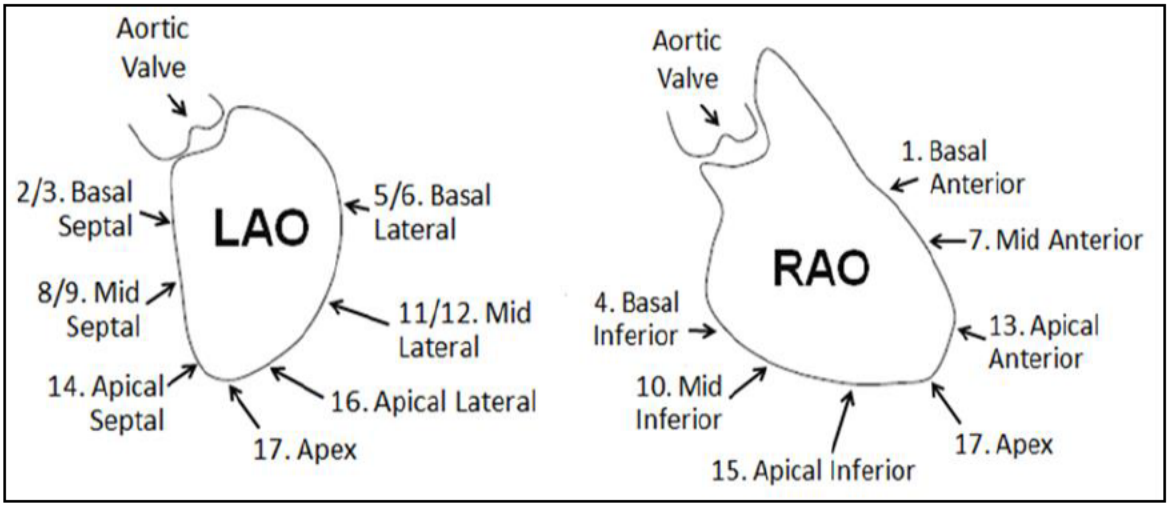
Preparation of the Cryopreserved Investigational Product

The cryopreserved rexlemestrocel-L is removed from the liquid nitrogen container within the cardiac catheterization laboratory to the area designated for thawing of rexlemestrocel-L. The vial containing the cryopreserved rexlemestrocel-L will be placed in a ziplock bag and immersed into a 37°C water bath that should either be on a permanent bench top or a portable cart. With gentle agitation (cells are not to be shaken), the cells should be thawed after approximately 4 to 6 minutes of submersion and just before the last crystal of ice has fully melted. Using an 18-gauge needle, the thawed rexlemestrocel-L should be aspirated into a 10-mL syringe, yielding a volume of approximately 4 mL. During any downtime or delay in the procedure, the syringe should be gently hand-rocked in order to prevent clumping. Additional details regarding the storage and preparation of rexlemestrocel-L are contained in the Pharmacy Manual.

Cardiac Mapping and Transendocardial Delivery of Investigational Product

An 8F femoral artery sheath will be inserted and a pigtail catheter advanced retrograde to the left ventricle for performance of contrast ventriculography using left anterior oblique (LAO) and right anterior oblique (RAO) views (Figure A- 3).

Figure A- 3: Diagrammatic Representation of Left Anterior Oblique and Right Anterior Oblique Views of the Left Ventricle Obtained During Contrast Angiography



Abbreviations: LAO=left anterior oblique; RAO=right anterior oblique.
Note: The regional assignments and numbers correspond to the traditional 17-segment "bull's eye map" of the left ventricle.

The orthogonal LV images will be used as references for the subsequent intracardiac mapping performed with the CARTO®.

The MyoStar™ injection catheter used with CARTO® will be prepared by adjusting the needle extension at 0° and 90° flex and 0.1 cc of rexlemestrocel-L to fill the needle dead space. To ensure safety and limit the potential for extracardiac administration of the injectate, the needle extension/wall thickness ratio will be ≤ 0.5 at all times.

The maximum needle extension permitted will be 6 mm. Needle movement is controlled by moving a piston on a second handle, the injection handle, located proximal to the deflection handle. Pushing and holding the thumb knob forward on the injection handle extends the needle. Rotating the thumb knob adjusts the length of needle extension.

Following insertion through the 8F femoral artery sheath, the injection catheter will be advanced under fluoroscopic guidance to the aortic valve. In a retrograde fashion, the catheter will cross the aortic valve into the left ventricle, and the catheter tip will be placed against the endocardium at the target area. In the event the catheter cannot be advanced, such as due to atherosclerotic disease precluding insertion, the cell delivery procedure will be aborted. Long femoral sheaths are recommended in patients with peripheral arterial disease. Each targeted myocardial site will be carefully evaluated prior to cell delivery to enhance safety and ensure transendocardial delivery of rexlemestrocel-L. The following represent the ideal criteria for mapping sites: perpendicular position of the catheter to the left ventricle wall; loop stability <3 mm; underlying voltage ≥6.9 mV; and presence of a premature ventricular contraction on extension of the needle into the myocardium.

Patients randomly assigned to active treatment will receive a single index cardiac catheterization involving the administration of 150 M transendocardially delivered rexlemestrocel-L in 4 mL of cell media. The cell delivery process should begin immediately following complete thawing of rexlemestrocel-L, so that fully thawed rexlemestrocel-L is transendocardially delivered within 90 minutes of complete thaw. After the completion of the mapping procedure, 15 to 20 appropriate myocardial sites will be identified (20 sites is ideal) for transendocardial delivery of rexlemestrocel-L. The injection sites will be captured by CARTO® and transcribed into electronic data capture (EDC). Independent of whether the NOGA® or CARTO® imaging system was employed to identify viable myocardium, the MyoStar™ Injection Catheter will be used for transendocardial delivery of rexlemestrocel-L. A 0.2 mL suspension of cells will be injected with each injection to the imaging identified myocardial locations; the total volume of study product administered must not exceed 4.0 mL. The total duration of the transendocardial delivery

procedure must not exceed 90 minutes from the time of completion of thaw of rexlemestrocel-L. During index cardiac catheterization, patients will be sedated and, if available, provided with headsets with music.

Stopping Rules for Cardiac Mapping and Cell Delivery Procedure

Circumstances may occur either during cardiac mapping with the CARTO®/MyoStar™ System or during transendocardial delivery of rexlemestrocel-L with the MyoStar™ Injection Catheter that could indicate serious deterioration of the patient's clinical condition.

- If any of the following events/symptoms occur, the cardiac mapping and cell delivery procedure should be temporarily halted and the patient should be reevaluated for suitability to continue with the treatment under investigation: administration of rexlemestrocel-L should be discontinued.
  - persistent complaints of chest pain
  - complaints of cardiac pain associated with injections
  - persistent hypotension
  - complaints of shortness of breath
  - implantable cardioverter defibrillator (ICD or any implanted device capable of defibrillation) shocks to stop ventricular tachycardia (VT)
  - direct current (DC) cardioversion or defibrillation for VT
  - there is any question as to the location of the catheter tip in relation to vasculature or the left ventricle.
- The cardiac mapping and cell delivery procedure will be terminated if any of the following events occurs:
  - sustained hypotension not responsive to fluid administration
  - clinical signs and symptoms indicating acute coronary syndrome
  - clinical signs and symptoms indicating a cerebrovascular accident
  - cardiac tamponade is strongly suspected or confirmed
  - hemopericardium requiring pericardiocentesis
  - 2 episodes of sustained ventricular tachycardia
  - the patient experiences one episode of ventricular fibrillation (VF)
  - identification of thrombus in the left ventricle or the aorta that was not previously present on echocardiogram or left ventriculogram.

Appendix 4: 6-Minute Walk Test Procedures

If the patient is unable to perform the test, the reason for the test not being completed will be noted on the case report form.

It is preferable to have the same technician perform the 6-minute walk tests for the duration of the study.

The 6-minute walk test will be conducted in an enclosed corridor (preferably free of distractions) on a course that is 20 meters long. The corridor will be divided into 2-meter sections using a method unnoticeable to the patient. Chairs will be placed at either end of the 20-meter course markers. The distance covered during the preceding walk test will not be revealed to the patient during the study. Before the test, the patient will sit quietly for 10 minutes in one of the course marker chairs. The following instructions will be read **verbatim** to the patient:

> *The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the chair at the end, then turn around and walk back. When you arrive back at the starting point, you will go back and forth again. You will go back and forth as many times you can in the 6-minute period. If you need to, you may stop and rest. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say stop, please stand right where you are.*
>
> *Do you have any questions about the test? Please explain to me what you are going to do.*

Repeat the entire instructions above if the patient does not seem to understand.
Repeat the following sentence:

> *The most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. Are you ready? Start when I say "GO."*

During the test, the walking pace of the patient should not be influenced. The test supervisor **must choose a midpoint in the course and stay stationary during the testing**—not walk with, rush up behind, or rush past the patient.

While walking, the patient will be encouraged every 30 seconds with the following phrases:

- 0 to 3 minutes
  - That's it; you've got the idea.
  - You're doing well.
  - Keep it up now.
- 3 to 6 minutes
  - Remember, as far as you can go.
  - We'll want you to go as far as you possibly can.
  - That's it; keep working at it.

The patient should be spoken to only at the 30-second encouragements and no response should be made to the patient's questions about the time and distance elapsed. If the patient is not concentrating on the walking, the patient can be reminded at a 30-second mark:

This is a walking test. Talking will utilize your energy reserve and interfere you're your performance.

Encouragement phrases can be repeated as needed. For example, if the patient is slowing down and expresses that he/she wants to stop, say:

Remember, if you need to, you may rest. Just remain where you are until you can go on again.

If necessary, the patient may rest in a course marker chair although he/she should not be encouraged to do so.

The patient will be told the time elapsed at 2 and 4 minutes as follows:

You have completed 2 minutes
You have completed 4 minutes

At the end of the test, the patient should not move from where he/she was told to "STOP" until the distance walked (measured to the nearest foot) has been recorded. The patient will then be directed to the nearest course marker chair and observed for at least 10 minutes.
Record the distance walked during the 6-minute walk test.

Appendix 5: Minnesota Living with Heart Failure® Questionnaire Completion Instructions

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**					**Very Much**
		Very Little				
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Appendix 6: EQ-5-D Questionnaire English (USA) Version 2.0

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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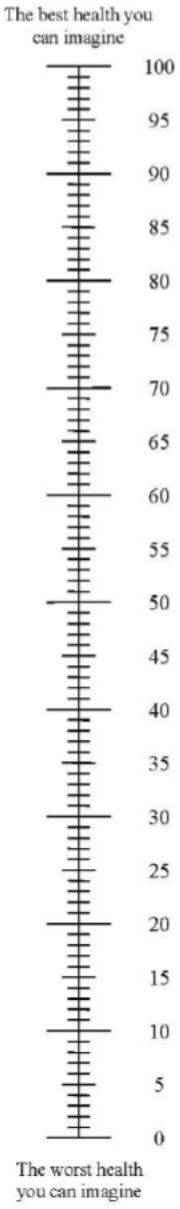
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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