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

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mesoblast

the regenerative medicine company

STATISTICAL ANALYSIS PLAN

Protocol MSB-MPC-CHF001

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
Product Name:	rexlemestrocel-L
Study Phase:	Phase III
Indication:	Treatment of chronic heart failure (HF) due to left ventricular (LV) systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy
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SAP Date:	20 October 2020
SAP Version:	6.0

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10.20.2020

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2-D	2-dimensional
6MWT	6-minute walk test
ACC/AHA/ESC)	American College of Cardiology/American Heart Association/European Society of Cardiology
AE	adverse event
AES	Accelerated Enrollment Solutions
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BDS	Biologics Delivery System
BP	blood pressure
Bpm	beats per minute
BSA	bovine serum albumin
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Clinical Endpoints Committee
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy device
CRT -P	cardiac resynchronization therapy pacemaker
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DSA	donor-specific antibody
DMC	Data Monitoring Committee
ECG	electrocardiography, electrocardiogram
EU	European Union
FAS	full analysis set
FDA	US Food and Drug Administration
GGT	gamma-glutamyl transpeptidase
HF	heart failure
HF-MACE	heart-failure-related major adverse cardiac event
HLA	human leukocyte antigen
hsCRP	high sensitivity C-reactive protein
ICD	implantable cardioverter defibrillator
IRT	Interactive Response Technology
IV	Intravenous
KM	Kaplan-Meier
LVAD	left ventricular assist device
LDH	lactate dehydrogenase
LOCF	last observation carried forwards
LV	left ventricular
LVEF	left ventricular ejection fraction

LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
M	million
MAR	missing at random
MDR	Medical device safety reporting
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MLHF	Minnesota Living with Heart Failure
MPC	mesenchymal precursor cells
MUGA	multi-gated acquisition (same as RVG)
NT-proBNP	N terminal-pro B-type natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PGx	pharmacogenomic
PRA	panel reactive antibodies
PT	preferred term
PVC	premature ventricular contractions
QOL	quality of life
QTcB	QTC Interval Bazett
QTcF	QTC Interval Fredericia
RCD	resuscitated cardiac death
RVG	radionuclide ventriculography
SAE	serious adverse event
SBP	systolic blood pressure
SCI	Statistics Collaborative, Inc.
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
TCE	terminal cardiac event
TEAE	treatment-emergent adverse event
ULN	upper limit of the normal range
VF	ventricular fibrillation
VT	ventricular tachycardia
WBC	white blood cell
WHO	World Health Organization

1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mesoblast, Inc. study MSB-MPC-CHF001 entitled:

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.

This phase 3 study evaluates patients with chronic heart failure (HF) due to left ventricular (LV) systolic dysfunction of either ischemic or nonischemic etiology who have received optimal medical and coronary revascularization therapy. Patients are randomized to either cell therapy involving 150 million (M) human bone marrow-derived allogeneic mesenchymal precursor cells (MPCs [rexlemestrocel-L]) or a control group undergoing a sham procedure. All randomized patients who proceed to dosing without a disqualifying event (i.e., at least one inclusion/exclusion criterion violation) undergo a single index cardiac catheterization, which includes contrast left ventriculography. The patients randomized to rexlemestrocel-L undergo cardiac mapping and transendocardial delivery of study product to 15-20 intracardiac sites characterized as viable myocardium. The sham group undergoes a pre-scripted blinded procedure in the catheterization laboratory that mimics the cardiac mapping and transendocardial delivery procedures but without insertion of mapping or injection catheters or study product administered.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the United States Food and Drug Administration (FDA) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol, Amendment 05, issued on 21 October 2016; Amendment 06 issued 15 March 2017; and Amendment 07 issued 04 October 2017
- Electronic case report forms (eCRFs) for Study MSB-MPC- CHF001 (version 39)
- Sponsor's Blinding Plan for Study MSB-MPC-CHF001 (19 September 2013)

- Data Monitoring Committee (DMC) Charter for Study MSB-MPC-CHF001 (05 June 2017)
- Clinical Endpoint Committee (CEC) Manual of Operations for Study MSB-MPC-CHF001 dated 13 November 2019
- ICH E9 Guidance on Statistical Principles for Clinical Trials
- ICH E3 Structure and Content of Clinical Study Reports.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing this study. When differences exist in descriptions or explanations provided in the protocol's statistical methods section and this SAP, the SAP prevails; the discrepancies will be explained in the CSR.

2. STUDY OBJECTIVES

The primary objectives of this study as per the protocol are presented below:

- 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 resuscitated cardiac death (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.
- 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 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:

- 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);
- 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: 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 (DRA) (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 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/revascularization therapy.

3. SELECTION AND WITHDRAWAL OF PATIENTS

Patient inclusion and exclusion criteria, in their entirety, are presented in Sections 3.1 and 3.2, respectively, of the final protocol v7.0 (Appendix 16.1.1 of the CSR). Importantly, a clarification is made to inclusion criterion "g" as detailed below following "NOTE":

- (inclusion criterion "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). NOTE: RVG imaging is also called MUGA scan. It will be performed if the echocardiogram (without or with contrast) is of inadequate quality to acceptably calculate LVESV, LVEDV, and LVEF. Additional information about the assessment of baseline of LVEF is provided in Section 3.9.1 of the protocol (Appendix 16.1.1 of the CSR), which includes the following: 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 non-evaluable quality 2-D echocardiographic imaging at screening will have an RVG performed.

If LV echocardiographic imaging at baseline was of insufficient technical quality, i.e., not evaluable, the data points from those images should not be used, even if recorded, and should be considered missing instead. In addition, if the baseline echocardiographic imaging quality was not evaluable, then all subsequent study visits will be considered to have non-evaluable echocardiographic data and should be considered as missing data.

As per the protocol, withdrawal criteria and procedures are detailed below.
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 the protocol.

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. Follow-up is counted from the randomization date.

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 (AE). 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 AE 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.

4. STUDY DESIGN

4.1 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/revascularization therapy. Overall, it is anticipated that an ischemic etiology of the patient's heart failure, as assessed by the study site on the baseline case report form, will be present in at least 60% of the patients who are randomly assigned to treatment.

Definition of Treated Patients: A patient is considered treated if he/she was randomized and underwent the 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.

The study comprises 3 main time periods: 1) a screening and randomization designation 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 minimum number of recurrent non-fatal HF-MACE (i.e., at least 531 decompensated HF events and/or successfully RCD events) is obtained and minimum follow-up of at least 6 months for all surviving subjects without TCEs. 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 the patient has survived that period of time without a TCE), and long-term safety and efficacy evaluations every 6 months after the Month 12 visit 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.

Clarification: a patient who underwent LVAD placement, heart transplant and/or artificial heart implantation will continue to be followed for determination of vital status (alive or dead) at the end of the study, AEs, potential primary and key secondary efficacy endpoint events, and ICD interrogation via telephone contact at the regularly scheduled time points until end of study or death. These follow-up data will be collected and utilized for safety and sensitivity efficacy analyses for the primary endpoint.

Written informed consent will be obtained for all patients 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. 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 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 an RVG (MUGA) 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 intent-to-treat (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 ischemic versus non-ischemic cardiomyopathy per the baseline CRF designation. 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.

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 for index cardiac catheterization (with or without intracardiac mapping and cell delivery) and will remain hospitalized on telemetry after index cardiac catheterization for a minimum of 1 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 who are 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 of the protocol [Appendix 16.1.1 of the CSR]). Fifteen to 20 appropriate myocardial locations will be identified (20 sites are 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 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 who are 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 (See Appendix 2 of the protocol [Appendix 16.1.1 of the CSR]). 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 as part of a scripted sham cardiac mapping

procedure. This will be followed by a scripted sham cell delivery procedure. Overall, the sham scripted procedure will simulate the 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 one of these systems 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 efficacy endpoint (i.e., recurrent non-fatal HF-MACE) 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 using the Joint Frailty Model (JFM) and included in the key secondary analysis.

For randomized patients who undergo the index cardiac catheterization, the following assessments will be performed during the follow-up period: 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]; patients who complete two 6MWTs during screening with either test [first or second] 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 AEs, CVA, MI, clinical laboratory tests, urinalysis, vital signs measurements, physical examinations, ECG recordings, 24-hour Holter monitor recordings (randomized patients across the US and ex-US), 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 1 and Table 2) will be conducted. 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 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, 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 protocol for all surviving patients who were randomized and underwent the scheduled 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) [redacted]

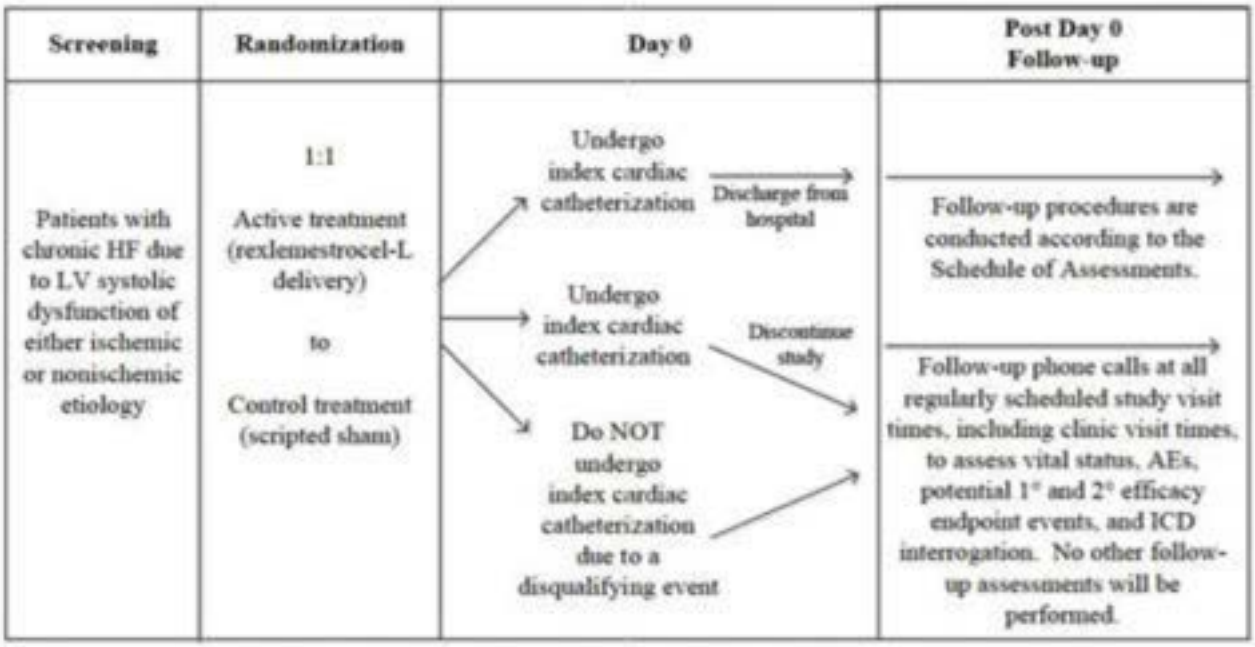
Blood samples will be collected from patients who provide informed consent for possible use in future PGx analyses for the assessment of possible associations between genetic polymorphisms and the response to rexlemestrocel-L therapy. Blood samples for PGx analyses will be collected at the end of screening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

The screening period may last up to 42 days before the date of the scheduled index cardiac catheterization. The first day of the screening period is the day the subject signs consent. For randomized patients who **DO** undergo the 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). A follow-up period continues until the required number of recurrent non-fatal HF-MACE (i.e., decompensated HF events and successfully RCD events) is obtained; a minimum of 6 months is required for all patients who survive and are without a TCE (see Table 2). 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 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 positively adjudicated recurrent non-fatal HF-MACE have occurred; 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 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 1.

Figure 1: Study Design



AEs=adverse events; HF=heart failure; ICD=implantable cardioverter defibrillator; LV=left ventricular; R=randomization; 1°=primary; 2°=secondary.

Note: Important: The timing of randomization relative to Day 0 will vary based on study drug availability and Biologics Delivery Systems 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 will continue 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 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 AEs, SAEs, TCEs, non-fatal HF-MACE (decompensated HF events or successfully resuscitated cardiac deaths), overall survival (includes all-cause deaths), coronary artery revascularization procedure, [redacted]

[redacted], CVA, and MI will be reviewed, evaluated, processed, and/or reported in accordance with the protocol. Additionally, for patients who undergo the index cardiac catheterization, the occurrence of all AEs on Days 0 through hospital discharge following index cardiac catheterization considered related to the intracardiac mapping or cell delivery procedure must be reported to the device manufacturer (Bioscience Webster, Inc. [per Biologics Delivery System (BDS) Safety Data Exchange Agreement] for the NOGA®/MyoStar™ or CARTO®/MyoStar™ Systems) and the unblinded medical monitor.

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. The ESC and CEC will be blinded to study treatment; the DMC will be unblinded. The 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 as defined in the Clinical Endpoints Adjudication Manual of Operations. 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]

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 pre-specified 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). Two pre-specified interim analyses to date were conducted during the study. For details, see Section 4.5.1. The DMC reviewed the results of the administrative IA1 without recommending protocol changes. The DMC also reviewed the results of the futility IA2 and provided pre-specified blinded information regarding study continuation to the ESC and the Sponsor.

Visit-specific procedures and assessments are presented in Table 1 and Table 2.

Table 1: 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

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
2-D echocardiography [m] or RVG (MUGA), if applicable	X				X [n]					X			X						X
Cardiac enzymes [o]			X		X														
Biomarker testing [p]	X									X			X						X
Index cardiac catheterization				X															
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

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
Overall survival (vital status) [a]					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 [f]	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 [g]	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 4.1 and 4.2 of the protocol (Appendix 16.1.1 of the CSR), 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 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. The first day of the screening period is the day the subject signs consent.
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 of the protocol [Appendix 16.1.1 of the CSR]) and none of the exclusion criteria (Section 4.2 of the protocol [Appendix 16.1.1 of the CSR]) will be eligible to participate in the study and will be scheduled for hospitalization at a cell injection center as described in the protocol. 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 the scheduled index cardiac catheterization 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, AE 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 non-qualifying for LVEF), MLHF questionnaire, EQ-5D questionnaire, 24-hour Holter monitor evaluation (randomized patients across the US and ex-US), 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 protocol 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 the protocol. 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 (MUGA scan) 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 (Table 1), 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 the protocol, 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 the protocol. 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 during the interval of Day 0 through hospital discharge 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 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 8.4.3).
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 tests, the reason for the tests 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 either of two 6MWTs with 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; MUGA= multi-gated acquisition scan; 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 2: 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)
	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 [MUGA], if applicable) [d]						X						X	
Biomarker testing [e]						X						X	
Electrocardiogram (ECG)			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)
	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	
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
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 (MUGA scan) 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; AE=adverse event; 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; MUGA=multi-gated acquisition scan; 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.

4.2 Primary and Secondary Measures and Endpoints

4.2.1 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.

The primary endpoint only considers recurrent 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 events 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 purposes of the primary efficacy analysis. However, for the purpose of the sensitivity analyses, successful RCDs may be considered as terminal events.

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. 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 (defined in Section 8.5.1) 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 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 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 used for adjustment in the primary analysis using the JFM and will be included in the key secondary analysis.

If death is non-cardiac and occurred after randomization but before study treatment, it will be considered a disqualifying event and date of death will be defined as Day 0 for this randomized but not treated patient.

If cardiac death occurred after randomization but before study treatment (a patient is randomized but not treated), her/his Day 0 is the date of cardiac death, which is considered a TCE for the JFM analysis purposes.

Adjudication of all potential non-fatal HF-MACE or TCE 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 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 non-sustained 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.

4.2.2 Secondary Efficacy Measures and Endpoints

4.2.2.1 Key Secondary Measure and Endpoint Relating to Terminal Cardiac Events

Time-from-Day 0 (defined in Section 6.5)-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).

The key secondary endpoint is a separate endpoint category due to its relationship to the primary endpoint and impact on the trial outcome interpretation. It will not be included in the hierarchical analysis as described in Section 6.3. (Note also that cardiac deaths that are included as a first TCE are not safety endpoints.)

A non-inferiority analysis will be performed to test if rexlemestrocel-L is non-inferior to control. The hazard ratio and associated 95% Wald Confidence Interval will be presented in a box-and-whisker plot.

4.2.2.2 Secondary Efficacy Measures and Endpoints

To protect the type 1 error rate, the secondary endpoints listed in this section will be tested using the hierarchical approach described in Section 6.3, in the following order:

- Time-to-nonfatal decompensated HF events associated with either hospital admission or urgent care outpatient visit beginning on Day 1 (recurrent events analysis)
- Time-to-first major cardiac event defined as a composite of non-fatal decompensated HF events associated with hospital admission or urgent care outpatient visit beginning on Day 1, and successfully RCD events.
- Time-to-first major cardiac event defined as a composite of non-fatal decompensated HF events associated with hospital admission or urgent care outpatient visit beginning on Day 1, and successfully RCD events, or TCE
- Time-to-successfully RCD events beginning on Day 1 (recurrent events analysis)

- Time-to-all-cause death.

4.2.2.3 Other Secondary Efficacy Measures and Endpoints

The endpoints and analyses listed in this section are to support the results of the primary and key secondary endpoint analyses and will not be included in the hierarchical analysis utilized to protect overall type 1 error rate for secondary endpoints. Since the type I error rate for these analyses may be inflated, the respective p-values will be provided for informational purposes only and should be viewed with caution. Also, due to relatively high expected TCE rate, the percentage of the imputed missing observations at 6 and 12 months may be relatively high. The outcomes of these analyses need to be viewed with caution.

1. The covariate analyses to explore impact of several covariates (NYHA Class, LVESV at baseline, and other) on study outcomes.
   - Time from Day 0-to-recurrent non-fatal HF-MACE adjusted for baseline NYHA Class (II vs. III)
   - Time from Day 0-to-recurrent non-fatal HF-MACE adjusted for baseline LVESV (≤100 mL vs. >100 mL)
   - Time from Day 0-to-first TCE adjusted for baseline NYHA Class (II vs. III)
   - Time from Day 0-to-first TCE adjusted for baseline LVESV (≤100 mL vs. >100 mL).

Same for additional covariates:

- hsCRP (hsCRP subgroups are defined by cut-off points of ≥2, ≥3 and ≥4mg/L)
- ICD (or CRT device [CRT-D]) /no ICD or CRT-D
- History of atrial fibrillation prior to Day 0 or atrial fibrillation at baseline yes/no
- NTproBNP >1000 vs. ≤1000 ng/mL.

2. LV remodeling will be assessed by change from baseline in LVESV, LVEDV, and LVEF as determined by 2-dimensional (2-D) echocardiography (echo-qualifying patients only). Changes in overall LV systolic function will be assessed by change from baseline LVEF in both the echo-qualified and the RVG-qualified patients.
3. Exercise capacity will be assessed by change from baseline in distance covered during the 6-minute walk test (6MWT).
4. Functional status will be assessed by change from baseline in NYHA functional class

5. Cardiac Biomarker status will be assessed by change from baseline in NTproBNP
6. Inflammation biomarker status will be assessed by change from baseline in hsCRP
7. QoL as assessed by change from baseline in the
   - Minnesota Living with Heart Failure (MLHF) total questionnaire score
   - EuroQol 5-dimensional Quality of Life (EQ-5D) questionnaire score.

4.2.3 Safety Measures and Endpoints

The safety and tolerability of rexlemestrocel-L will be assessed throughout the study (according to the schedule provided in Table 1 and Table 2) 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 ex-US who undergo the index cardiac catheterization), 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 related to index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 hospitalization through discharge for that hospitalization (for patients who are randomized and undergo the index cardiac catheterization)
- occurrence of treatment-emergent AEs (TEAEs) throughout the study
- 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 ex-US)
- physical examination findings
- review of important cardiovascular safety events of interest from CEC adjudicated data which include: 1) non-cardiac deaths; 2) coronary artery revascularization procedure; 3) pre-specified ventricular arrhythmic events that do not fulfill criteria for positively adjudicated HF-MACE; 4) non-fatal CVA; and 5) non-fatal MI.

4.2.4 [redacted] Pharmacodynamics/ [redacted]

[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.

4.2.5 Immunogenicity Measures and Endpoints

The immunogenicity variables and endpoints are as follows:

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

[redacted]

- [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/revascularization therapy.
- [redacted]

4.3 Sample Size and Power Considerations

The sample size is based on Monte-Carlo simulations: 600 patients with an estimated total of at least 531 recurrent non-fatal decompensated HF events 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 non-fatal decompensated HF events 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 the study would have a follow-up period substantially longer than 2 years unless they experienced a TCE).

The assumption regarding TCE rate is 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.

4.3.1 Simulation Algorithm for Sample Size and Power Calculations

There were 500-1000 simulated datasets for each simulation run, where a simulation run was defined by a unique combination of possible parameters characterizing the patient population: sample size, background recurrent and terminal event rates ($r_0(t)$ and $\lambda_0(t)$), censoring rate ($\lambda_{censoring}$), $HR_{recurrent}$ and $HR_{terminal}$, variance of the frailty (ω) between recurrent events (θ), the strength of correlation between recurrent and terminal events (γ), and maximum follow-up time (t_{max}). Greater variance of the frailty corresponds to stronger correlation between gap times (recurrent events); zero variance corresponds to independent recurrent events. On the other hand, a large value of variance θ also specifies a large between-subjects variation with respect to event recurrences and terminal events. The simulation process is described as follows:

- Subjects were randomly assigned to a treatment group (active or placebo) based on a Bernoulli (0.5) distribution.
- Calendar timescale was used relative to time of dosing = Day 0; e.g., an event that happened on Day 20 happened on the 20th day after randomization.

- A random censoring time was drawn for each subject (corresponding to lost-to-follow-up time), based only on the simulation parameter $\lambda_{censoring}$; i.e., it was assumed that lost-to-follow-up censoring is independent of recurrent events (non-informative). As these patients had very advanced HF, very few of them were expected to withdraw consent or otherwise to have been lost to follow-up.
- A random time of the terminal event was drawn for each subject, based on the simulation parameters $\lambda_0(t)$, $HR_{terminal}$, and ω^γ, where ω represents the randomly generated frailty and γ – any number (positive or negative); greater positive γ represents higher correlation between recurrent and terminal events.
- If either the censoring or terminal event time was greater than t_{max}, the subject was considered censored at t_{max}.
- A random gap time was drawn for each subject, based on the simulation parameters $r_0(t)$, $HR_{recurrent}$, and ω. The gap time was added to the previous event time (or 0 if no previous event) to arrive at the time of the current event.
- Generation of recurrent event times for a given subject continued until the time of censoring, end of study, or terminal event (whichever was sooner) was exceeded. If by chance a recurrent event time equaled the terminal event time, the time was "assigned" to the terminal event and not the recurrent event.
- Data from each simulation run were analyzed using PROC NLMIXED implementation of a JFM. Parameter estimates, standard errors (SEs), and significance levels were retained from each simulation run.
- Mean parameter estimates ($HR_{recurrent}$, $HR_{terminal}$, θ, γ) and mean SEs were calculated over all runs.
- An empirical SE for each estimated parameter was calculated as the SE of the estimate over all runs.
- For $HR_{recurrent} < 1.0$, $HR_{terminal} < 1.0$, separate power was calculated as the proportion of runs for which the estimated HR significantly differed from 1.0 with significance level α=0.05.

The Joint Frailty Model is used on Simulated Datasets

Time to terminal events, time to censoring and gap times between recurrent events will be randomly generated using SAS function RAND with "WEIBULL" option. The density of the Weibull distribution is given by

$$f(x) = \frac{a}{b^a} x^{a-1} exp\left\{-\left(\frac{x}{b}\right)^a\right\}$$

for $x \geq 0$, with shape parameter a > 0 and scale parameter b > 0. For a = 1, this is the exponential distribution with rate parameter b > 0.

Parameters a and b will be defined as follows:

- Censoring: a=1, b= $1/\lambda_{censoring}$
- Recurrent event: a=1, b= $1/r_i(t)$
- Terminal event: a=1, b= $1/\lambda_d(t)$

Under the JFM assumption, and with $\log(HR_{recurrent}) = \beta_1^T$, $\log(HR_{terminal}) = \beta_2^T$, $r_i(t)$ and $\lambda_d(t)$ are defined as follows:

$$r_i(t) = \exp(\beta_1^T Z_i)\, r_o(t)\, \omega_i$$
$$\lambda_d(t) = \exp(\beta_2^T Z_i)\, \lambda_o(t)\, \omega_i^\gamma$$

Note only one covariate, Zi (treatment group), will be considered. The correlation between these two processes is introduced by the shared frailty ωi which can have a different impact on $r_i(t)$ and $\lambda_d(t)$ due to the parameter γ.

Two different distributions for ω may be considered:

(a) Gamma(1, θ)
(b) Normal(0, θ)

For example, for ω ~ Gamma(1, θ), a random frailty with the mean of 1 and variance of θ is drawn for the ith subject using the SAS statement

$$w_i = \text{RANGAM}(\text{seed}, 1/\theta) * \theta$$

Then, a random terminal event time is drawn using the SAS statement

$$ft_i = \text{RAND}(\text{"WEIBULL"}, 1, 1/b_{2\_i})$$

where

$$b_{2\_i} = \exp(\beta_2^T Z_i)\, w_i^\gamma\, \lambda_o(t)$$

$\lambda_o(t) = (-\ln(1 - \text{rate}_{terminal}))/12$ for time expressed in months

$\text{rate}_{terminal}$ = baseline annual terminal event rate

Similarly, the jth gap time for a recurrent event for the ith subject is drawn using the SAS statement

$$rt_{i\_j} = \text{RAND}(\text{"WEIBULL"}, 1, 1/b_{1\_i})$$

where

$b_{1\_i} = \exp(\beta_1^T Z_i)\, w_i\, r_0(t)$

$r_0(t) = (-\ln(1 - rate_{recurrent}))/12$ for time expressed in months

$rate_{recurrent}$ = baseline annual recurrent event rate

Through a trial-and-error process, we will determine appropriate values for $rate_{recurrent}$ based on target levels of number of events per subject. For example, if the target is 1.2 events per subject per year, setting $rate_{recurrent}$ to 1.2 will not necessarily yield the desired target due to the dependencies imposed by the frailties.

Lastly, the censoring time for the ith subject is drawn using the SAS statement

$$ct_i = \text{RAND}(\text{"WEIBULL"}, 1, 1/c)$$

where

$c = \lambda_{censoring}$

$\lambda_{censoring} = (-\ln(1 - rate_{censoring}))/12$ for time expressed in months

$rate_{censoring}$ = annual censoring rate = 0.05.

4.4 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 interactive response technology (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. At least 20% of the patient population in the study will be women.

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. 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 (Table 1 and Table 2), 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 all 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, will undergo the scheduled index cardiac catheterization in which the catheter is passed through the aortic valve and 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, of the protocol (Appendix 16.1.1 of the CSR)).

All patients randomly assigned to the control group and 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 full procedural requirements used for the actual treatment cohort transendocardial delivery of rexlemestrocel-L to the myocardium (Appendix 2 of the protocol [Appendix 16.1.1 of the CSR]). These patients will not undergo placement of the NogaStar® navigation catheter and the MyoStar™ catheter. The scripted sham cardiac mapping and cell delivery procedure will not include internal mapping but is designed to correspond to the operational steps that are used for intracardiac transendocardial delivery of rexlemestrocel-L using the NOGA® Mapping System/MyoStar™ catheter or the CARTO® Mapping System/MyoStar™ catheter. 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.

Patients, as well as non-interventional 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 2.

Figure 2: 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 AE 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.

4.5 Sequence of Planned Analyses

4.5.1 Interim Analyses

4.5.1.1 Interim Analysis #1

The details of interim statistical analysis #1 (IA1) are provided in the IA1 SAP (see Appendix 2). The report on the pre-specified outcomes of the IA1 is provided in Appendix 3. It should be noted that IA1 was completed prior to change in the primary endpoint definition and respective analytical approach (FDA minutes dated 22 June 2015). Respectively, the current primary endpoint (recurrent non-fatal HF MACE) was not analyzed or reviewed during IA1.

IA1 was to be performed by Statistics Collaborative, Inc. (SCI) after the first approximately 120 patients had undergone index cardiac catheterization and been followed for at least 6 months. Randomized patients who 1) did not undergo index cardiac catheterization, or 2) underwent index cardiac catheterization after the cutoff date for IA1 were to be excluded from the analysis. The cutoff date was defined as the date on which approximately the 120th patient reached the 6-month follow-up visit. IA1 did not include a formal safety or efficacy review by the Data Monitoring Committee (DMC) and was neither used to re-evaluate the number of required HF-MACE events nor to stop the study early for success.

The objective of this administrative review was to determine whether predefined thresholds had been met on the basis of analyses of 2-D echocardiographic-determined secondary endpoints for non-clinical event measurement (i.e., left ventricular ejection fraction [LVEF], end-systolic volume [LVESV], and end-diastolic volume [LVEDV]), and the then-primary endpoint (HF-MACE). The potential actions were to terminate or continue study financing. The outcomes were pre-specified in the manner consistent with the futility analysis.

The predefined thresholds for IA1 were as follows:

- Left **ventricular echocardiographic endpoints:** Absolute mean change from baseline at Month 6 in LVEF is not at least 2.5% greater in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm < +2.5%)

  OR

Absolute mean change from baseline at Month 6 in LVESV and LVEDV is not at 5 mL lower in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm > –5 mL);

- **HF-MACE**: The log-rank statistic for HF-MACE is less than the critical value derived under the Hwang, Shih, and DeCani beta-spending function (γ= –2).

No formal open or closed report was prepared at this interim analysis. SCI conducted the unblinded IA1 and communicated to the sponsor and Executive Steering Committee (ESC) whether the predefined thresholds are 'met' or 'not met' for the measurement of interest and then-primary endpoints. This communication did not include any numeric results; rather, it consisted of two binary responses: one corresponding to whether the threshold has been met for the left ventricular (LV) echocardiographic endpoints and the other for whether the threshold has been met for HF-MACE. The DMC was not involved in the conduct of IA1 and was not responsible for conveying a recommendation to the ESC based on its results.

- The analysis of the LV echocardiographic endpoint included only patients who underwent index cardiac catheterization on or before the IA1 cutoff date and had baseline and Month 6 measurements. SCI provided the sponsor and ESC with a single "yes/no" response as to whether the LV threshold has been met on the basis of the three LV echocardiographic endpoints (LVESV, LVEDV, and LVEF). A response of "yes" indicates an unfavorable finding for rexlemestrocel-L relative to sham patients.
- The HF-MACE analysis included only events for the subset of patients who underwent index cardiac catheterization on or prior to the cutoff date for IA1. All events for such patients were incorporated in the analysis, including events which occurred after the first six months of follow-up (i.e., no events were censored). Teva estimated that roughly 20 to 30 HF-MACE events were to occur and were to be positively adjudicated at the time of IA1. Assuming observation of 314 events at the conclusion of the study, this would represent an information fraction of roughly 6 to 10% (i.e., 20/314 to 30/314).

With an information fraction of 7%, the critical value derived under the Hwang, Shih, and DeCani[2] beta spending function (γ= –2) would be a z-score of -1.85 (with negative z-scores corresponding to an increased hazard rate in the rexlemestrocel-L group relative to sham patients). Hence, SCI would report "yes" to the sponsor and ESC if the z-score is less than -1.85. As with the LV threshold, a response of "yes" indicated an unfavorable finding for rexlemestrocel-L relative to sham patients.

Interim Analysis #1 Outcomes

For a report of the outcomes, see Appendix 3.

The response YES (unfavorable) was provided to ESC based on the results of LV echocardiographic endpoints.

The response NO (favorable) was provided to ESC based on the results of HF-MACE analysis.

It was decided that study would continue as planned.

IA1 outcomes were pre-defined in a manner consistent with the futility analysis. Because the DMC did not review the data of IA1, and because stopping for superiority and change in number of events/patients were not planned outcomes of the review (i.e., no alpha spending was involved), no adjustment of alpha level will be required at the time of final analysis.

4.5.1.2 Interim Analysis #2

Mesoblast conducted the Study MSB-MPC-CHF001 futility Interim Analysis #2 (IA2) (Appendix 4) based on the evaluation of recurrent non-fatal HF-MACE adjusted for TCEs (Appendix 2). These are the same clinical events that will be incorporated into the trial's primary endpoint at completion of the study. For IA2, the analysis data cut-off date was December 31, 2016. All positively adjudicated recurrent non-fatal HF-MACE and all TCEs that occurred on or before this date were included in IA2. The subjects with less than 3 months of follow-up were excluded from IA2.

IA2 was performed using the JFM approach[3] which is designed to avoid the introduction of bias due to dependent censoring associated with mortality or other terminal clinical events. Approximately 270 patients had been randomized, underwent Day 0 index cardiac catheterization, and with a minimum of 3-months follow-up data were included in IA2. A total of 141 positively adjudicated recurrent non-fatal HF-MACE were included in IA2, which represented 26.6% of the 531 recurrent non-fatal HF-MACE expected at the end-of-the-trial. An independent unblinded statistician performed the IA2 data evaluation. This individual reviewed the results and informed the Sponsor, the DMC and the trial's Executive Steering Committee of its findings relating to pre-defined hazard ratio futility thresholds. The IA2 output did not include any analysis or data review for superiority, p-value determinations, or any other early stopping of the trial for success. Rather, the IA2 analysis was a futility analysis with a pre-specified stopping rule threshold for recurrent non-fatal HF events

calculated for rexlemestrocel-L vs the sham group using JFM. Interim Analysis 2 has been completed and study was continued.

The **IA2** is a **futility analysis** with a stopping rule threshold for **recurrent non-fatal HF events** at HR ≥0.92 calculated for rexlemestrocel-L therapy vs. the sham group using JFM. The specific question that the independent statistician will address will be "**Using the JFM analysis, is the HR <0.92**?" The response from the independent statistician will be a YES, NO, "INDETERMINATE" answer to the following sub-category questions:

- Using the JFM analysis, is the HR for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. the sham group for the aggregated NYHA Class II plus NYHA class III patients?
- Using the JFM analysis, is the HR for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. the sham group for the NYHA Class II patients alone? This analysis may not be feasible due to small number of recurrent non-fatal HF-MACE and/or TCEs.
- Using the JFM analysis, is the HR for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. the sham group for the NYHA Class III patients alone? This analysis may not be feasible due to small number of recurrent non-fatal HF-MACE and/or TCEs.

Throughout the IA2 process, Mesoblast remained fully blinded to the quantitative results and was informed only if the sub-category HR could be calculated using JFM or not. The only answers that Mesoblast received were whether the calculated HRs for each of the 3 sub-categories was below the pre-defined HR futility boundary (i.e., independent statistician's response was "YES", "NO", "INDETERMINATE").

Action planned:

If the response to ANY ONE OR MORE OF THE THREE SUB-CATEGORY QUESTIONS is that the HR <0.92 then crossing the FUTILITY BOUNDARY WILL BE REJECTED as an outcome and the STUDY WILL CONTINUE AS PLANNED.

The STUDY WILL BE STOPPED FOR FUTILITY ONLY IF ALL THREE SUB-CATEGORIES HAVE A CALCULATED HR and EACH HR >0.92.

IF ANY OF THE THREE SUB-CATEGORIES DOES NOT HAVE A CALCULATED HR due to insufficient number of recurrent non-fatal HF-MACE and/or TCEs (i.e., JFM does not converge and HR could not be calculated), **THAT SUB-CATEGORY'S ANALYSIS WILL BE REPORTED AS "INDETERMINATE"**.

- In the event that at least one of the three sub-category analyses is INDETERMINATE and either or both of the other sub-category analyses pass futility then the conclusion will be that the futility boundary is rejected, and the study will continue as planned.
- In the event that at least one of the three sub-category analyses is INDETERMINATE and neither of the other sub-category analyses pass futility, the study will continue as planned and a subsequent futility analysis will be considered when more recurrent non-fatal HF-MACE and TCEs and a longer duration of patient follow-up has been achieved.

Table 3 summarizes the possible outcomes of the futility analysis decision process.

Table 3: Possible Outcomes of Futility Analysis Decision Criteria: Answer to the Question: Is the HR for Recurrent Non-Fatal HF Events <0.92?

Sub-categories by NHYA Class at Baseline			DMC Recommendation
NYHA Class II+III	NYHA Class II Only	NYHA Class III Only	
Answer given to ESC/Sponsor = YES (PASSES FUTILITY)			
YES	YES	YES	Study Continues
YES	NO or Not Calculated	NO or Not Calculated	Study Continues
NO or Not Calculated	YES	NO or Not Calculated	Study Continues
NO or Not Calculated	NO or Not Calculated	YES	Study Continues
YES	YES	NO or Not Calculated	Study Continues
NO or Not Calculated	YES	YES	Study Continues
YES	NO or Not Calculated	YES	Study Continues
Answer given to ESC/Sponsor = INDETERMINATE ANALYSIS			
Not Able to Calculate	NO	NO	Study Continues
NO	Not Able to Calculate	NO	Study Continues
NO	NO	Not Able to Calculate	Study Continues
NO	Not Able to Calculate	Not Able to Calculate	Study Continues
Not Able to Calculate	NO	Not Able to Calculate	Study Continues
Not Able to Calculate	Not Able to Calculate	NO	Study Continues
Not Able to Calculate	Not Able to Calculate	NO or Not Calculated	Study Continues
Answer given to ESC/Sponsor = NO (STUDY IS FUTILE)			

Sub-categories by NHYA Class at Baseline			
NYHA Class II+III	NYHA Class II Only	NYHA Class III Only	DMC Recommendation
NO	NO	NO	Study Stopped

Since the study was not to be stopped for superiority of rexlemestrocel-L to control and since the number of recurrent non-fatal HF-MACE was not to be changed based on the IA2 results, a significance level adjustment at the time of final analysis will not be performed.

4.5.2 Final Analyses and Reporting

All planned analyses identified in this SAP will be performed when a pre-specified number of recurrent non-fatal decompensated HF events have been positively adjudicated and the last enrolled patient has completed at least 6 months of follow-up assuming that he/she has not discontinued from the trial and/or had a TCE.

Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

5. POPULATIONS /ANALYSIS SETS

5.1 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.

5.2 Safety Population

All safety analyses will be produced for the safety population as defined in the protocol and may be also produced for the subpopulations described below (Sections 5.3.1 and 5.3.2) as described in Section 9.1.

5.3 Safety Population as Defined by Protocol

The safety population as defined in the protocol will include all patients in the ITT population who underwent the 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.

Note: Patients who were randomized and not treated will be included in the ITT population but not included into the safety population. Their safety data will be reported in separate patient listings.

As defined in Section 4.1, a patient is considered treated if he/she was randomized and underwent the 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.

5.3.1 Subpopulation 1: Patients within Safety Population who had LVAD placement, artificial heart or heart transplant

This population will include patients who had LVAD placement, artificial heart, or heart transplant.

5.3.2 Subpopulation 2: Patients within Safety Population who did not have LVAD placement, artificial heart or heart transplant

This population will include patients who did not have LVAD placement, artificial heart, or heart transplant.

5.4 Full Analysis Set (FAS)

The definition of the full analysis set (FAS) is the same as that for the safety population as defined in the protocol (Section 5.3). Therefore, safety analyses will be the same as the FAS. 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.

5.5 Echo-qualifying Patients

The echo-qualifying patients are those in FAS who have a baseline 2-D echocardiography assessment and did not have baseline RVG (MUGA) performed. 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.

5.6 RVG-qualifying Patients

The RVG-qualifying patients are those in FAS who have a baseline RVG (MUGA) assessment. 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.

[redacted]

5.8 Sub-group Analysis Sets

Subgroup analyses will be provided using the same analysis model as specified for the primary and/or key secondary efficacy endpoint. Here is the list of potential subgroups:

- Baseline NYHA class (Functional Class II versus Functional Class III)
- Gender (male, female)
- Age (≥ 65, <65)
- Age (<50, $50-<65$, ≥ 65)
- Race (White vs. Black vs. Asian vs. Native Americans vs. Other)
- Ethnicity (depending on the outcome of a blinded data review)
- Geographic region (US versus ex-US)
- Presence of ischemic versus non-ischemic cardiomyopathy per the baseline CRF designation
- Baseline diagnosis of diabetes mellitus (yes; no)
- Subjects with implanted defibrillator (ICD or CRT-D) vs. those with no implanted defibrillator (no ICD or CRT-D)
- Subjects with any type of CRT (CRT, CRT-D or CRT pacemaker [CRT-P]) vs. subjects without CRT, CRT-D, or CRT-P (no CRT, CRT-D, or CRT-P)
- LVESV ≤ 100 mL vs. >100 mL
- LVEF $\geq 30\%$ vs. $<30\%$
- NT-proBNP ≤ 1000 ng/mL vs. >1000 ng/mL

- hsCRP <2 vs ≥ 2, <3 vs ≥ 3, <4 mg/L vs. ≥ 4 mg/L
- Concomitant Medications: ACEI &/or ARB, Yes/No
- Concomitant Medications: Angiotensin-Neprilysin Inhibitor, Yes/No
- Concomitant Medications: Aldosterone Antagonist, Yes/No
- Concomitant Medications: Beta Blocker, Yes/No
- Concomitant Medications: Diuretics (Aldosterone Antagonists plus others), Yes/No
- Concomitant Medications: Digitalis, Yes/No
- Concomitant Medications: Statins, Yes/No
- Concomitant Medications: Oral Anticoagulants, Yes/No
- Concomitant Medications: Anti-Platelet Agents, Yes/No
- Concomitant Medications: Heparin, Yes/No
- Concomitant Medications: Diabetes Medications, Yes/No
- Atrial Fibrillation History or present at BL, Yes vs. No
- Time Since Diagnosis of HFrEF, <1 year vs. >1 to 5 years vs. >5 years
- Decompensated HF Event 1-9 months prior to screening, Yes vs. No

Additional subgroup analyses may be performed using other baseline patient characteristics.

6. GENERAL ISSUES FOR DATA ANALYSIS

6.1 General

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error of the mean, median, minimum, and maximum. If inferential statistics are computed, it will also include least square mean and standard error of the least square mean. Descriptive statistics for categorical variables include patient counts and percentages.

Summaries of clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and early termination visits).

The 'Last Assessment' for an analysis is the last observed non-missing post-baseline data.

6.2 Specification of Baseline Values

Unless otherwise stated for the purpose of the efficacy or safety summaries, the baseline value is defined as the last non-missing assessment prior to the Day 0 study intervention.

For 6MWT, 2 tests are required during screening separated by at least 1 calendar day. The maximum value of the 2 eligible 6MWTs (i.e., distance obtained from each test must be 450 meters) obtained during screening will be used for the baseline 6MWT distance value.

6.3 Multiple Comparisons and Multiplicity

Starting in the latter part of 2017, only patients with NYHA Class III at baseline were enrolled in this study. The motivation, details, and statistical approach to this population enrichment/adaptation are described in Appendix 1 to this SAP.

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 4.2.2.2 while controlling the overall Type I error rate at 5% (2-sided alpha of 0.05).

If the resulting 2-sided p-value from the primary endpoint comparison is less than the alpha level, then the next comparison of interest (first secondary endpoint listed in Section 4.2.2.2) will be interpreted inferentially at the alpha level of 0.05 two-sided. This process continues through the secondary endpoints listed in Section 4.2.2.2 until either all comparisons of interest are interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest is greater than 0.05. After the point where p-value is greater than 0.05, no further comparisons will be interpreted inferentially and respective analyses will be performed descriptively.

6.4 Data Handling and Missing Data

6.4.1 Missing Data

Methods of data handling for efficacy endpoints will be described in Section 8.3, where applicable.

6.4.2 Partial Dates

Adverse event start dates will be imputed for the purposes of determining whether or not events are treatment emergent. If the month and year are available, then the Day will be estimated as the first day (01) of the month. If only the year is available, then Month will be estimated as mid-year (July) and day will be estimated as previously defined, unless otherwise noted. Adverse event end dates will not be imputed.

Medication start and end dates will not be imputed but partial dates will be utilized to determine whether medications taken during the course of the study are either prior medications or concomitant medications. In order to determine if a medication is considered to be a concomitant medication a comparison should be made between the medication end date and the treatment date. If only the year is available, then compare the medication year to the treatment year. If the medication year is less than the treatment year, then it is not a concomitant medication. If the year and month are available, then compare the medication year and month to the treatment year and month. If the medication year and the treatment year are equal but the medication month is less than the treatment month, then it is not considered a concomitant medication. Otherwise, partial dates will be considered as a concomitant medication. Similarly, in order to determine if a medication is considered to be a prior medication, then a comparison should be made between the medication start date and the treatment date. If only the year is available, then compare the medication year to the treatment year. If the medication year is greater than the treatment year, then it is not a prior medication. If the year and month are available, then compare the medication year and month to the treatment year and month. If the medication year and the treatment year are equal but the medication month is greater than the treatment month, then it is not considered a prior medication. Otherwise, partial dates will be considered as a prior medication.

Patient listings will contain original dates as collected, not imputed.

The imputations for partial dates are only for calculation purpose. Original date variables will not be imputed. Listings will list dates as collected.

6.5 Study Days and Visit Windows

For by-visit summaries, if there are multiple assessments at a post-baseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits. For patients who withdraw from the study, data at the early

termination visit will be excluded from the by-visit summaries but will be included in the endpoint summaries.

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

- 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), which is the patient's equivalent of his/her Day 0;
- for patients who are randomized and **DO** undergo the index cardiac catheterization as the date of the index cardiac catheterization;
- study days will be numbered relative to Day 0 (i.e., ... –2, –1, 0, 1, 2, ...). For example, Day 1 will be the day after Day 0.
- The by-visit analysis windows for this study were constructed with a medians-based approach around the protocol-specified visit. Data collection schedules varied from one data domain to the next, necessitating a distinct set of windows for each domain. Additional details are presented in Appendix 7.

Any adjudicated primary endpoint events (recurrent non-fatal HF-MACE) or key secondary event (cardiac terminal event) occurring after randomization will be included in the primary ITT analysis even if the randomized patient did not undergo the index cardiac catheterization.

6.6 Data After Terminal Cardiac Event

For all secondary efficacy variables other than time-to-event data, any measurements listed after TCE should be considered as a missing data point for the summary tables but should still be present in by-patient listings. Missing data handling for efficacy endpoints other than time-to-event are described in Section 8.3.

6.7 Vital Status Determination for Lost to Follow-Up Patients (Life Status Follow-Up)

Accelerated Enrollment Solutions (AES) was contracted by Mesoblast to assist in the determination of vital status (i.e., alive or dead) for study subjects who were randomized into the Dream HF-1 study but who failed to return for their last study assessment visit and who were unresponsive to multiple telephone outreaches and a certified mailing. Those patients were categorized as "Lost-To-Follow Up" (i.e., L2FU).

The L2FU specialists at AES employed a secure web portal that was HIPAA, GDPR and US-EU Privacy Shield compliant. This secure web portal was used by DREAM HF-1 study sites to upload subject information in order to initiate and facilitate AES' search. Only specific users at the study

sites had access to data related to their specific site. AES conducted a worldwide search of publicly available databases to determine if individual study subjects had a documented death. The results of AES' Vital Status search were uploaded to the secure AES website by AES associated search agency investigators. The results of the L2FU determination was then reviewed internally by AES and only allowable information was passed on to the sites. These data were then incorporated into the study subject's clinical trial records.

6.8 Calculation of Duration of Follow-Up

Calculation of the duration of patients' follow-up will be performed as follows:

1. For Primary Efficacy Endpoint and Key Secondary Endpoint: Duration of follow-up time is defined as time from Day 0 until first TCE or end-of-study.
2. For All-cause Deaths: Duration of follow-up time is defined as time from Day 0 to death of any cause or end-of-life status follow-up.

7. STUDY POPULATION

7.1 General

The ITT population 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.

7.2 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 (same as FAS), and 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 randomized but did not receive treatment, and patients randomized but did not complete the index cardiac catheterization.

Two patients at Site # [redacted] were randomized twice and assigned two different patients identification numbers. Details regarding the handling of these 2 patients are presented in Appendix 5.

7.3 Demographics 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, ischemic versus non-ischemic cardiomyopathy per the baseline CRF designation, 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 menopause status will be summarized using descriptive statistics.

Missing categories will be presented if necessary.

7.4 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.

7.5 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.

7.6 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.

7.7 Protocol Violations

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

7.8 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.

8. EFFICACY ANALYSIS

8.1 General

Efficacy analyses will be based on the ITT population unless otherwise noted. Summaries will be presented by treatment group as randomized/assigned unless otherwise specified. Day 0 for all time-to-event analyses is defined in Section 6.5.

For time-to-event analyses, time-to-event is defined as the interval in days from study Day 0 to the date of event occurrence or date of last follow-up/contact, unless otherwise specified. For a partial date with missing day only, the first day of the month will be used for the purpose of calculation. If month and/or year are missing from a date, set the calculation to missing.

For event-based efficacy endpoints, the analyses will be based only on those events positively adjudicated by CEC.

The distance covered by 6MWT recorded in feet will be converted to meters in analysis data. Meters will be calculated as feet/0.3048.

8.2 Censoring Rules and Event Recording Conventions

8.2.1 Time-to-Recurrent Event Analysis

The censoring rules for time-to-recurrent event analysis include the following:

- If a patient experienced no HF-MACE (neither decompensated HF events nor successfully RCD events) and no TCE while on study, the patient will be censored at the end of study

date (censoring indicator = 0, even if patient died for non-cardiac or unknown reason or had vital status of "dead" at EOS).

- If patient experienced no TCE, then in the last record for this patient, the censoring indicator = 0
- As vital status was determined for all randomized patients, no patient was lost to follow-up.
- If a patient experienced one or more recurrent non-fatal HF-MACE, then the date of each event will be recorded and for each event censoring indicator will be set to 1 (censoring indicator = 1).
- If a patient experienced a TCE, the censoring indicator=2 and terminal event date will be recorded.

8.2.2 Event Recording Conventions

- If TCEs and recurrent non-fatal HF-MACE occur on the same day, only the TCE counts
- If a terminal event occurs after 24 hours from heart failure hospitalization or outpatient treatment, both a heart failure and terminal event will be considered to have occurred.
- Resuscitated cardiac death events will be adjudicated if they occur on separate calendar days and the CEC is able to determine the events as distinct episodes and not a continuation of one another, such as continuous clinical episodes that span over midnight or cases of incessant VT.
- First TCE precludes the observation of further recurrent non-fatal HF-MACE and TCEs for primary analysis purposes.
- Any non-cardiac death would be treated as a censoring event but not a TCE (censoring indicator = 0).
- The patient who was randomized but was not dosed will not be censored until end-of-study and will be followed for recurrent non-fatal HF-MACE and TCEs;
- For heart failure hospitalization, the event will be considered to start at the time that the patient arrives and is checked in to either the emergency room or the hospital. Outpatient treatment events will be considered to have commenced at the time the patient arrives at the facility where the treatment is given.
- The 24-hour period during which a terminal event would preempt a heart failure event refers to the initial continuous 24 hours following arrival in the hospital, emergency room or, in the case of outpatient treatment, at the facility where the treatment was administered.
- Elective admissions for either LVAD or transplant will not be considered a heart failure event.

The censoring rules for time-to-TCE analysis:

- Only first TCE will be accounted for in the primary and key secondary analyses. For example, if a patient had LVAD placement followed by heart transplant and then died, only LVAD placement will be accounted for in the analysis. However, all positively adjudicated TCEs will be accounted for in the sensitivity analysis
- Occurrence of a terminal event within the first 24-hour period following a heart failure event (either hospitalization or outpatient treatment as defined in the protocol) will be considered a terminal event only. This situation is likely to occur only for resuscitated SCD or death and is unlikely to occur for either durable LVAD or cardiac transplantation.
- If a patient experienced no TCEs, this patient will be censored at the end of study (censoring indicator = 0)
- If a patient experienced a TCE, censoring indicator will be set to 2 at the time of first TCE.

8.2.3 Event Recording for patients randomized but not treated

If patient was randomized but not treated AND had no events (neither recurrent non-fatal HF-MACE nor TCE nor any follow up information) after Day 0, the End of Study date is equal to Day 0 date.

If patient was randomized but not treated AND at least one recurrent non-fatal HF-MACE or TCE (or both) occurred after Day 0, the recording format for these events is identical to that for treated patients.

8.3 Missing Data Handling for Efficacy Endpoints Other Than Time-to-Event

There are two sources of missingness:

- Missing due to TCE or non-cardiac death, or unknown death, including vital status of death at the study end
  - To handle this data appropriately and minimize the bias associated with missing data we are proposing a specific way of data analysis: trimmed means as a primary, and median comparisons as sensitivity. The methodology is described in more detail in Appendix 6.
- Missing due to missed assessment
  - Data missing due to missed assessment will be imputed using multiple imputation techniques, assuming the data is missing at random (MAR).

- Multiple imputations procedure will be performed within each treatment group based on the within-group distribution of non-missing data. To account for uncertainty around the true value, multiple (5) values will be estimated. These values will then be used in the analysis at 6 months and 12 months as described in Section 8.5.6 and then results will be combined. Number of missing values can be summarized for LVESV, for example, using PROC MEANS with option NMISS. The missing data patterns will be examined using PROC MI with the ODS option MISSPATTERN. Use NIMPUTE option for PROC MI to specify the number of imputations (5 is usually sufficient). Then, for each imputation, the specified analysis will be performed and the results will be combined using PROC MIANALYZE.

8.3.1 Ambiguous/Missing Response in MLHF Questionnaire Data

The MLHF questionnaire comprises 21 questions with responses of 0 to 5; higher scores indicate poorer quality of life. Two dimension scores and a total score will be calculated for the analyses. See Section 8.5.6.2 for more description.

If more than one response is selected for a question for a visit, then the ambiguous responses will be treated as a missing value.

For purpose of calculating dimension scores and the total score, if more than 15% of questions needed for a calculation are missing, then the calculated score will be set to missing. If ≤15% of questions needed for a calculation are missing, the score calculated based on non-missing responses will be multiplied by (# of questions needed for the calculation) / (# of needed questions with non-missing responses), and rounded to one decimal. For example, of total score calculation (need 21 questions), if missing response for 2 questions and summation of responses with non-missing response (from 19 questions) is 90, then the total score would be 90*(21/19) = 99.5.

8.3.2 EQ-5D Data

The EQ-5D questionnaire comprises questions for 5 dimensions with 5 level responses for each question; see Section 8.5.6.3 and Appendix 6 of the protocol for more description (Appendix 16.1.1 of the CSR).

If more than one response to a question is entered for a same visit, then the ambiguous responses will be treated as missing values.

Health state (range from 100 to 0) will be collected. Missing response will not be imputed.

8.4 Primary Efficacy Variable and Analyses

8.4.1 Primary Efficacy Endpoint

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 or successfully resuscitated cardiac death events. Day 0 is defined in Section 6.5. The primary endpoint only considers non-fatal HF-MACE that occur prior to the first TCE. However, all recurrent and TCEs 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 JFM analysis. Adjudication of non-fatal HF-MACE and TCEs will be performed by an independent, blinded CEC (See CEC Manual of Operations).

Resuscitated cardiac death will be adjudicated when a patient experiences sudden death or cardiac arrest and is successfully resuscitated by cardioversion, defibrillation, or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness and received a successful appropriate shock from any type of implanted cardiac defibrillator (ICD or CRT-D) with meaningful recovery will also meet these criteria. This definition excludes known transient losses of consciousness such as seizure or vasovagal episodes that do not reflect significant cardiac dysfunction. These events will be considered recurrent (non-terminal) events for the purpose of the primary efficacy analysis and will be considered TCEs in sensitivity analyses.

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 5.4 for definition of FAS). The details of various sensitivity analyses of the primary efficacy endpoint are described in Section 8.4.6. All sensitivity analyses will use methods similar to that described for the primary analysis, unless otherwise stated.

8.4.2 Statistical Model Background and Rationale

Several aspects of the NYHA class III HF patient population with advanced HF may complicate the determination of the treatment effect on disease-related events. This patient population is characterized by frequent HF-related hospitalizations, high mortality and continued worsening of the

disease, often leading to surgical interventions such as LVAD implantation, artificial heart, and/or heart transplant. Patients who experienced non-fatal HF-MACE may be at an increased risk of having additional non-fatal HF-MACE or a TCE. Therefore, recurrent non-fatal HF-MACE and a TCE (LVAD implant, heart transplant, artificial heart, or cardiac death) within a patient may not be independent. As such, the risks of recurrent non-fatal HF-MACE and TCEs are likely to be correlated and may need to be jointly estimated to avoid any substantial bias. Other challenges include the possibility that the impact of a treatment on the risk of recurrent non-fatal HF-MACE may be different than on the risk of a TCE. In addition, random between-patient variations (unobserved covariates) may impact treatment outcomes.

The evaluation of therapy on reducing both recurrent non-fatal HF-MACE and TCEs is important; however, the unbiased assessment of the impact of therapy on recurrent non-fatal HF-MACE can be confounded by the competing risk of TCEs and the differential follow-up times between treatment groups. To address these challenges, the JFM, a semi-parametric analysis that accounts for recurrent clinical events, unequal follow-up times between treatment groups and terminal events as a competing risk, will be used for the study primary analysis. The JFM provides a quantified measure of comparison between treatment groups (hazard ratio), taking into account the risk of recurrent clinical events confounded by the competing risk of TCEs.

Specifically, this model (Rogers et al 2016, Zsebo et al, 2014)[4,5]:

- Takes into account the differences in follow-up times due to TCEs and their impact on recurrent non-fatal HF-MACE rates: when TCEs occur relatively early, the follow-up time is shorter thereby reducing the potential for recurrent non-fatal HF-MACE.
- Accounts for the impact of random between-subject differences on the risk of both TCEs and recurrent non-fatal HF-MACE.
- Takes into account and quantifies the substantially increased risk of a TCE (death, heart transplant, artificial heart implantation, LVAD implantation) due to recurrent non-fatal HF-MACE related hospitalizations.
- Takes into account a possibility of a differential treatment effect for recurrent non-fatal HF-MACE related hospitalizations and TCEs; risks of recurrent non-fatal HF-MACE and TCEs are jointly estimated preventing possible bias due to independent analyses of related processes.
- Accounts for recurrent events correlation within patient. For example, after decompensated HF hospitalization occurs, re-admission due to decompensated HF becomes more likely. The impact of a patient with multiple recurrent events is not proportional to the number of

events. For example, a patient with 10 events does not have 5 times more impact on the analysis outcome vs. patient with 2 events.

Following the model of Liu, et al., 2004[3], the joint model for the hazard functions for recurrent events and terminal events is shown below (as specified in Rondeau et al., 2010[6]).

$$\begin{cases} r_i(t|\omega_i) = \omega_i r_0(t)\, exp\left(\beta_1^{'}\ Z_i(t)\right) = \omega_i r_i(t) \\ \lambda_i(t|\omega_i) = \omega_i^{\alpha}\lambda_0(t) exp\left(\beta_2' Z_i(t)\right) = \omega_i^{\alpha}\lambda_i(t) \end{cases}$$

r_i – Recurrent events hazard function for i-th patient conditioned on patient-specific random frailty ω_i (gamma-distributed with the mean of 1 and variance theta; frailty is shared between recurrent and terminal events models).
λ_i – Terminal events hazard function for i-th patient conditioned on patient-specific random frailty ω_i.
β_1', β_2' – Covariate coefficients (Z_i=treatment group, etc.) for recurrent and terminal events, respectively.
ω_i – Random effects (frailties describing random between-subject differences) are independent and have gamma-distribution with the mean of 1 and variance of theta (θ).
α – In the JFM when $\alpha < 0$, higher frailty will result in a higher risk of recurrence and lower risk of a terminal event; $\alpha = 0$ means that the recurrent event process is not informative for terminal event rate, so recurrent and terminal event rates are not associated and can be analyzed separately. When $\alpha = 1$ the impact of frailty is identical on recurrent and terminal event rates. When $\alpha > 0$, the recurrent event rate and the terminal event rate are positively associated; higher frailty will result in greater risk of recurrence and higher risk of a terminal event.[4]

In the frailty models the frailty terms are often assumed to follow a gamma distribution, mainly for mathematical convenience: an analytical solution for the integrals in the likelihood function becomes possible. When a log-normal distribution is used, the analytical solution is not possible and numerical integrations need to be performed.

Due to these properties, gamma is thought to be an appropriate distribution to model frailties (reflecting random differences between patients caused by unobserved covariates) in the JFM used to describe the risk of recurrent events in presence of terminal events.[3,7]

The gamma distribution function is defined as

$$f(x;k,\theta) = \frac{1}{\theta^k}\frac{1}{\Gamma(k)} x^{k-1} e^{-\frac{x}{\theta}} \text{ for } x \geq 0 \text{ and } k, \theta > 0$$

This distribution has the mean=k*θ and variance = k*(θ**2). As in the JFM the mean is equal to 1, it follows that the variance = θ.[8]

Implementation of the Joint Frailty Model

Each simulated data set will be analyzed using the SAS procedure NLMIXED.
Ten quantiles r01,...,r10 of recurrent event times and 5 quantiles h01,...,h05 of terminal event times are used in the parameter estimation process. The baseline hazards for recurrent and terminal events, cum_haz_recur and cum_haz_term, respectively, are estimated as linear combinations of the corresponding quantiles.

As the RANDOM option in NLMIXED allows only a normal distribution to be specified, we are following the approach (and code) described by Liu et al to model data with gamma-distributed frailty.[7]

The likelihood functions for recurrent and terminal events are modeled as:

```
loglik_recurrent=-exp(beta1*Z + w) * cum_haz_recur;
loglik_ terminal =-exp(beta2*Z + gamma*w) * cum_haz_term;
```

The final combination of all possible events (terminal, lost to follow up and recurrent event) is as follows:

```
if event=1 then loglik= beta1*Z + w +  log(base_haz_recur) ;
    /*log likelihood for recurrent event */
if event=2 then loglik=beta2*Z + gamma*w + log(base_haz_term) + loglik_recurrent +
loglik_terminal;
    /*log likelihood for terminal event */
if event=0 then loglik=loglik_recurrent + loglik_terminal;
    /*log likelihood for censoring */
```

For the time of an event (recurrent, terminal, or censor) the general model is used:

```
model StopTime ~ general(loglik);
```

Initial values of parameters r01,...,r10, beta1 and theta are estimated by the model for recurrent events only (fitted with PROC NLMIXED). Initial values of parameters h01,h05 and beta2 are estimated by the model for terminal events only (fitted with PROC NLMIXED or the SAS procedure PHREG).

NLMIXED options include "QPOINTS=10" and "METHOD=GAUSS" (the SAS default method). The QPOINTS option specifies the number of quadrature points to be used during evaluation of

integrals. For METHOD=GAUSS, qpoints equals the number of points used in each dimension of the random effects, resulting in a total of qpoints^r points, where r is the number of dimensions.

8.4.3 Analysis of Primary Efficacy Endpoint

The primary endpoint of time-to-recurrent non-fatal HF-MACE adjusted for TCEs (cardiac death, LVAD placement, heart transplant, or artificial heart implantation) will be analyzed using the JFM[3] with treatment as the main effect.

The key sensitivity analysis will be performed for baseline NYHA Class III only patients (Appendix 1). The statistical methodology for this sensitivity analysis will be exactly the same as for the primary analysis.

Consistent with the stratification factors used for randomization (analyze as randomized approach), adjustment for baseline NYHA Class (Functional Class II versus Class III), geographic region (US versus ex-US), and presence of ischemic versus non-ischemic etiology of cardiomyopathy per baseline CRF designation as covariates in the model may be utilized for sensitivity analysis purposes. Additionally, LVESV (≤100 ml vs.>100ml) will be used as a covariate. 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 TCEs as well as individual patients' frailties. Other subgroup analyses may be performed and covariates tested. Potential covariates/subgroups are listed in Section 5.8.

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 JFM.

Censoring indicator rules for recurrent non-fatal HF-MACE or TCEs are described in Section 8.2.1. Only the first TCE 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, inclusion in the primary endpoint analysis begins at Study Day 0 (as defined in Section 6.5).

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 ≠1. The null hypothesis H_0 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.

8.4.4 Recurrent Event Mean Cumulative Rate (MCR) Plot

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. The following algorithm will be used.

1st Step - Order all event time points: Order all recurrent and terminal time points from smallest to largest. If a recurrence time for a subject is the same as its terminal event time, recurrent event is not counted.

2nd Step - Calculate the Number: The number, r_i, of patients without terminal events and not lost to follow-up after time (t_i) – (time in days) will be calculated, as follows:

$r_i = r_{i-1}$ if t_i is a recurrence time
$r_i = r_{i-1} - 1$ if t_i is a terminal event time
N is the total number of subjects and $r_i = N$ at baseline

3rd Step - Calculate *MCR* Estimate, $M^*(t)$: For each recurrence time t_i, calculate the mean cumulative function estimate as follows:

$$M^*(t_i) = \frac{1}{r_i} + M^*(t_{i-1})$$

where:

$$M(t_i) = \frac{1}{r_1}$$

at the earliest observed recurrence time t_i

Example:

The following table (Table 4) gives the recurrent non-fatal HF-MACE and TCE time for each subject, where the + sign indicates a terminal event.

Table 4: Sample Data (Table #1)

Subject ID	Time
1	5, 10, 15, 17+
2	6, 13, 17, 19+
3	12, 20, 25, 26+
4	13, 15, 24+
5	16, 22, 25, 28+

The MCR estimate is obtained as follows (F indicates recurrent event, S indicates terminal event) (Table 5):

Table 5: Sample Data (Table #2)

ID	Time, t_i	State	r_i	$\frac{1}{r_i}$	$M^*(t_i)$
1	5	F	5	0.20	0.20
2	6	F	5	0.20	0.20 + 0.20 = 0.40
1	10	F	5	0.20	0.40 + 0.20 = 0.60
3	12	F	5	0.20	0.60 + 0.20 = 0.80
2	13	F	5	0.20	0.80 + 0.20 = 1.00
4	13	F	5	0.20	1.00 + 0.20 = 1.20
1	15	F	5	0.20	1.20 + 0.20 = 1.40
4	15	F	5	0.20	1.40 + 0.20 = 1.60
5	16	F	5	0.20	1.60 + 0.20 = 1.80
2	17	F	5	0.20	1.80 + 0.20 = 2.0
1	17	S	4		
2	19	S	3		
3	20	F	3	0.33	2.00 + 0.33 = 2.33
5	22	F	3	0.33	2.33 + 0.33 = 2.66
4	24	S	2		
3	25	F	2	0.50	2.66 + 0.50 = 3.16
5	25	F	2	0.50	3.16 + 0.50 = 3.66
3	26	S	1		
5	28	S	0		

8.4.5 Sub-group Analysis of Primary Endpoint

Subgroup analyses for the following variables will be performed for primary endpoint in the manner analogous to the primary analysis – see Section 5.8 for the list of potential subgroups:
The analyses will be based on ITT population and may be repeated on FAS population.

8.4.6 Sensitivity Analyses of Primary Endpoint

1. The sensitivity analysis will be performed on ITT population with Day 0 defined as a randomization date.
2. For sensitivity analyses purposes, patients will be followed after LVAD implantation, artificial heart, or heart transplant until either death or the End-of-Study. All non-fatal HF-MACE, LVAD implantations, heart transplants, artificial heart placements, and deaths (from any cause) will be collected and adjudicated by a blinded independent clinical endpoints committee. Any LVAD placement, heart transplant, and artificial heart implantation will be treated as recurrent non-fatal HF-MACE; only cardiac death will be treated as a TCE. All adjudicated clinical events including those occurring between the time of LVAD implantation or heart transplant and death or End-of-Study, will be included in the analysis. Subjects alive at the End-of-Study will be censored; subjects lost to follow-up will be censored at the time of last contact.
3. Patients who were randomized but not treated will be excluded from the dataset and the primary analysis will be repeated.
4. The sensitivity analysis of the primary efficacy endpoint with successfully RCD defined as one of the terminal events will be performed.

8.5 Secondary Efficacy Variables and Analyses

8.5.1 Key Secondary Efficacy Endpoint

Time-to-first TCE will be evaluated as the only key secondary efficacy endpoint 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 analysis of the key secondary endpoint relating to TCEs will be conducted as follows:

- Time-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 (see details in Section 8.5.3). The hazard ratio and associated 95% Wald Confidence Interval will be presented in a box-and-whisker plot.

8.5.2 Secondary Endpoints

To protect the type 1 error rate, the secondary endpoints listed in this section will be tested using the hierarchical approach described in Section 6.3. All variables are listed in Section 4.2.2.2.

8.5.3 Analyses of Key Secondary Efficacy Endpoint

8.5.3.1 Main Analysis for Key Secondary Efficacy Endpoint

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. Hazard ratios and the associated 95% Wald Confidence Intervals will be calculated using sham control as the reference group.

The Kaplan-Meier curves by treatment group will be generated. The patients with TCE will have censoring indicator set to cnsr=2; the patients without TCEs will be censored at the end of study (censoring indicator=0). Hazard ratios and the associated 95% Wald confidence Intervals will be presented for each subgroup identified in section 5 using a forest plot.

8.5.3.2 Sensitivity Analyses for Key Secondary Efficacy Endpoint

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), and ischemic versus non-ischemic cardiomyopathy etiology per baseline CRF designation 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. The planning of TCE non-inferiority analysis in the DREAM-HF clinical program is based on the enoximone clinical program, which was reviewed and approved by FDA Cardio-Renal division, as indicated in Lowes et al, 2005[9] and Metra et al, 2009[1]. In the enoximone clinical program, the primary endpoint analysis (time to all-cause death or CV hospitalization), interim mortality analysis, and final mortality analysis were based on the pooled data from two Phase III clinical trials. The mortality non-inferiority analysis was designed to ensure that the non-inferiority test can rule out a 30% increase in mortality risk with enoximone (hazard ratio of 1.30) with 90% power when the true reduction in risk with enoximone is 10% (hazard ratio of 0.90).

In the DREAM-HF clinical trials, the key secondary endpoint is defined as time from Day 0-to-first TCE (cardiac death, LVAD placement, heart transplant, or artificial heart). Under the assumptions of proportional hazard and true hazard ratio of 0.916 (active treatment to sham procedure, 8.4% risk reduction), a non-inferiority analysis is designed to show that an active treatment is non-inferior to the sham procedure within a non-inferiority margin defined as HR of active to sham of 1.3. In other words, the risk of TCE (hazard ratio upper confidence limit calculated using proportional hazards model) on active treatment cannot exceed that risk in the sham treatment group by more than 30%; at least 971 subjects in both Phase III studies combined (of which at least 485 are in the active treatment group and 485 are in the sham procedure group, both studies combined) and at least 256 TCEs are required to achieve 80% power at a 0.025 one-sided significance level. The required numbers of events and patients needed are extremely sensitive to the assumptions of true hazard ratio: increase in true hazard ratio from 0.916 to 0.94 (increase of 2.6%) would require 299 TCEs (increase of 16.8%) generated by 1132 patients total.

To achieve 90% power for non-inferiority, 650 patients per group and 343 events would be required under the same set of assumptions. Assuming 28 months of mean follow-up, it is expected that about 179 TCEs will occur in each of the two, Phase III studies, based on the NYHA Class III patient enrichment/adaptation strategy, as described in the Adaptation Position Paper (see Appendix 1).

8.5.3.3 Additional Sensitivity Analysis for Key Secondary Efficacy Endpoint

One additional sensitivity analysis will also be performed consistent with Protocol Amendment 7 and the enrichment for NYHA Class III patients (see Appendix 1). This analysis will be conducted utilizing the inverse normal combination function as described in Lechmacher and Wassmer. Since this methodology has not been studied for JFM, we'll apply this analysis to the key secondary endpoint, i.e., time-to-first TCE. The log rank test will be applied separately to the TCE that occurred for patients before and after the adaptation implementation, and respective p-values will be combined using inverse normal combination function. The respective weights in the inverse normal combination function will be fixed and calculated based on the proportion of TCE that occurred for patients enrolled prior to and after the adaptation implementation. The adaptation implementation date was planned for the latter part of 2017 and occurred on 11 November 11 2017. Four hundred forty-five patients were randomized before 11 November 11 2017, and 120 patients were randomized on or after that date. One hundred thirty-eight patients randomized before 11 November 2017 had at least one TCE, and 19 patients randomized on or after 11 November 2017 had at least one TCE.

8.5.4 Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints are analyzed using the ITT Population and FAS population.

8.5.4.1 Analysis of Time-to-Nonfatal Decompensated HF Events Associated with Hospital Admission or Urgent Care Outpatient Visit Beginning on Day 1 (Recurrent Events Analysis)

Multiple hospital admissions or urgent care visits 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 JFM in a manner analogous with the methods described in Section 8.4.3, with the hospital admissions or urgent care HF visits considered recurrent events; the TCEs are defined identically to that in the primary analysis.

8.5.4.2 Analysis of Time-to-First HF Major Adverse Cardiac Event (HF-MACE) Defined as a Composite of Non-Fatal Decompensated HF Events Associated with Hospital Admission or Urgent Care Outpatient Visit Beginning on Day 1 or Successfully RCD Events (Time-to First Event Analysis)

Time-to-first major cardiac event 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), ischemic versus non-ischemic etiology of cardiomyopathy per baseline CRF designation 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 major cardiac event, their time-to-event will be censored (cnsr=0) at their last follow up date. For patients with major cardiac events the censoring indicator will be set to 1 at the time of first event. Hazard ratios and the associated 95% Wald Confidence Intervals will be presented for each subgroup identified in Section 5 using a forest plot.

8.5.4.3 Analysis of Time-to-First HF Major Adverse Cardiac Event (HF-MACE) Defined as a Composite of Non-Fatal Decompensated HF Events Associated with Hospital Admission or Urgent Care Outpatient Visit Beginning on Day 1 or Successfully RCD Events or TCE (Time-to First Event Analysis)

The time from Day 0-to-first event analysis will be performed as described in Section 8.5.4.2.

The data will be analyzed using a Cox proportional hazard regression 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 ischemic versus non-ischemic etiology for cardiomyopathy per baseline CRF designation as covariates in the model. The time to cardiac survival will be presented graphically by Kaplan-Meier (KM) curves stratified by treatment group. The median time to cardiac survival and its 95% confidence intervals will be estimated. Hazard ratios and the associated 95% Wald Confidence Intervals will be presented for each subgroup identified in Section 5 using a forest plot.

8.5.4.4 Analysis of Time to Successfully Resuscitated Cardiac Death Events (Recurrent Event Analysis)

This time to recurrent events analysis will be performed using the JFM similar to the primary endpoint analysis, with recurrent events defined as successful RCD events only. The terminal events will be defined as in the primary endpoint analysis.

8.5.4.5 Analysis of Overall Survival (Time-to-All-Cause Death) (Time-to-First Event Analysis)

This is a time-to-first event analysis with the event defined as death from any cause. Overall survival will be analyzed in the manner analogous to the analysis described in Section 8.5.4.4. Death from any cause will be considered as an event (censr=2). For patients who are alive at the time of analysis, their time to event will be censored at the date of their last follow-up/contact (cnsr=0).

8.5.5 Other Secondary Efficacy Endpoints

Variables are described in Section 4.2.2.3.

8.5.6 Analysis of Other Secondary Efficacy Endpoints

All continuous other secondary variables (LVESV, LVEDV, LVEF, 6MWT, MLHF, EQ-5D as well as [redacted]) at Months 3, 6, and 12 and every 6 months thereafter until study conclusion will be analyzed using trimmed means approach as a primary main approach methodology and [redacted] (see Appendix 6 for details).

Multiple imputation procedure will be used as described in Section 8.3.

Data collected after Month 60 will be summarized descriptively only. Baseline is defined as the data value obtained at screening.

8.5.6.1 Analysis of NYHA Functional Class

Patients with baseline NYHA functional Class II or III are eligible to the study (however, after adaptation is implemented, only baseline NYHA Class III patients will be eligible to be enrolled, as described in the Appendix 1). Post-baseline NYHA functional class will be recorded at levels of I, II, III, or IV if applicable.

Change from baseline will be categorized as an ordinal variable as follows:

1. improved by 2 classes (from Class III at baseline to Class I post-baseline)
2. improved by 1 class (from Class III at baseline to Class II post-baseline or Class II at baseline to Class I post-baseline)
3. no change
4. worsened by 1 class (from Class II at baseline to Class III post-baseline or Class III at baseline to Class IV post-baseline)
5. worsened by 2 classes (from Class II at baseline to Class IV post-baseline).
6. worsened to TCE (when patient experienced a TCE at or prior to a given time point).

The change from baseline to each visit (at Months 3, 6, 12, 18, 24 and 36) in above category will be evaluated using Cochran-Mantel-Haenszel (CMH) test for row mean score difference, after controlling for baseline NYHA. The data in the original functional class scale will also be presented at each visit.

8.5.6.2 Analysis of MLHF Questionnaire

The MLHF questionnaire comprises 21 questions that assess the impact of heart failure on a patient's ability to live as desired. Each of the 21 questions is answered using a 6-point Likert scale, with responses of 0 (no impairment) to 5 (very much impairment). Higher scores indicate poorer quality of life. A more detailed description can be found in Appendix 6 of the protocol (Appendix 16.1.1 of the CSR).

The following scores will be calculated as suggested in MLHF user manual:

- Total Score = summation of scores from 21 questions, range: 0 - 105
- Physical Dimension Score = summation of scores from questions #2 - #7, #12, and #13 (8 questions), range: 0 - 40
- Emotional Dimension Score = Summation of scores from questions #17 – #21 (5 questions), range: 0 - 25.

Baseline dimension or total scores will be calculated from responses obtained at screening. Change from baseline in the total, physical dimension, and emotional dimension scores at Months 3, 6, 12, 18, 24 and 36 will be analyzed using MMRM, respectively, as described in Section 8.5.6.

Methods of handling missing or ambiguous response are described in Section 8.3.

8.5.6.3 Analysis of EQ-5D Questionnaire

The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels of responses:

- 1=no problem
- 2=slight problems
- 3=moderate problems
- 4=severe problems
- 5=extreme problems.

More detailed descriptions can be found in Appendix 6 of the protocol (Appendix 16.1.1 of the CSR). See Section 8.3.2 for handling missing or ambiguous response.

Health state (score 0 to 100) will be collected with score 100 means the best state and 0 the worst state.

Change from baseline in the health state at Months 3, 6, 12, 18, 24 and 36 will be analyzed using MMRM in a manner analogous to the method described in Section 8.5.6. The data in the original scale (5 levels described above) and binary scale with value of "No Problem" (i.e., level 1) and "Problem" (i.e., levels 2 to 5) will also be summarized using descriptive statistics for each dimension.

8.5.6.4 Analysis of Echocardiograms and RVG

Efficacy endpoints of left ventricular function include LVEF, LVESV, and LVEDV. For each parameter, descriptive statistics will be provided at each visit, as well as the change from baseline to each visit. Summaries for LVEF will include echocardiogram, RVG, and combined echocardiogram and RVG data. Separate summaries will be created that include only echocardiogram data.

[redacted]

- 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 they respond to rexlemestrocel-L therapy.

[redacted]

8.6.2.3 Analysis of Additional Secondary Endpoints

For patients who are randomized and undergo the index cardiac catheterization, biomarker data will be collected at screening (all patients), Months 3, 6, and 12 and every 12 months thereafter until study conclusion. 24-hour Holter monitor data will be collected at screening, Day 0 post-procedure, Day 10, and at Months 1 and 3 during the 12-month follow-up period. PGx data will be collected at screening visit only.

[redacted]

[redacted]

[redacted]

8.7 Immunogenicity Variables and Analyses

The immunogenic potential of rexlemestrocel-L will be evaluated by testing for the development of anti-HLA DSA formation. For patients who are randomized and undergo the index cardiac catheterization, blood serum samples for immunogenicity analyses will be collected during the screening period (all patients), 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 protocol 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]

[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 [redacted].

9. SAFETY ANALYSIS

9.1 General

The safety population will be used for all safety analyses, unless otherwise stated. Summaries will be presented by treatment group (active versus sham) as actually received unless specified otherwise.

By-subject listings of AEs/SAEs will be provided for all for patients who were randomized but did not meet the definition of treated patients in Section 4.1.

Summaries of major safety analyses, including all AEs, all SAEs, AEs of special interest and other, non-CEC adjudicated AEs/SAEs of special interest potentially related to LVAD, artificial heart placement, or heart transplant (e.g., serious infections, GI bleeds; see Appendix 9) will be displayed in four ways:

1. Safety population as defined in the protocol, ie, all randomized and treated (see Section 5.2)
2. Patients within the safety population who did not have LVAD placement, artificial heart, or heart transplant
3. Patients within the safety population who had LVAD placement, artificial heart, or heart transplant – before the event
4. Patients within the safety population who had LVAD placement, artificial heart, or heart transplant – after the event.

All other safety analyses will be produced for the safety population and may be also produced for the subpopulations above as warranted.

9.2 Study Drug Administration

Study intervention (i.e., a single-treatment index cardiac catheterization with or without intracardiac mapping and cell delivery) will be performed during hospitalization on Day 0 only.

Duration (days) of study participation and duration (days) of hospitalization for the study intervention will be summarized by treatment group using descriptive statistics.

Duration of study participation will be determined from Day 0 to the last day the patient participates in the study. Duration of hospitalization will be calculated from the hospital admission and discharge for the study intervention.

The total duration (minutes) of injections, the total number of injections delivered, the total product volume (mL) administered, and product volume (mL) per injection will be summarized by presence or absence of ischemia for patients in rexlemestrocel-L group using descriptive statistics.

Loop stability, premature ventricular contractions (PVC), and unipolar voltage will be recorded during the product injection process. Data will be listed.

9.3 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be treatment-related (overall and by severity), serious adverse events (SAEs), and AEs causing withdrawal. Adverse events occurring prior to any study procedures on study Day 0 will be considered to be "Non-Treatment-Emergent" AEs and those occurring at or post the study procedure as "Treatment-Emergent" AEs.

The incidence of AEs will be summarized using descriptive statistics by MedDRA System Organ Class (SOC) and preferred term (PT) and by treatment group (active versus sham). Patients are counted only once in each SOC category, and only once in each PT category. Treatment-related adverse event summaries will include AEs with missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity. Adverse events missing the flag indicating serious will be excluded from the summary of SAEs but included in the summary of non-serious adverse events.

Occurrence of AEs relative to index cardiac catheterization (with or without intracardiac mapping and cell delivery) on Day 0 hospitalization through discharge for that hospitalization (for patients who are randomized and undergo the index cardiac catheterization) will be summarized using descriptive statistics by SOC and PT and by treatment group (active versus sham).

Adverse events determined by the investigator to be treatment-related, study procedure-related, or catheter-related AEs will be summarized using descriptive statistics. Relationship to the study procedure or to catheter will be included as well as alternate etiology.

The number and proportion of patients in the safety population may be summarized by treatment group (active versus sham) for the subgroups listed in Section 5.8. Summary tables by the subgroups will include overall TEAEs.

Additionally, some AEs will be summarized and presented separately:

- AEs of special interest (positively-adjudicated cardiac events) that include the following:
  - myocardial infarction,
  - cerebrovascular accident/stroke,
  - coronary revascularization procedure, and
  - ventricular arrhythmias of interest defined as ventricular arrhythmias that were not positively adjudicated as resuscitated cardiac death (RCD). These include (1) appropriate ICD (or CRT-D) firing for VT and NOT associated with loss of consciousness and/or syncope, (2) successful anti-tachycardia pacing without ICD (or CRT-D) firing or VT which spontaneously reverts to baseline rhythm.
- Other AEs of special interest (non-adjudicated events) that would potentially be associated with LVAD, artificial heart or heart transplant. Examples would include serious infections, gastrointestinal bleeding, cerebral hemorrhage, or thrombotic stroke. Preferred Terms for the non-adjudicated AEs of interest are provided in Appendix 9.

Listings for AEs leading to death, SAEs, AEs leading to discontinuation, AEs of special interest (positively-adjudicated cardiac), other events of special interest (non-adjudicated events listed above), MedDRA dictionary terms for AE descriptions, and adverse event PTs by patient number will be presented by SOC and PT.

9.4 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.

9.5 Deaths

If any patient dies during the study, all relevant information will be discussed in the patient's narrative and included in the CSR. A summary table will be provided for all deaths during the study, using ITT and FAS populations. A by-patient listing will be provided for all deaths.

9.6 Clinical Laboratory Tests

Clinical chemistry and hematology laboratory tests will be performed at screening, on Day 0 post-procedure, Day 10, during 12-month follow-up (at Months 1, 3, 6, and 12 visits), and every 6 months during long term follow-up. Urinalysis laboratory tests will be performed at screening, on Day 10, during 12-month follow-up (at Months 1, 3, 6, and 12 visits), and every 6 months during long-term follow-up.

Laboratory tests results and changes from baseline to each visit and last assessment will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit will be summarized using patient counts for chemistry and hematology laboratory tests. The incidence of potentially clinically significant abnormal results will be summarized for selected laboratory data using descriptive statistics with the criteria specified in Table 6. Listings for clinically significant abnormal laboratory data will be presented.

Table 6: Criteria for Clinically Significant Laboratory Values

Test	Criterion Value
Serum chemistry	
Alanine aminotransferase (ALT)	≥3x ULN
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase	≥3x ULN
Gamma-glutamyl transpeptidase (GGT)	≥3x ULN
Lactate dehydrogenase (LDH)	≥3x ULN
Glucose (Glu)	>180 mg/dL
Sodium (Na)	>145 mmol/L
Potassium (K)	>5.5 mmol/L
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine (Cr)	≥177 µmol/L

Test		Criterion Value
Uric acid (UA)	Men	≥625 µmol/L
	Women	≥506 µmol/L
Bilirubin (total)		≥34.2 µmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
White blood cell (WBC) counts		≤3 x 10^9/L or ≥20 x 10^9/L
Eosinophils		≥10%
Absolute neutrophil counts (ANC)		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L or ≥700 x 10^9/L
Urinalysis		
Blood (HGB)		Any value which is not "negative"
Glucose		≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline
Total protein		Any value which is not "negative"

9.7 Vital Signs

For patients who are randomized and undergo the index cardiac catheterization, vital signs will be measured at screening (all patients), Day 0 pre-procedure and post-procedure (at 2, 4, 8, 12 hours and at discharge), Day 1, Day 10, during 12-month follow-up (at Months 1, 3, 6, and 12 visits), and every 6 months during long term follow-up.

For patients who are randomized and did not undergo the index cardiac catheterization, vital signs will be measured at screening and at any subsequent visit if they were still in the study (at Months 1, 3, 6, and 12 visits), and every 6 months during long term follow-up.

Vital signs results and changes from baseline to each time point and last assessment will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Table 7 specifies the criteria for identifying vital signs as clinically significant abnormal. Note that in order to be identified as clinically significant abnormal, a value would need to meet both

conditions below (i.e., have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column).

Table 7: Criteria for Clinically Significant Vital Signs

Vital Sign		Criterion value
Pulse	High	>100 bpm and increase from baseline ≥15 bpm
	Low	<50 bpm and decrease from baseline ≥15 bpm
Systolic blood pressure:	High	≥140 mm Hg and increase from baseline ≥20 mm Hg
	Low	≤90 mm Hg and decrease from baseline ≥20 mm Hg
Diastolic blood pressure	High	≥90 mm Hg and increase from baseline ≥10 mm Hg
	Low	≤50 mm Hg and decrease from baseline ≥10 mm Hg

9.8 Electrocardiography

Electrocardiography includes the following: telemetry, electrocardiograms (ECG), 24-hour Holter monitoring, and ICD or any implanted device capable of defibrillation.

9.8.1 Telemetry

Telemetry monitoring will commence prior to the procedure (the index cardiac catheterization) and continue overnight post-procedure.

- **Telemetry** eCRF: Telemetry findings judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be reported as an AE on the AE eCRF.

Table 8: Telemetry Data from eCRF

Variable Description	Units or Category
NOT DONE	
Date of Assessment	dd MMM yyyy
Start Date/Time	DD mmm YYYY
Stop Date/Time	HH nn
Telemetry	DD mmm YYYY
Clinically Significant Specify	HH nn

During and after the single-treatment procedure, clinically significant arrhythmias will be listed and tabulated by treatment group.

9.8.2 Electrocardiograms

For patients who are randomized and undergo the index cardiac catheterization, ECGs will be performed at screening (all patients), Day 0 prior and post the procedure, Day 1, Day 10, during 12-month follow-up (at Months 1, 3, 6, and 12 visits), and every 6 months during long term follow-up.

For patients who are randomized and did not undergo the index cardiac catheterization, ECGs will be performed at screening and at any subsequent visit if they still stay on study (at Months 1, 3, 6, and 12 visits), and every 6 months during long term follow-up.

Individual 12-lead ECGs will be extracted at specified time points and will be evaluated by a core electrocardiogram 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.

Table 9: Electrocardiogram Variables

Variable Description	Units or Category
PR Interval	msec
QRS Interval	msec
QT Interval	msec
QTC Interval Bazett	msec
QTC Interval Fridericia	msec
Heart Rate	bpm
RR Interval	msec
Interpretation	*Normal *Abnormal *Unable to Evaluate
Description	ECG readout by the investigator

The primary QTc parameter will be QTcF. Secondary parameters (QTcB, QT, QRS complex, and HR) and waveforms (T waves) will be evaluated. Summary statistics will be provided for actual values and changes from baseline by treatment and visit.

Interpretation and description are to be provided in patient listing.

9.8.3 Holter Monitor

Holter monitor substudy was performed on US patients only. For patients who are randomized and undergo the index cardiac catheterization, 24-hour Holter monitor data will be collected at screening (all patients), Day 0 post-procedure, Day 10, and at Months 1 and 3 during the 12-month follow-up period.

For patients who are randomized and did not undergo the index cardiac catheterization, 24-hour Holter monitor data will be collected at screening (all patients), and at Months 1 and 3 during the 12-month follow-up period if applicable (Table 10).

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 pre-procedure baseline measurement in each of the numeric parameters at each post-procedure observation by treatment group.

Summary statistics will be provided for actual values and changes from baseline by treatment group 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. Reviewer's comments (Holter data interpretation by the investigator) will be presented in a patient listing of this data.

Table 10: Holter Monitor Parameters

Atrial Fibrillation Peak Average Rate
Atrial Fibrillation Percentage
Bradycardia Longest Episode Duration
Bradycardia Slowest Episode Average HR
Number RR greater than 2 Seconds
Number of Tachycardia Counts
Pauses Longest RR Duration
Reviewer's Comments (text field)
Summary (Max) Heart Rate
Summary (Mean) Heart Rate
Summary (Min) Heart Rate
Supraventricular Ectopy Couplets
Supraventricular Ectopy Fastest Run HR

Supraventricular Ectopy Longest Run Duration
Supraventricular Ectopy Runs
Supraventricular Ectopy Singles
Supraventricular Ectopy Total Count
Tachycardia Fastest Episode Average HR
Tachycardia Longest Episode Duration
Ventricular Ectopy Couplets
Ventricular Ectopy Fastest Run HR
Ventricular Ectopy Longest Run Duration
Ventricular Ectopy R on T
Ventricular Ectopy Runs
Ventricular Ectopy Singles
Ventricular Ectopy Total Count

9.8.3.1 Ventricular Ectopy

Ventricular arrhythmias will be assessed in a subset of patients (randomized patients across the US) 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 10.

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 cell delivery) and will remain hospitalized on telemetry after the index cardiac catheterization for a minimum of one night or until hospital discharge is clinically indicated.

Patients who have an ICD will have their device interrogated at regularly scheduled intervals (see Table 1 and Table 2) for ventricular and other arrhythmias associated with episodes of firing of the device.

9.8.4 Automated Implantable Cardioverter Defibrillator (ICD or CRT-D device)

For patients who have an ICD or any implanted device capable of defibrillation (including CRT-D), ventricular arrhythmias (arrhythmias obtained by device interrogation) will be listed by treatment group. Only patient listings will be created.

If device interrogation revealed an AE-SAE and/or Endpoint, including, non-fatal HF-MACE, or other arrhythmic events, these events were added to the Adverse Event and Endpoint Event eCRF pages as shown in Table 11.

Table 11: ICD - Implanted Device eCRF

Variable Description	Units or Category
NOT DONE	
Does patient currently have an ICD device in place?	1=Y 2=N
If No, was device removed since last visit?	1=Y 2=N
Was an ICD interrogation performed at this Visit?	1=Y 2=N
If Yes, Date of Interrogation:	dd MMM yyyy
If No, Select Primary Reason interrogation was not performed:	01=Technician/Rep not available 02=Interrogation equipment unavailable 03=Unscheduled Visit 04=Site error 05=Other, specify
Other, specify	
Any updates to current Device and/or placement of New Device since last visit?	1=Y 2=N
If Yes, complete Device Type information below.	
Device Type	1=A-ICD without CRT 2=CRT-D 3=CRT-P 4=Other CRT
Device Placement/Removal	
Leads	
Battery changes	
General Maintenance	
Other	
Other, specify details	
Since the last visit did patient receive a new device?	1=Y 2=N

If a subject received a New ICD Device since the last visit, this form is required as shown in Table 12.

Table 12: New Device eCRF

New Device Type	1=A-ICD without CRT 2=CRT-D 3=CRT-P 4=Other CRT
Name of New Device	
Date of New Device Placement	dd MMM yyyy

9.9 Cardiac Imaging

An important inclusion criterion in the DREAM HF-1 trial was that all patients have chronic heart failure with reduced LVEF (HFrEF) as calculated by a Core Cardiac Imaging Laboratory. This was defined as 40% or less as measured by 2-D echocardiogram or 35% or less as measured by radionuclide ventriculography (RVG). To fulfill this inclusion criterion during the screening period, all potential patients for the trial underwent cardiac imaging which consisted, at a minimum, of a 2-D echocardiogram with Doppler. If echocardiographic imaging was of insufficient technical quality for calculation of LV volumes and LVEF then an RVG [also known as a multiple-gated acquisition (MUGA) scan] was to be performed to assess LVEF to determine if the patient fulfilled the LVEF inclusion. Note: If echocardiographic imaging was of insufficient technical quality and RVG was performed, the measurements from the insufficient quality echocardiographic image should not be used; rather, it should be considered missing.

9.9.1 Echocardiogram and Doppler Imaging data

The analysis of this data will be performed on echo-qualifying patients. Echocardiogram parameters are presented in Table 13.

Table 13: ECHO Measurements

ECHO Quality Evaluation
Heart Rate
Blood Pressure, Diastolic
Blood Pressure, Systolic
Left Atrial End Systolic Volume
Left Atrial End Systolic Volume Index
Left Ventricular Dimension at End-Diastole
Left Ventricular Dimension at End-Systole

Left Ventricular Fractional Shortening
Left Ventricular End Diastolic Volume
Left Ventricular End Diastolic Volume Index
Left Ventricular End Systolic Volume
Left Ventricular End Systolic Volume Index
Left Ventricular Ejection Fraction
Left Ventricular Mass
Left Ventricular Mass Index
Left Ventricular Out Flow Diameter
Left Ventricular Outflow Tract VTI
Left Ventricular Posterior Wall Thickness Diastole
Aortic Valve Regurgitation
Mitral Valve Regurgitation by Color
Mitral Valve, E/A Ratio
Mitral Valve, Deceleration Time
Peak Mitral Inflow Velocity A (A-Point)
Peak Mitral Inflow Velocity E (E-Point)
Pulmonary Artery Pressure, Systolic
Right Atrial Pressure
Septal Wall Thickness Diastole
Tricuspid Regurgitant Peak Velocity
Tricuspid Valve Regurgitation

9.9.2 Radionuclide Ventriculography (RVG) Imaging (MUGA Scan)

Because this is an electrocardiographic timed (or gated) procedure, which is based on radioactive counts in areas of interest within the patient's chest rather than cardiac structure and anatomy, the only physiologic parameters that are generated by RVG (MUGA) imaging are Heart Rate (from the electrocardiogram) and LVEF calculated using the following formula:

LVEF = (LV end-diastolic counts – LV end-systolic counts)/LV end-diastolic counts

Data will be presented using descriptive statistics in summary tables and listings based on the RVG-qualified patient population.

NOTE: LVEF data will be summarized separately for RVG assessment, separately for echocardiogram assessment, and combined.

9.10 Physical Examinations

A full physical examination will be performed at screening (all patients), at Month 12 during

12-month follow-up and yearly during long term follow-up for randomized patients who undergo the index cardiac catheterization. Physical examination findings that are judged by the investigator as a clinically significant change (worsening) compared to a baseline will be considered an AE and reported as such. Newly occurring abnormalities in the physical examinations will be identified and listed. Body weight measurement will be listed as changes from baseline.

9.11 Concomitant Medications

All concomitant medications will be coded using the WHO Drug Dictionary (Version March 2013). The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and ATC code. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken while the patient takes study drug.

Separate summaries will be provided for prior medications and concomitant medications, and all medications will be listed.

Some concomitant medications were classified into more general groups (e.g., beta-blockers, ace inhibitors and/or angiotensin II antagoinsts, diuretics, etc.). Details are provided in Appendix 8.

10. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

11. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Not applicable.

12. REFERENCES

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7. Liu L and Zhangsheng Y. A likelihood reformulation method in non-normal random effects models. Statist. Med. 2008;27:3105-24.
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13. LIST OF SUMMARIES, FIGURES, AND LISTINGS

Presented below is a Table of Contents for all summary tables, figures, and listings as generated on 09 October 2020.

Type	Rho Name	Number	Title	Population
Table	DS_TAA	14.1.1	Subject Disposition	All Subjects
Table	DM_TAA	14.1.2.1	Demographics by Treatment Group	ITT Population
Table	DM_TAB	14.1.2.2	Demographics by Treatment Group	Safety Population
Table	DM_TAC	14.1.2.3	Demographics by Treatment Group	Full Analysis Set
Table	DM_TAH	14.1.2.4	Demographics by Treatment Group	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	DM_TAI	14.1.2.5	Demographics by Treatment Group	Safety Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	DM_TAD	14.1.2.6	Demographics by Treatment Group	Echo-Qualifying Population
Table	DM_TAE	14.1.2.7	Demographics by Treatment Group	[redacted]
Table	DM_TAF	14.1.2.8	Demographics by Treatment Group	ITT Population - with 24-Hour Holter Monitor Data
Table	DM_TAG	14.1.3.1	Baseline Characteristics	ITT Population
Table	DM_TAJ	14.1.3.2	Baseline Characteristics	Full Analysis Set
Table	MH_TAA	14.1.4	Non-Cardiovascular Medical History	ITT Population
Table	MH_TAB	14.1.5	Cardiovascular History	ITT Population
Table	EG_TAA	14.1.6.1	Baseline Electrocardiography Findings	ITT Population

Type	Rho Name	Number	Title	Population
Table	EG_TAG	14.1.6.2	Baseline Holter Findings	Safety Population
Table	PE_TAA	14.1.7	Baseline Physical Examination	ITT Population
Table	EX_TAA	14.1.8	Study Drug Administration, Rexlemestrocel-L Treatment Group	ITT Population
Table	LB_TAI	14.1.9	Baseline Laboratory Results	ITT Population
Table	DS_TAB	14.1.10	Investigator Site by Treatment Group	ITT Population
Table	MH_TAC	14.1.11	Abnormal Finding in General Medical History	ITT Population
Table	CM_TAB	14.1.12.1	Prior Medications by Therapeutic Class, Preferred Term, and Treatment Group	ITT Population
Table	CM_TAC	14.1.12.2	Prior Medications by Therapeutic Class, Preferred Term, and Treatment Group	Full Analysis Set
Table	DV_TAA	14.1.13	Protocol Violations	ITT Population
Table	EF_TAA	14.2.1.1.1	Primary Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events	ITT Population
Table	EF_TAB	14.2.1.1.2	Primary Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events	Full Analysis Set
Table	EF_TAC	14.2.1.1.3	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Gender	ITT Population
Table	EF_TAD	14.2.1.1.4	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Gender	Full Analysis Set
Table	EF_TAE	14.2.1.1.5	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Age Group (<65 or >=65)	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TAF	14.2.1.1.6	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Age Group (<65 or >=65)	Full Analysis Set
Table	EF_TAG	14.2.1.1.7	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Race Group (White, Black, or Other)	ITT Population
Table	EF_TAH	14.2.1.1.8	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Race Group (White, Black, or Other)	Full Analysis Set
Table	EF_TAI	14.2.1.1.9	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Ethnicity Group	ITT Population
Table	EF_TAJ	14.2.1.1.10	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Ethnicity Group	Full Analysis Set
Table	EF_TAK	14.2.1.1.11	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NYHA (Function Class II or III)	ITT Population
Table	EF_TAL	14.2.1.1.12	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NYHA (Function Class II or III)	Full Analysis Set
Table	EF_TAM	14.2.1.1.13	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Geographic Region (US or ex-US)	ITT Population
Table	EF_TAN	14.2.1.1.14	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Geographic Region (US or ex-US)	Full Analysis Set
Table	EF_TAO	14.2.1.1.15	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Etiology (Ischemic or Non-ischemic)	ITT Population
Table	EF_TAP	14.2.1.1.16	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Etiology (Ischemic or Non-ischemic)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TAQ	14.2.1.1.17	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline Diabetes Mellitus	ITT Population
Table	EF_TAR	14.2.1.1.18	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline Diabetes Mellitus	Full Analysis Set
Table	EF_TAS	14.2.1.1.19	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for subjects with ICD or CRT-D vs. those without ICD or CRT-D	ITT Population
Table	EF_TAT	14.2.1.1.20	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for subjects with ICD or CRT-D vs. those without ICD or CRT-D	Full Analysis Set
Table	EF_TAU	14.2.1.1.21	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for subjects with CRT, CRT-D, or CRT-P vs. subjects without CRT, CRT-D, or CRT-P	ITT Population
Table	EF_TAV	14.2.1.1.22	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for subjects with CRT, CRT-D, or CRT-P vs. subjects without CRT, CRT-D, or CRT-P	Full Analysis Set
Table	EF_TJA	14.2.1.1.23	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Age Group (<50, 50-<65, >=65)	ITT Population
Table	EF_TJB	14.2.1.1.24	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Age Group (<50, 50-<65, >=65)	Full Analysis Set
Table	EF_TJC	14.2.1.1.25	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVESV (<=100 mL vs. >100 mL)	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TJD	14.2.1.1.26	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVESV (<=100 mL vs. >100 mL)	Full Analysis Set
Table	EF_TJE	14.2.1.1.27	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVEF (<30% vs. >=30%)	ITT Population
Table	EF_TJF	14.2.1.1.28	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVEF (<30% vs. >=30%)	Full Analysis Set
Table	EF_TJG	14.2.1.1.29	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NT-proBNP (<=1000 ng/mL vs. >1000 ng/mL)	ITT Population
Table	EF_TJH	14.2.1.1.30	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NT-proBNP (<=1000 ng/mL vs. >1000 ng/mL)	Full Analysis Set
Table	EF_TJI	14.2.1.1.31	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	ITT Population
Table	EF_TJJ	14.2.1.1.32	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	Full Analysis Set
Table	EF_TJS	14.2.1.1.33	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Atrial Fibrillation History or Presence at BL (yes vs. no)	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TJT	14.2.1.1.34	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Atrial Fibrillation History or Presence at BL (yes vs. no)	Full Analysis Set
Table	EF_TJU	14.2.1.1.35	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Time Since Diagnosis of HFrEF (<1 year, >1 to 5 years, >5 years)	ITT Population
Table	EF_TJV	14.2.1.1.36	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Time Since Diagnosis of HFrEF (<1 year, >1 to 5 years, >5 years)	Full Analysis Set
Table	EF_TJW	14.2.1.1.37	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Any Decompensated HF Event 1-9 Months Prior to Screening (yes vs. no)	ITT Population
Table	EF_TJX	14.2.1.1.38	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Any Decompensated HF Event 1-9 Months Prior to Screening (yes vs. no)	Full Analysis Set
Table	EF_TJY	14.2.1.1.39	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NYHA + LVESV Group (Class II + LVESV <=100 mL vs. Class II + >100 mL vs. Class III + <=100 mL vs. Class III + >100 mL)	ITT Population
Table	EF_TJZ	14.2.1.1.40	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline NYHA + LVESV Group (Class II + LVESV <=100 mL vs. Class II + >100 mL vs. Class III + <=100 mL vs. Class III + >100 mL)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TKA	14.2.1.1.41	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVEF + LVESV Group (LVEF <30% + LVESV <=100 mL vs. LVEF <30% + >100 mL vs. LVEF >=30% + <=100 mL vs. LVEF >=30% + >100 mL)	ITT Population
Table	EF_TKB	14.2.1.1.42	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Baseline LVEF + LVESV Group (LVEF <30% + LVESV <=100 mL vs. LVEF <30% + >100 mL vs. LVEF >=30% + <=100 mL vs. LVEF >=30% + >100 mL)	Full Analysis Set
Table	EF_TJK	14.2.1.1.43	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Concomitant Medication Usage	ITT Population
Table	EF_TJL	14.2.1.1.44	Sub-group Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events by Concomitant Medication Usage	Full Analysis Set
Table	EF_TAW	14.2.1.2.1	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for the Baseline NYHA Class III Subjects	ITT Population
Table	EF_TAX	14.2.1.2.2	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for the Baseline NYHA Class III Subjects	Full Analysis Set
Table	EF_TAY	14.2.1.2.3	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events with Successfully RCD Defined as a Terminal Cardiac Event	ITT Population
Table	EF_TAZ	14.2.1.2.4	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events with Successfully RCD Defined as a Terminal Cardiac Event	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TBA	14.2.1.2.5	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for Subjects Who Were Randomized with Day 0 Defined as Randomization Date	ITT Population
Table	EF_TBB	14.2.1.2.6	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events for Subjects Who Were Randomized with Day 0 Defined as Randomization Date	Full Analysis Set
Table	EF_TBC	14.2.1.2.7	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE for Subjects Followed after LVAD Implantation, Artificial Heart, or Heart Transplant until Either Death or the End of Study	ITT Population
Table	EF_TBD	14.2.1.2.8	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE for Subjects Followed after LVAD Implantation, Artificial Heart, or Heart Transplant until Either Death or the End of Study	Full Analysis Set
Table	EF_TBE	14.2.1.2.9	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events Excluding Subjects Who Were Randomized but Did Not Undergo a Day 0 Cardiac Catheterization Procedure	ITT Population
Table	EF_TBF	14.2.1.2.10	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events Before and After the Adaptation Implementation for Baseline NYHA Class III Subjects	ITT Population
Table	EF_TBG	14.2.1.2.11	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Terminal Cardiac Events Before and After the Adaptation Implementation for Baseline NYHA Class III Subjects	Full Analysis Set
Table	EF_TBT	14.2.1.2.12	Sensitivity Analysis: Time-to-Recurrent Non-Fatal HF MACE Adjusted for Terminal Cardiac Events using First Randomization Date as Day 0 for Twice Randomized Patients	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TIA	14.2.1.3.1	Summary of Primary Endpoint (HF-MACE) and Secondary Endpoint (TCE) Cardiac Events	ITT Population
Table	EF_TIB	14.2.1.3.2	Summary of Primary Endpoint (HF-MACE) and Secondary Endpoint (TCE) Cardiac Events	Full Analysis Set
Table	EF_TMA	14.2.1.4.1	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Gender	ITT Population
Table	EF_TMB	14.2.1.4.2	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Gender	Full Analysis Set
Table	EF_TMC	14.2.1.4.3	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Age Group (<65 or >=65)	ITT Population
Table	EF_TMD	14.2.1.4.4	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Age Group (<65 or >=65)	Full Analysis Set
Table	EF_TME	14.2.1.4.5	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Race Group (White, Black, or Other)	ITT Population
Table	EF_TMF	14.2.1.4.6	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Race Group (White, Black, or Other)	Full Analysis Set
Table	EF_TMG	14.2.1.4.7	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Ethnicity Group	ITT Population
Table	EF_TMH	14.2.1.4.8	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Ethnicity Group	Full Analysis Set
Table	EF_TBH	14.2.1.4.9	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline NYHA Class (II vs. III)	ITT Population
Table	EF_TBI	14.2.1.4.10	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline NYHA Class (II vs. III)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TMI	14.2.1.4.11	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Geographic Region (US or ex-US)	ITT Population
Table	EF_TMJ	14.2.1.4.12	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Geographic Region (US or ex-US)	Full Analysis Set
Table	EF_TMK	14.2.1.4.13	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Etiology (Ischemic or Non-ischemic)	ITT Population
Table	EF_TML	14.2.1.4.14	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Etiology (Ischemic or Non-ischemic)	Full Analysis Set
Table	EF_TMM	14.2.1.4.15	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline Diabetes Mellitus	ITT Population
Table	EF_TMN	14.2.1.4.16	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline Diabetes Mellitus	Full Analysis Set
Table	EF_TBN	14.2.1.4.17	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Subjects with ICD or CRT-D vs. Subjects without ICD or CRT-D	ITT Population
Table	EF_TBO	14.2.1.4.18	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Subjects with ICD or CRT-D vs. Subjects without ICD or CRT-D	Full Analysis Set
Table	EF_TMO	14.2.1.4.19	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for subjects with CRT, CRT-D, or CRT-P vs. subjects without CRT, CRT-D, or CRT-P	ITT Population
Table	EF_TMP	14.2.1.4.20	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for subjects with CRT, CRT-D, or CRT-P vs. subjects without CRT, CRT-D, or CRT-P	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TMQ	14.2.1.4.21	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Age Group (<50, 50-<65, >=65)	ITT Population
Table	EF_TMR	14.2.1.4.22	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Age Group (<50, 50-<65, >=65)	Full Analysis Set
Table	EF_TBJ	14.2.1.4.23	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline LVESV (<=100 mL vs. >100 mL)	ITT Population
Table	EF_TBK	14.2.1.4.24	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline LVESV (<=100 mL vs. >100 mL)	Full Analysis Set
Table	EF_TMS	14.2.1.4.25	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline LVEF (<30% vs. >=30%)	ITT Population
Table	EF_TMT	14.2.1.4.26	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline LVEF (<30% vs. >=30%)	Full Analysis Set
Table	EF_TBR	14.2.1.4.27	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline NTproBNP (>1000 ng/mL vs. <=1000 ng/mL)	ITT Population
Table	EF_TBS	14.2.1.4.28	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline NTproBNP (>1000 ng/mL vs. <=1000 ng/mL)	Full Analysis Set
Table	EF_TBL	14.2.1.4.29	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	ITT Population
Table	EF_TBM	14.2.1.4.30	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TBP	14.2.1.4.31	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Atrial Fibrillation History or Presence at BL (yes vs. no)	ITT Population
Table	EF_TBQ	14.2.1.4.32	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Atrial Fibrillation History or Presence at BL (yes vs. no)	Full Analysis Set
Table	EF_TNC	14.2.1.4.33	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Time Since Diagnosis of HFrEF (<1 year, >1 to 5 years, >5 years)	ITT Population
Table	EF_TND	14.2.1.4.34	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Time Since Diagnosis of HFrEF (<1 year, >1 to 5 years, >5 years)	Full Analysis Set
Table	EF_TNE	14.2.1.4.35	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Any Decompensated HF Event 1-9 Months Prior to Screening (yes vs. no)	ITT Population
Table	EF_TNF	14.2.1.4.36	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Any Decompensated HF Event 1-9 Months Prior to Screening (yes vs. no)	Full Analysis Set
Table	EF_TMU	14.2.1.4.37	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Concomitant Medication Usage	ITT Population
Table	EF_TMV	14.2.1.4.38	Covariate Analysis: Time-to-Recurrent Non-Fatal HF-MACE Adjusted for Concomitant Medication Usage	Full Analysis Set
Table	EF_TCA	14.2.2.1	Key Secondary Analysis: Time-to-First Terminal Cardiac Event	ITT Population
Table	EF_TCB	14.2.2.2	Key Secondary Analysis: Time-to-First Terminal Cardiac Event	Full Analysis Set
Table	EF_TCC	14.2.2.3	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline NYHA Class (II vs. III)	ITT Population
Table	EF_TCD	14.2.2.4	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline NYHA Class (II vs. III)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TCE	14.2.2.5	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline LVESV (<=100 mL vs. >100 mL)	ITT Population
Table	EF_TCF	14.2.2.6	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline LVESV (<=100 mL vs. >100 mL)	Full Analysis Set
Table	EF_TCQ	14.2.2.7	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	ITT Population
Table	EF_TCR	14.2.2.8	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	Full Analysis Set
Table	EF_TCS	14.2.2.9	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Subjects with ICD or CRT-D vs. Subjects without ICD or CRT-D	ITT Population
Table	EF_TCT	14.2.2.10	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Subjects with ICD or CRT-D vs. Subjects without ICD or CRT-D	Full Analysis Set
Table	EF_TCU	14.2.2.11	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Atrial Fibrillation History or Presence at BL (yes vs. no)	ITT Population
Table	EF_TCV	14.2.2.12	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Atrial Fibrillation History or Presence at BL (yes vs. no)	Full Analysis Set
Table	EF_TCW	14.2.2.13	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline NTproBNP (>1000 ng/mL vs. <=1000 ng/mL)	ITT Population
Table	EF_TCX	14.2.2.14	Covariate Analysis: Time-to-First Terminal Cardiac Event Adjusted for Baseline NTproBNP (>1000 ng/mL vs. <=1000 ng/mL)	Full Analysis Set
Table	EF_TCG	14.2.2.15	Sensitivity Analysis: Time-to-First Terminal Cardiac Event with Baseline NYHA Class, Baseline NT-proBNP, and Baseline LVESV as Covariates	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TCH	14.2.2.16	Sensitivity Analysis: Time-to-First Terminal Cardiac Event with Baseline NYHA Class, Baseline NT-proBNP, and Baseline LVESV as Covariates	Full Analysis Set
Table	EF_TCI	14.2.2.17	Sensitivity Analysis: Time-to-First Terminal Cardiac Event with Baseline NYHA Class, Country (US versus Canada), and Presence of Epicardial CAD (ischemic versus nonischemic) as Covariates	ITT Population
Table	EF_TCJ	14.2.2.18	Sensitivity Analysis: Time-to-First Terminal Cardiac Event with Baseline NYHA Class, Country (US versus Canada), and Presence of Epicardial CAD (ischemic versus nonischemic) as Covariates	Full Analysis Set
Table	EF_TLA	14.2.2.19	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Presence of Epicardial CAD (ischemic versus nonischemic)	ITT Population
Table	EF_TLB	14.2.2.20	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Presence of Epicardial CAD (ischemic versus nonischemic)	Full Analysis Set
Table	EF_TLC	14.2.2.21	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NYHA (Function Class II or III)	ITT Population
Table	EF_TLD	14.2.2.22	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NYHA (Function Class II or III)	Full Analysis Set
Table	EF_TLE	14.2.2.23	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVESV (<=100 mL vs. >100 mL)	ITT Population
Table	EF_TLF	14.2.2.24	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVESV (<=100 mL vs. >100 mL)	Full Analysis Set
Table	EF_TLG	14.2.2.25	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVEF (<30% vs. >=30%)	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TLH	14.2.2.26	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVEF (<30% vs. >=30%)	Full Analysis Set
Table	EF_TLI	14.2.2.27	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NT-proBNP (<=1000 ng/mL vs. >1000 ng/mL)	ITT Population
Table	EF_TLJ	14.2.2.28	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NT-proBNP (<=1000 ng/mL vs. >1000 ng/mL)	Full Analysis Set
Table	EF_TLK	14.2.2.29	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline Diabetes Mellitus	ITT Population
Table	EF_TLL	14.2.2.30	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline Diabetes Mellitus	Full Analysis Set
Table	EF_TLM	14.2.2.31	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NYHA + LVESV Group (Class II + LVESV <=100 mL vs. Class II + >100 mL vs. Class III + <=100 mL vs. Class III + >100 mL)	ITT Population
Table	EF_TLN	14.2.2.32	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline NYHA + LVESV Group (Class II + LVESV <=100 mL vs. Class II + >100 mL vs. Class III + <=100 mL vs. Class III + >100 mL)	Full Analysis Set
Table	EF_TLO	14.2.2.33	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVEF + LVESV Group (LVEF <30% + LVESV <=100 mL vs. LVEF <30% + >100 mL vs. LVEF >=30% + <=100 mL vs. LVEF >=30% + >100 mL)	ITT Population
Table	EF_TLP	14.2.2.34	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline LVEF + LVESV Group (LVEF <30% + LVESV <=100 mL vs. LVEF <30% + >100 mL vs. LVEF >=30% + <=100 mL vs. LVEF >=30% + >100 mL)	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TLQ	14.2.2.35	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	ITT Population
Table	EF_TLR	14.2.2.36	Sub-group Analysis: Time-to-First Terminal Cardiac Event by Baseline hsCRP (<2 mg/L vs. >=2 mg/L, <3 mg/L vs. >=3 mg/L, <4 mg/L vs. >=4 mg/L)	Full Analysis Set
Table	EF_TCO	14.2.3.1	Non-inferiority Analysis of Rexlemestrocel-L to Control	ITT Population
Table	EF_TCP	14.2.3.2	Non-inferiority Analysis of Rexlemestrocel-L to Control	Full Analysis Set
Table	EF_TDA	14.2.4.1.1	Secondary Analysis: Time-to-Recurrent Non-Fatal Decompensated HF Events Associated with Hospital Admission or Urgent Care Outpatient Visit Beginning on Day 0	ITT Population
Table	EF_TDB	14.2.4.1.2	Secondary Analysis: Time-to-Recurrent Non-Fatal Decompensated HF Events Associated with Hospital Admission or Urgent Care Outpatient Visit Beginning on Day 0	Full Analysis Set
Table	EF_TDC	14.2.4.2.1	Secondary Analysis: Time-to-Recurrent Successfully Resuscitated Cardiac Death Events Beginning at Day 0	ITT Population
Table	EF_TDD	14.2.4.2.2	Secondary Analysis: Time-to-Recurrent Successfully Resuscitated Cardiac Death Events Beginning at Day 0	Full Analysis Set
Table	EF_TDE	14.2.4.3.1	Secondary Analysis: Time-to-First Composite of Non-Fatal HF-MACE	ITT Population
Table	EF_TDF	14.2.4.3.2	Secondary Analysis: Time-to-First Composite of Non-Fatal HF-MACE	Full Analysis Set
Table	EF_TDG	14.2.4.4.1	Secondary Analysis: Time-to-First Composite of Non-Fatal HF-MACE or Terminal Cardiac Event	ITT Population
Table	EF_TDH	14.2.4.4.2	Secondary Analysis: Time-to-First Composite of Non-Fatal HF-MACE or Terminal Cardiac Event	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TDK	14.2.4.5.1	Secondary Analysis: Time-to-All Cause Death by Treatment Group	ITT Population
Table	EF_TDL	14.2.4.5.2	Secondary Analysis: Time-to-All Cause Death by Treatment Group	Full Analysis Set
[redacted]				
Table	EF_TGP	14.2.5.1	Change from Baseline in Continuous Echocardiography Measurements at Each Visit by Treatment Group	Echo-Qualifying Population
Table	EF_TGO	14.2.5.2	Comparison of RVG and 2-D Echocardiography Results at Each Visit by Treatment Group	ITT Population
Table	EF_TGQ	14.2.5.3	Shift from Baseline in Categorical Echocardiography Measurements at Each Visit by Treatment Group	ITT Population
Table	EF_TEG	14.2.5.4.1	Other Secondary Analysis: Change from Baseline in 6-Minute Walk Test (6MWT) in Meters at Each Visit by Treatment Group	ITT Population
Table	EF_TEH	14.2.5.4.2	Other Secondary Analysis: Change from Baseline in 6-Minute Walk Test (6MWT) in Meters at Each Visit by Treatment Group	Full Analysis Set
Table	EF_TEI	14.2.5.5.1	Other Secondary Analysis: Change from Baseline in NYHA Functional Class at Each Visit by Treatment Group	ITT Population

Type	Rho Name	Number	Title	Population
Table	EF_TEJ	14.2.5.5.2	Other Secondary Analysis: Change from Baseline in NYHA Functional Class at Each Visit by Treatment Group	Full Analysis Set
Table	EF_TEK	14.2.5.6.1	Other Secondary Analysis: Shift from Baseline in NYHA Functional Class at Each Visit by Treatment Group	ITT Population
Table	EF_TEL	14.2.5.6.2	Other Secondary Analysis: Shift from Baseline in NYHA Functional Class at Each Visit by Treatment Group	Full Analysis Set
Table	EF_TEM	14.2.5.7.1	Other Secondary Analysis: NYHA Functional Class by Visit and Treatment Group	ITT Population
Table	EF_TEN	14.2.5.7.2	Other Secondary Analysis: NYHA Functional Class by Visit and Treatment Group	Full Analysis Set
Table	EF_TEO	14.2.5.8.1	Other Secondary Analysis: Change from Baseline in MLHF Total Score at Each Visit by Treatment Group	ITT Population
Table	EF_TEP	14.2.5.8.2	Other Secondary Analysis: Change from Baseline in MLHF Total Score at Each Visit by Treatment Group	Full Analysis Set
Table	EF_TEQ	14.2.5.9.1	Other Secondary Analysis: Change from Baseline in MLHF Physical Dimension Score at Each Visit by Treatment Group	ITT Population
Table	EF_TER	14.2.5.9.2	Other Secondary Analysis: Change from Baseline in MLHF Physical Dimension Score at Each Visit by Treatment Group	Full Analysis Set
Table	EF_TES	14.2.5.10.1	Other Secondary Analysis: Change from Baseline in MLHF Emotional Score at Each Visit by Treatment Group	ITT Population
Table	EF_TET	14.2.5.10.2	Other Secondary Analysis: Change from Baseline in MLHF Emotional Score at Each Visit by Treatment Group	Full Analysis Set

Type	Rho Name	Number	Title	Population
Table	EF_TEU	14.2.5.11.1	Other Secondary Analysis: Change from Baseline in Health State Score in EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group	ITT Population
Table	EF_TEV	14.2.5.11.2	Other Secondary Analysis: Change from Baseline in Health State Score in EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group	Full Analysis Set
Table	EF_TEW	14.2.5.12.1	Other Secondary Analysis: EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group	ITT Population
Table	EF_TEX	14.2.5.12.2	Other Secondary Analysis: EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group	Full Analysis Set
Table	EF_TEY	14.2.5.13.1	Other Secondary Analysis: EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group - No Problem versus Problem	ITT Population
Table	EF_TEZ	14.2.5.13.2	Other Secondary Analysis: EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Visit and Treatment Group - No Problem versus Problem	Full Analysis Set
[redacted]				

Type	Rho Name	Number	Title	Population
Table	AE_TZZ	14.3.1.1	Overall Summary of Treatment-emergent Adverse Events by Treatment Group	Safety Population
Table	AE_TAA	14.3.1.2.1	All Treatment-emergent Adverse Events by System Organ Class and Preferred Term, by Treatment Group	Safety Population
Table	AE_TBA	14.3.1.2.2	All Treatment-emergent Adverse Events by System Organ Class and Preferred Term, by Treatment Group -- Events Before LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBB	14.3.1.2.3	All Treatment-emergent Adverse Events by System Organ Class and Preferred Term, by Treatment Group -- Events After LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBC	14.3.1.2.4	All Treatment-emergent Adverse Events by System Organ Class and Preferred Term, by Treatment Group	Safety Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TAB	14.3.1.3	Treatment-emergent Adverse Events by Preferred Term, and Treatment Group in Descending Frequency Based on Total	Safety Population
Table	AE_TAC	14.3.3.1	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Related to Study Drug	Safety Population
Table	AE_TAD	14.3.3.2	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population
Table	AE_TAE	14.3.4.1	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group	Safety Population

Type	Rho Name	Number	Title	Population
Table	AE_TAF	14.3.4.2	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population
Table	AE_TAG	14.3.4.3	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group -Related to Study Drug	Safety Population
Table	AE_TAH	14.3.4.4	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group – Related to Study Procedure	Safety Population
Table	AE_TAI	14.3.4.5	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group – Related to Injection Catheter	Safety Population
Table	AE_TAJ	14.3.4.6	Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group – Related to Mapping Catheter	Safety Population
Table	AE_TAK	14.3.5.1.1	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table	AE_TBJ	14.3.5.1.2	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group -- Events Before LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBK	14.3.5.1.3	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group -- Events After LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant

Type	Rho Name	Number	Title	Population
Table	AE_TBL	14.3.5.1.4	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TAL	14.3.5.2	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Related to Study Drug	Safety Population
Table	AE_TAM	14.3.5.3	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group – Related to Injection Catheter	Safety Population
Table	AE_TAN	14.3.5.4	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Related to Mapping Catheter	Safety Population
Table	AE_TAO	14.3.5.5	Serious Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table	AE_TAP	14.3.5.6	Serious Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group - Related to Study Drug	Safety Population
Table	AE_TAQ	14.3.5.7	Serious Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group - Related to Injection Catheter	Safety Population
Table	AE_TAR	14.3.5.8	Serious Treatment-emergent Adverse Events that Occurred on Day 0 Hospitalization Through Discharge by System Organ Class, Preferred Term, and Treatment Group - Related to Mapping Catheter	Safety Population

Type	Rho Name	Number	Title	Population
Table	AE_TAT	14.3.6	Treatment-emergent Adverse Events Causing Study Drug Withdrawal by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table	AE_TAY	14.3.7.1	Summary of Deaths by Treatment Group	ITT Population
Table	AE_TAZ	14.3.7.2.1	Summary of Deaths by Treatment Group	Full Analysis Set
Table	AE_TBN	14.3.7.2.2	Summary of Deaths by Treatment Group -- Events Before LVAD Implantation, Artificial Heart, or Heart Transplant	Full Analysis Set Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBO	14.3.7.2.3	Summary of Deaths by Treatment Group -- Events After LVAD Implantation, Artificial Heart, or Heart Transplant	Full Analysis Set Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBP	14.3.7.2.4	Summary of Deaths by Treatment Group	Full Analysis Set Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TAV	14.3.8	Efficacy Endpoint Events (Key Secondary) by Preferred Term and Treatment Group	ITT Population
Table	AE_TAW	14.3.9.1.1	Treatment-emergent Cardiac Events of Special Interest	Safety Population
Table	AE_TBD	14.3.9.1.2	Treatment-emergent Cardiac Events of Special Interest -- Events Before LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBE	14.3.9.1.3	Treatment-emergent Cardiac Events of Special Interest -- Events After LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant

Type	Rho Name	Number	Title	Population
Table	AE_TBF	14.3.9.1.4	Treatment-emergent Cardiac Events of Special Interest	Safety Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TAX	14.3.9.2.1	Treatment-emergent Other Events of Special Interest	Safety Population
Table	AE_TBG	14.3.9.2.2	Treatment-emergent Other Events of Special Interest -- Events Before LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBH	14.3.9.2.3	Treatment-emergent Other Events of Special Interest -- Events After LVAD Implantation, Artificial Heart, or Heart Transplant	Safety Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	AE_TBI	14.3.9.2.4	Treatment-emergent Other Events of Special Interest	Safety Patients Excluding Patients Who Had LVAD Implantation, Artificial Heart, or Heart Transplant
Table	LB_TAA	14.3.10.1	Serum Chemistry Laboratory Tests Results and Changes From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	LB_TAB	14.3.10.2	Serum Chemistry Laboratory Tests Results Shifts From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	LB_TAC	14.3.10.3	Serum Chemistry Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	Safety Population
Table	LB_TAD	14.3.11.1	Hematology Laboratory Tests Results and Changes From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population

Type	Rho Name	Number	Title	Population
Table	LB_TAE	14.3.11.2	Hematology Laboratory Tests Results Shifts From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	LB_TAF	14.3.11.3	Hematology Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	Safety Population
Table	LB_TAG	14.3.12.1	Urinalysis Laboratory Tests Results and Changes From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	LB_TAH	14.3.12.2	Urinalysis Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	Safety Population
Table	VS_TAA	14.3.13.1	Vital Signs Values and Changes From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	VS_TAB	14.3.13.2	Vital Signs Clinically Significant Abnormal Values by Treatment Group	Safety Population
Table	EG_TAB	14.3.14.1	Electrocardiogram Variables Results and Changes From Baseline to Each Visit and Last Assessment by Treatment Group	Safety Population
Table	EG_TAC	14.3.14.2	Electrocardiogram Findings Shifts From Baseline to Overall, Each Visit, and Last Assessment by Treatment Group	Safety Population
Table	EG_TAD	14.3.15	Telemetry Results (Clinically Significant Arrhythmias) During and After Treatment Procedure by Treatment Group	Safety Population
Table	EG_TAE	14.3.16	24-hour Holter Monitor Results at Each Time Point by Treatment Group	Safety Population
Table	PE_TAB	14.3.17	Physical Examination Findings Shifts From Baseline to Last Assessment in by Treatment Group	Safety Population
Table	CM_TAA	14.3.18	Concomitant Medications by Therapeutic Class and Treatment Group	Safety Population

Type	Rho Name	Number	Title	Population
Table	IM_TAA	14.4.1	Blood Concentration at Each Time Point by Treatment Group	ITT Population
Table	IM_TAB	14.4.2	Immunogenicity Analyses by Time points and by Treatment Group	ITT Population
Figure	EF_FAA	14.2.7.1.1	Mean Cumulative Rate (MCR) of Recurrent Non-Fatal HF-MACE Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	ITT Population
Figure	EF_FAB	14.2.7.1.2	Mean Cumulative Rate (MCR) of Recurrent Non-Fatal HF-MACE Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	Full Analysis Set
Figure	EF_FAG	14.2.7.2.1	Kaplan-Meier Plot for Time-to-First Terminal Cardiac Event (TCE) by Treatment Group	ITT Population
Figure	EF_FAH	14.2.7.2.2	Kaplan-Meier Plot for Time-to-First Terminal Cardiac Event (TCE) by Treatment Group	Full Analysis Set
Figure	EF_FAO	14.2.7.3.1	Non-inferiority Plot for Time to First Terminal Cardiac Event (TCE)	ITT Population
Figure	EF_FAP	14.2.7.3.2	Non-inferiority Plot for Time to First Terminal Cardiac Event (TCE)	Full Analysis Set
Figure	EF_FAC	14.2.7.4.1	Kaplan-Meier Plot for Time-to-Cardiac Death by Treatment Group	ITT Population
Figure	EF_FAD	14.2.7.4.2	Kaplan-Meier Plot for Time-to-Cardiac Death by Treatment Group	Full Analysis Set
Figure	EF_FAE	14.2.7.5.1	Kaplan-Meier Plot for Time-to-All Cause Death by Treatment Group	ITT Population
Figure	EF_FAF	14.2.7.5.2	Kaplan-Meier Plot for Time-to-All Cause Death by Treatment Group	Full Analysis Set
Figure	EF_FAM	14.2.7.6.1	Kaplan-Meier Plot for Time-to-First Composite of Non-Fatal HF-MACE by Treatment Group	ITT Population
Figure	EF_FAN	14.2.7.6.2	Kaplan-Meier Plot for Time-to-First Composite of Non-Fatal HF-MACE by Treatment Group	Full Analysis Set

Type	Rho Name	Number	Title	Population
Figure	EF_FAQ	14.2.7.7.1	Kaplan-Meier Plot for Time-to-First Composite of Non-Fatal HF-MACE or Terminal Cardiac Event (TCE) by Treatment Group	ITT Population
Figure	EF_FAR	14.2.7.7.2	Kaplan-Meier Plot for Time-to-First Composite of Non-Fatal HF-MACE or Terminal Cardiac Event (TCE) by Treatment Group	Full Analysis Set
Figure	EF_FAS	14.2.7.8.1	Mean Cumulative Rate (MCR) of Successfully Resuscitated Cardiac Death Events Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	ITT Population
Figure	EF_FAT	14.2.7.8.2	Mean Cumulative Rate (MCR) of Successfully Resuscitated Cardiac Death Events Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	Full Analysis Set
Figure	EF_FAU	14.2.7.9.1	Mean Cumulative Rate (MCR) of Non-Fatal HF-MACE Associated with Hospital Admission or Urgent Care Visit Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	ITT Population
Figure	EF_FAV	14.2.7.9.2	Mean Cumulative Rate (MCR) of Non-Fatal HF-MACE Associated with Hospital Admission or Urgent Care Visit Over Time, Adjusted for Terminal Cardiac Events, by Treatment Group	Full Analysis Set
Figure	EF_FAW	14.2.7.10.1	Kaplan-Meier Plot for Time-to-Cardiac Death as the First Terminal Cardiac Event (TCE) by Treatment Group	ITT Population
Figure	EF_FAX	14.2.7.10.2	Kaplan-Meier Plot for Time-to-Cardiac Death as the First Terminal Cardiac Event (TCE) by Treatment Group	Full Analysis Set
Figure	EF_FBA	14.2.8.1.1	Forest Plot for Time-to-First Terminal Cardiac Event by Subgroups	ITT Population
Figure	EF_FBB	14.2.8.1.2	Forest Plot for Time-to-Recurrent Non-fatal HF-MACE Adjusted for Terminal Cardiac Events by Subgroups	ITT Population
Figure	EF_FCA	14.2.8.2.1	Forest Plot of Time-to-Event Hazard Ratios	ITT Population

Type	Rho Name	Number	Title	Population
Figure	EF_FCB	14.2.8.2.2	Forest Plot of Time-to-Event Hazard Ratios	Full Analysis Set
Listing	RD_LAB	16.1.7	Randomization by Treatment Group	ITT Population
Listing	DS_LAA	16.2.1.1	Patient Disposition by Treatment Group	ITT Population
Listing	DS_LAB	16.2.1.2	Inclusion and Exclusion Criteria	Screen Failures
Listing	DS_LAC	16.2.1.3	Patients Randomized but Did not Receive Treatment	ITT Population
Listing	DS_LAD	16.2.1.4	Patients Randomized but Did not Complete the Index Cardiac Catheterization	ITT Population
Listing	DV_LAA	16.2.2	Protocol Violations by Treatment Group	ITT Population
Listing	DS_LAE	16.2.3	Analysis Sets	ITT Population
Listing	DM_LAA	16.2.4.1	Demographics by Treatment Group	ITT Population
Listing	DM_LAB	16.2.4.2	Substance Usage by Treatment Group	ITT Population
Listing	SC_LAA	16.2.4.3	Childbearing Potential by Treatment Group (Females Only)	ITT Population
Listing	MH_LAA	16.2.4.4	General Medical History by Treatment Group	ITT Population
Listing	MH_LAB	16.2.4.5.1	Cardiovascular History by Treatment Group	ITT Population
Listing	MH_LAD	16.2.4.5.2	Cardiovascular History - ICD/CRT Device by Treatment Group	ITT Population
Listing	EG_LAE	16.2.4.5.3	ICD Device by Treatment Group	ITT Population
Listing	EG_LAF	16.2.4.5.4	ICD Device Interrogation by Treatment Group	ITT Population
Listing	EG_LAG	16.2.4.5.5	New Device by Treatment Group	ITT Population
Listing	MH_LAC	16.2.4.6	Surgery History by Treatment Group	ITT Population
Listing	EX_LAA	16.2.5.1	Study Drug Administration by Treatment Group - NOGASTAR Mapping	Safety Population

Type	Rho Name	Number	Title	Population
Listing	EX_LAB	16.2.5.2	Study Drug Administration by Treatment Group – Thaw	Safety Population
Listing	EX_LAC	16.2.5.3	Study Drug Administration by Treatment Group – Injection	Safety Population
Listing	EX_LAD	16.2.5.4	Study Drug Administration by Treatment Group – Injection Details	Safety Population
Listing	EX_LAE	16.2.5.5	Hospitalization For Study Intervention by Treatment Group	ITT Population
Listing	EX_LAF	16.2.5.6	Catheter Accountability by Treatment Group	Safety Population
Listing	EF_LAA	16.2.6.1	Primary Efficacy Data – Non-fatal HF-MACE by Treatment Group	ITT Population
Listing	EF_LAB	16.2.6.2.1	Key Secondary Efficacy Data – Terminal Cardiac Events by Treatment Group	ITT Population
Listing	EF_LAN	16.2.6.2.2	LVAD Implantation, Artificial Heart, or Heart Transplant by Treatment Group	ITT Population
Listing	EF_LAC	16.2.6.3	Secondary Efficacy Data - Hospital Admissions or Urgent HF Visit for Non-fatal Decompensated HF Events Beginning on Day 0	ITT Population
Listing	EF_LAD	16.2.6.4	Secondary Efficacy Data – Cardiac Deaths by Treatment Group	ITT Population
Listing	EF_LAE	16.2.6.5	Secondary Efficacy Data – Nonfatal MI, Nonfatal CVA, Coronary Revascularization, or Ventricular Arrhythmias by Treatment Group	ITT Population
Listing	EF_LAF	16.2.6.6	Other Secondary Efficacy Data: 2-D Echocardiography Data (LVEF, LVEDV, and LVESV) by Treatment Group	ITT Population
Listing	EF_LAG	16.2.6.7	Other Secondary Efficacy Data: 2-D Echocardiography Data(All) by Treatment Group	ITT Population
Listing	EF_LAH	16.2.6.8	Other Secondary Efficacy Data: Radionuclide Ventriculography (RVG) Data by Treatment Group	ITT Population
Listing	EF_LAI	16.2.6.9	Other Secondary Efficacy Data: 6-Minute Walk Test Data by Treatment Group	ITT Population

Type	Rho Name	Number	Title	Population
Listing	EF_LAJ	16.2.6.10	Other Secondary Efficacy Data: NYHA Functional Class by Treatment Group	ITT Population
Listing	EF_LAK	16.2.6.11	Other Secondary Efficacy Data: Minnesota Living with Heart Failure (MLHF) Questionnaire by Treatment Group	ITT Population
Listing	EF_LAL	16.2.6.12	Other Secondary Efficacy Data: EuroQoL 5-dimensional Quality of Life (EQ-5D) Questionnaire by Treatment Group	ITT Population
Listing	EF_LAM	16.2.6.13	Endpoint Events by Treatment Group	ITT Population
Listing	DS_LAF	16.2.6.14	Vital Status by Treatment Group	All Randomized Subjects
Listing	AE_LAA	16.2.7.1	Adverse Events by Treatment Group	ITT Population
Listing	AE_LAB	16.2.7.2	Adverse Events Leading to Death by Treatment Group	ITT Population
Listing	AE_LAC	16.2.7.3	Serious Adverse Events by Treatment Group	ITT Population
Listing	AE_LAD	16.2.7.4	Adverse Events Causing Drug Withdrawal by Treatment Group	ITT Population
Listing	AE_LAE	16.2.7.5	Adverse Events that Occurred on Day 0 by Treatment Group	ITT Population
Listing	AE_LAF	16.2.7.6	Adverse Events that Occurred from Day 0 Through Hospital Discharge by Treatment Group	ITT Population
Listing	AE_LAG	16.2.7.7	Procedure-Related Adverse Events by Treatment Group	ITT Population
Listing	AE_LAH	16.2.7.8	Injection Catheter-Related Adverse Events by Treatment Group	ITT Population
Listing	AE_LAI	16.2.7.9	Mapping Catheter-Related Adverse Events by Treatment Group	ITT Population
Listing	AE_LAJ	16.2.7.10	Non-Fatal HF-MACE by Treatment Group	ITT Population
Listing	AE_LAK	16.2.7.11	Cardiovascular Events of Special Interest by Treatment Group	ITT Population
Listing	AE_LAN	16.2.7.12	Other Events of Special Interest by Treatment Group	Safety Population

Type	Rho Name	Number	Title	Population
Listing	AE_LAM	16.2.7.13	Adverse Events for Patients Who Did Not Meet Screening Criteria	Screen Failures
Listing	LB_LAA	16.2.8.1	Laboratory Reference Ranges	ITT Population
Listing	LB_LAB	16.2.8.2	Serum Chemistry Laboratory Tests Results by Treatment Group	ITT Population
Listing	LB_LAC	16.2.8.3	Hematology Laboratory Tests Results by Treatment Group	ITT Population
Listing	LB_LAD	16.2.8.4	Urinalysis Laboratory Tests Results by Treatment Group	ITT Population
Listing	LB_LAE	16.2.8.5	Urine Pregnancy Test Results by Treatment Group (Females Only)	ITT Population
Listing	LB_LAF	16.2.8.6	Serum Chemistry Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	ITT Population
Listing	LB_LAG	16.2.8.7	Hematology Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	ITT Population
Listing	LB_LAH	16.2.8.8	Urinalysis Laboratory Tests Clinically Significant Abnormal Results by Treatment Group	ITT Population
Listing	RD_LAA	16.2.8.9	Treatment Schedule by Treatment Group	ITT Population
Listing	VS_LAA	16.2.8.10	Vital Signs Values by Treatment Group	ITT Population
Listing	VS_LAB	16.2.8.11	Vital Signs Clinically Significant Abnormal Values by Treatment Group	ITT Population
Listing	EG_LAA	16.2.8.12	Electrocardiogram Findings by Treatment Group	ITT Population
Listing	EG_LAB	16.2.8.13	Electrocardiogram Variable Results by Treatment Group	ITT Population
Listing	EG_LAC	16.2.8.14	Telemetry Results by Treatment Group	ITT Population
Listing	EG_LAD	16.2.8.15	24-Hour Holter Monitor Results by Treatment Group	ITT Population
Listing	PE_LAA	16.2.8.16	Physical Examination Findings by Treatment Group	ITT Population

Type	Rho Name	Number	Title	Population
Listing	SC_LAB	16.2.8.17	Menstruation by Treatment Group	ITT Population
Listing	CM_LAA	16.2.8.18	Medications by Treatment Group	ITT Population
Listing	YB_LAA	16.2.8.19	Telephone Contact by Treatment Group	ITT Population
[redacted]				

14. APPENDICES

- Appendix 1: Rationale and Statistical Approach for an Enrollment Adaptation Enriching for and Replenishing Patients with Baseline NYHA Class III in the MSB-MPC-CHF001 Clinical Trial
- Appendix 2: Dream HF-1 Protocol C41750/3100 DMC Interim Analysis Plan Version 1.7 (May 4, 2016)
- Appendix 3: TEVA C4175/3100 Interim Analysis #1 Predefined Threshold Outcome Report
- Appendix 4: MSB-MPC-CHF001 (Dream-HF #1) Interim Analysis #2 (IA2) – Design and Results as Reported by the Independent Data Monitoring Committee on 8 April 2017
- Appendix 5: SAP Addendum for Two Patients from Site # [redacted] who were Randomized Twice: Patient # [redacted] and Patient # [redacted]
- Appendix 6: Missing Data Handling for Efficacy Endpoints Other Than Time-to-Event for Secondary Biomarkers or Other Non-clinical Event Measurements That are Missing Due to Absence of Follow-Up Visits and/or Terminal Events
- Appendix 7: Visit Windows
- Appendix 8: Review of Concomitant Medications by ATC Classification
- Appendix 9: Review of Adverse Events of Interest

Appendix 1: Rationale and Statistical Approach for an Enrollment Adaptation Enriching for and Replenishing Patients with Baseline NYHA Class III in the MSB-MPC-CHF001 Clinical Trial

Appendix 1: Rationale and Statistical Approach for an Enrollment Adaptation Enriching for and Replenishing Patients with Baseline NYHA Class III in the MSB-MPC-CHF001 Clinical Trial

The rationale and statistical approach for the MSB-MPC-CHF001 trial population enrichment and replenishment adaptation for NYHA Class III patients can be understood based on the following two components of this document:

1. Enrichment Goals and Motivation for Replenishment of Class III Patients in the MSB-MPC-CHF001 Trial
2. Statistical Approach to Adaptation of the Clinical Trial Patient Population.

1. ENRICHMENT GOALS AND MOTIVATION FOR REPLENISHMENT OF CLASS III PATIENTS IN THE MSB-MPC-CHF001 TRIAL

Advanced chronic heart failure (HF) due to left ventricular (LV) systolic dysfunction is associated with HF-related recurrent non-fatal major adverse cardiac events (HF-MACE) as well as terminal cardiac events (TCE including cardiac death, implantation of left ventricular assist devices [LVAD], heart transplant or placement of an artificial heart). A key characteristic of advanced HF is the direct relationship between an increase in hospitalizations for decompensated HF and increased risk for subsequent TCE. When evaluating the advanced HF state, it is important to consider this interaction since it reflects the aggregate impact of these events on overall health-economics and ultimately patient survival.

The ongoing Phase 3 trial MSB-MPC-CHF001 is enrolling patients pre-specified as having either NYHA Class II or Class III heart failure. Independent of baseline NYHA Class or Class III, all patients were considered to be at high risk of recurrent hospitalization events based on the same study entry criteria that include either a prior hospitalization within the past 9 months and/or high levels of the HF biomarker NT-pro-BNP. At study commencement, it was expected that rates of recurrent non-fatal HF-MACE and TCEs would be similar between the pre-specified NYHA Class II and Class III patient populations considered to be at high risk for HF disease burden. Consequently, the trial's primary endpoint is a comparison of recurrent non-terminal HF-MACE between active (rexlemestrocel-L) and control patients with either late NYHA Class II or Class III heart failure. The primary endpoint analysis method utilizes a joint frailty model (JFM) which takes into account simultaneously analyzed recurrent non-fatal HF-MACE and an associated time to terminal event while accounting for the relationship between the two processes. [1,2] The specific components of the trial's primary efficacy endpoint are defined in our prior correspondence to FDA dated 6 April 2017.

In July 2016, the independent statistician for the MSB-MPC-CHF001 trial conducted a pre-specified blinded-to-treatment review of pooled subject demographics, cardiovascular history, baseline concomitant medications, baseline LV echocardiographic measurements, baseline NT pro-BNP measurements, and baseline 6-minute walk test results. Additionally, the independent statistician conducted a pre-specified blinded-to-treatment review of the number and timing of TCEs associated with early trial termination defined as cardiac death, implantation of a LVAD, heart transplantation or placement of an artificial heart. These blinded-to-treatment summaries were performed for the entire study population (combined Class II and Class III) as well as separately for baseline NYHA Class II and separately for baseline NYHA Class III. The database included information for 231 randomized HF patients who had undergone an index cardiac catheterization on Day 0 of the trial. The mean follow-up time was 9.8 months, a value that was similar for the baseline Class II and Class III patients.

The results of the blinded data review were most remarkable for a 3.2-fold higher rate of TCE for patients who at baseline were NYHA Class III compared with Class II. In addition, there was a 2.0-fold higher rate of recurrent non-fatal HF-MACE in the Class III compared with Class II patients. Since TCEs are thought to follow recurrent prior hospitalizations for decompensated HF, we were concerned that the very high rate of observed TCEs in NYHA Class III patients relative to Class II patients would skew the trial's primary endpoint of recurrent non-fatal HF-MACE by resulting in a progressively greater proportion of surviving NYHA class II patients remaining in the trial over time. This observation raised several critical issues that must be addressed regarding the conduct of the trial:

a. The disparity of event rates between Class III and Class II patients would be expected to have an adverse impact on the timely completion of the trial due to failure to accumulate recurrent non-fatal HF-MACE at the anticipated rate
b. Based on the treatment blinded TCE data, the NYHA Class III patients clearly have a much greater unmet medical need than the Class II patients and therefore need to be the focus of the clinical trial evaluation
c. Due to the mechanism of action of rexlemestrocel-L and its propensity to have greater clinical effect when more severe local tissue disease is present, it is anticipated that Class III patients would be more likely to benefit from the active treatment in the trial.

Thus, a concern was raised regarding the need to enrich and replenish enrollment of baseline NYHA Class III patients in the ongoing trial.

On 23 February 2017, Mesoblast had a Type C meeting with FDA to discuss the Statistical Analysis Plan and stopping rules for a pre-specified futility Interim Analysis (IA#2) to be

conducted by the independent statistician for the trial. At this time, Mesoblast also discussed its interest in adapting the study for enrichment and replenishment of baseline NYHA Class III patients if the IA#2 resulted in the trial's continuation. During that meeting, as well as in the subsequent meeting minutes, the Agency provided Mesoblast with recommendations to follow if the Sponsor decided to conduct an adaptation in the patient population (i.e., enrichment and replenishment for baseline NYHA Class III patients) for the remainder of the MSB-MPC-CHF001 trial (See Section 2).

In April 2017, a pre-specified futility Interim Analysis (IA#2) was conducted for 270 randomized subjects who were known to have undergone an index cardiac catheterization on Day 0 of the trial. The chairperson of the trial's Independent Data Monitoring Committee (DMC) reported the treatment blinded futility results of the IA#2 to the Chairmen of the trial's Executive Steering Committee (ESC) and the Sponsor. The IA#2 output did not include (nor did the independent statistician perform) any analysis or data review for superiority, any p-value determinations, or any information relating to early stopping of the trial for success or other purposes. Rather, IA#2 was purely a futility analysis with a pre-specified stopping rule threshold for recurrent non-fatal HF-MACE calculated for rexlemestrocel-L vs. the sham group using JFM. Throughout the IA#2 process, Mesoblast remained fully blinded to the quantitative results and was provided only YES, NO or INDETERMINATE answers to whether the calculated hazard ratios (HRs) for each of the pre-specified patient categories was below the pre-defined HR futility boundary. Importantly, an INDETERMINATE response was pre-specified to occur if JFM did not converge and respective HR could not be calculated due to insufficient number of recurrent non-fatal HF-MACE and/or terminal events. The futility only IA#2 has resulted in continuation of the trial.

At approximately the same time as IA#2, an updated blinded-to-treatment review was conducted by an outside contractor who was blinded to treatment assignment in order to assess the rate of TCEs for the entire study population and by baseline NYHA Class (i.e., separately for Class II and separately for Class III). The mean follow-up was similar for baseline Class II and Class III patients (approximately 13.5 months). The Sponsor was provided blinded-to-treatment summaries of the results. Strikingly, and consistent with the earlier blinded-to-treatment analysis that was conducted in 231 randomized patients at a mean follow-up of 9.8 months, there was a 4.2-fold higher number of TCEs for the baseline NYHA Class III than Class II patients ($p=0.0014$ by Kaplan Meier log-rank analysis). This occurred at a time that the ratio of recurrent non-fatal HF-MACE was in excess of 1.6-fold higher for the Class III patients.

Critically, the greater than 4-fold higher number of TCEs in the more vulnerable Class III HF patient population and their subsequent censoring of non-fatal HF-MACE from the trial are important since the TCE censored Class III patients had 3.2-fold higher rate of recurrent non-fatal HF-MACE prior to the time of censoring than did the censored Class II patients. This would be expected to substantially reduce the rate of accumulation of recurrent non-fatal HF-MACE as Class III patients are eliminated from the trial due to censoring. The result would be a very negative impact on the operational feasibility of the trial, thereby jeopardizing the completion of the study. For these reasons, enrichment and replenishment of the trial with baseline NYHA Class III patients is necessary. This will be accomplished by enriching for patients who have been classified as NYHA Class III during the screening evaluation. This enrichment aligns well with the anticipation that patients with the most advanced chronic HF will have the largest beneficial response to rexlemestrocel-L therapy, potentially due to greater activation of rexlemestrocel-L by factors produced within the local damaged myocardium seen in more advanced HF states. The subsequent release of paracrine factors is thought to result in activation of myocardial downstream signaling pathways that enhance the regenerative therapy response.

Accordingly, it is necessary to maintain an adequate number of ongoing baseline NYHA Class III patients in the trial over time. This will be achieved by enrolling an enriched and replenished study population consisting exclusively of baseline NYHA Class III patients. This 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 been randomized into the trial resulting in a baseline Class III/Class II ratio of 2:1. In order to achieve this target, an enrollment cap of ~200 patients with 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.

2. STATISTICAL APPROACH TO ADAPTATION OF CLINICAL TRIAL PATIENT POPULATION

The adaptation for the MSB-MPC-CHF001 trial will be implemented only after its description and related statistical approach are included in the protocol and Statistical Analysis Plan (SAP) and FDA has been given an opportunity to review these documents. As all details of this adaptation are pre-specified prior to the beginning of its implementation, this adaptation is a planned adaptation. In pre-specifying the adaptation, Mesoblast has been adhering to the following FDA responses in the 23 February 2017 meeting minutes.

- In FDA's response to Question 4a the Agency stated: "If you modify study MSB-MPC-CHF001 to enroll only patients with NYHA class III chronic heart failure based on the IA#2 results, please note that this will be considered as an adaptation to the study design. Performing a study adaptation without sufficient pre-specification of the statistical methodology for the adaptation will adversely affect the interpretability of the study outcomes. Therefore, if you are intending to perform such an adaptation, you will need to revise your SAP to pre-specify the statistical procedures for the study population enrichment. We can review the complete updated SAP."
- In FDA's response to Question 4b the Agency stated: "Yes, in principle, you may perform a study adaptation to enrich the study population, provided that you pre-specify the detailed methodology for the adaptation (see FDA Response to Comment #4a for additional details) in the SAP and SOPs prior to performing the adaptation."

Accordingly, and in response to FDA's responses to Questions 4a and 4b, the following important considerations will determine the statistical methodology for this adaptation.

- This adaptation is driven by the necessity to replenish the NYHA Class III patient population in the study as they are having TCEs resulting in censoring at a greater than 4-fold higher rate than Class II patients. This shows that the Class III patients as a group truly have "advanced heart failure" with a high unmet clinical need. The marked disparity between TCE rates in baseline Class III vs. Class II patients is expected to significantly change the intended patient population composition relative to the trial's primary efficacy endpoint. The details are presented in Section 1 above.
- Additionally, this adaptation is being planned after the unblinded independent DMC completed interim futility analysis #2. This futility-only IA#2 was pre-planned and agreed upon by FDA. No superiority assessment was performed. In addition, no efficacy estimates based on group comparisons were evaluated or reported by independent statistician to either the trial's Executive Steering Committee (ESC) or Sponsor. Furthermore, no event rates by treatment group were estimated or reported by the unblinded independent statistician. The event rates by NYHA functional Class at baseline were reviewed strictly in a blinded fashion by the statistician who had not had access to unblinded treatment assignments. The details of the IA#2 futility only results are discussed in the Section 1 above. As an isolated futility analysis does not affect the

Type 1 error rate, no significance level adjustment would need to be performed as a result of this interim futility analysis.

The following considerations are affecting the choice and implementation of the statistical approach to adaptation.

- This is an event-driven trial with the planned number of recurrent non-fatal HF-MACE of at least 531. This pre-specified minimum number of events will not be changed as a result of this adaptation. There will be no resizing of this study. Only event rates observed and reviewed in a blinded manner will need to be increased by enrolling more baseline NYHA Class III patients.
- All randomized patients, both enrolled prior to and after adaptation implementation, will be included in the final ITT analysis. No patients will be excluded from final ITT analysis as a result of this adaptation.
- No changes in eligibility criteria (beyond enrolling baseline NYHA Class III patients only); all Class II patients randomized prior to adaptation will be included in final analysis. Of note, throughout the entire conduct of the MSB-MPC-001 trial, the baseline NYHA Class II and Class III patients have been randomized separately for appropriate treatment balance. This procedure (randomization stratified by NYHA Class at Baseline) will be continued for the remainder of the trial.
- No change in the hypothesis being tested will occur.

These considerations lead us to believe that based on sections V-B and VI-D of the FDA Adaptive Design Guidance for Clinical Trials for Drugs and Biologics [3], no significance level adjustment is needed as Type 1 error rate is not affected by this adaptation.

- Guidance Line 652: "In studies using a discrete outcome (event) endpoint, a blinded examination of the study overall event rate can be compared with the assumptions used in planning the study. Examining the data in this blinded analysis does not introduce statistical bias and no statistical adjustments are required."
- Guidance Line 1100: "Adaptive methods that have been proposed include (1) changing only the eligibility criteria, with no change in the study overall sample size and with the final analysis including the entire study population, or (2) modifying the plan for the final analysis to include only patients with the preferred characteristic."
- In our case, despite enriching for Class III patients there will be no change in the planned number of recurrent non-fatal HF-MACE, with the final analysis including the entire study ITT population, i.e., all baseline NYHA Class II and Class III randomized patients.

Relative to the trial's hypothesis:

- Guidance Line 1106: "There may be no statistical adjustment necessary if there are no changes in the hypotheses tested."
- In our case, there will be no change in the hypothesis tested.

Since we would like to comply with the strictest interpretation of the Adaptive Design Guidance, we suggest the following statistical approach:

- The primary analysis will be performed as previously planned and stated in the SAP based on the entire ITT population of all randomized Class II and Class III patients enrolled both prior to and after this adaptation. The hypothesis tested will be as previously pre-specified. The Type 1 error rate is not affected and no alpha level adjustment will be performed.
- A sensitivity analysis will also be performed consistent with Protocol Amendment 7 and the enrichment for NYHA Class III patients. This analysis will be conducted utilizing the inverse normal combination function as described in Lechmacher and Wassmer. [4] Since this methodology has not been studied for JFM, we'll apply this analysis to the key secondary endpoint, i.e., time-to-first TCE. The log rank test will be applied separately to the TCEs that occurred for patients before and after the adaptation implementation, and respective p-values will be combined using inverse normal combination function. The respective weights in the inverse normal combination function will be fixed and calculated based on the proportion of TCEs that occurred for patients enrolled prior to and after the adaptation implementation. The adaptation implementation date was planned for the latter part of 2017 and occurred on 11 November 2017. Four hundred forty-five patients were randomized before 11 November 2017, and 120 patients were randomized on or after that date. One hundred thirty-eight patients randomized before 11 November 2017 had at least one TCE, and 19 patients randomized on or after 11 November 2017 had a at least one TCE. Per Wassmer [5], as long as these weights are fixed prior to adaptation implementation, the type I error is controlled despite data-dependent design changes (in our case, enrichment with baseline NYHA Class III patients based on the blinded review of the event rates for Class III and Class II patients).
- The statistical methods of Type 1 error control in adaptive designs are used when design changes include changes to the targeted number of events, primary endpoints, or hypothesis tested. [6] None of these design changes are planned in this trial and we believe that Type 1 error is not affected by this particular adaptation. Respectively, the sensitivity analysis based on inverse normal combination function with fixed weights is a very conservative approach.

3. REFERENCES

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Appendix 2: Dream HF-1 Protocol C41750/3100 DMC Interim Analysis Plan Version 1.7 (May 4, 2016)

Teva Pharmaceutical Industries

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
Protocol C41750/3100

DMC interim analysis plan
Version 1.7

May 4, 2016

(Updated to reflect change in recipient of IA1 threshold outcome report)

Prepared by:

Statistics Collaborative, Inc.

CONFIDENTIAL

Contents

Abbreviations

CEC	Clinical Endpoints Committee
DMC	Data Monitoring Committee
ESC	Executive Steering Committee
HF	heart failure
IA	interim analysis
ICD	implantable cardioverter defibrillator
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVEDV	left ventricular end-diastolic volume
MACE	major adverse cardiovascular event
SCI	Statistics Collaborative, Inc.
SD	standard deviation
VF	ventricular fibrillation

1. Introduction

Teva's protocol C41750/3100 is a Phase 3, randomized, double-blind, sham procedure-controlled, parallel group study designed to assess the efficacy and safety of allogeneic mesenchymal precursor cells (rexlemestrocel-L; also referred to as CEP-41750) in patients with chronic heart failure due to left ventricular systolic dysfunction of either ischemic or nonischemic etiology. The trial's primary endpoint is time to first heart failure-related major adverse cardiovascular event (HF-MACE), defined as a composite of terminal HF-MACE (i.e., cardiac death, resuscitated cardiac death, LVAD placement, heart transplant, and artificial heart implantation) and nonfatal decompensated heart failure (HF) events. Resuscitated cardiac death includes successful firing of an implantable cardioverter defibrillator (ICD) for ventricular fibrillation (VF) in patients who have an ICD or any implanted device capable of defibrillation. Investigators are instructed to report any event that they assess as potentially being a component in the primary composite endpoint of HF-MACE. They are also instructed to report the following secondary endpoint events, which are collectively called MACE-Plus: any death from CV causes, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and coronory artery revascularization. All these events will be submitted to the CEC for adjudication.

This document summarizes statistical and logistical aspects of the two interim analyses that Statistics Collaborative, Inc. (SCI) will perform. SCI has updated this document in accordance with Amendment 2 of the protocol, dated July 29, 2015.

2. Protocol amendment 2

Protocol amendment 2 changed several of the statistical design characteristics of the study:

- Because Teva plans to conduct a second Phase 3 trial, Teva changed this trial's Type I error rate from a two-sided significance level of 0.01 to 0.05.
- Consequently, the required number of patients with HF-MACE was reduced from 465 to 314, and the estimated enrollment was reduced from 1,730 to 1,165 patients.

- The protocol added stopping guidelines for benefit to Interim Analysis 2. The analysis is projected to occur after 50% information time (i.e., 157 patients with HF-MACE), rather than 40% information time.

3. Interim Analysis (IA) 1

SCI will perform Interim analysis 1 (IA1) after the first approximately 120 patients have undergone index cardiac catheterization and been followed for at least 6 months. Randomized patients who 1) did not undergo index cardiac catheterization, or 2) underwent index cardiac catheterization after the cutoff date for IA1 will be excluded from the analysis. The cutoff date is defined as the date on which approximately the 120th patient reaches the 6-month follow-up visit. IA1 does not include a formal safety or efficacy review by the Data Monitoring Committee (DMC) and will neither be used to re-evaluate the number of required HF-MACE events nor to stop the study early for success. The objective of the analysis is to determine whether predefined thresholds have been met on the basis of analyses of 2-D echocardiographically determined surrogate endpoints (left ventricular ejection fraction [LVEF], end-systolic volume [LVESV], and end-diastolic volume [LVEDV]), and the primary endpoint (HF-MACE). The predefined thresholds for IA1 are as follows:

- **Left ventricular surrogate endpoints:**

  Absolute mean change from baseline at Month 6 in LVEF is not at least 2.5% greater in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm < +2.5%)

  OR

  Absolute mean change from baseline at Month 6 in LVESV and LVEDV is not at least 5 mL lower in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm > –5 mL);

- **HF-MACE**: The log-rank statistic for HF-MACE is less than the critical value derived under the Hwang, Shih, and DeCani beta-spending function (γ=–2).

No formal open or closed report will be prepared at this interim analysis. SCI will conduct the unblinded analysis described in Table 1 and communicate to the sponsor and Executive

Steering Committee (ESC) whether the predefined thresholds are 'met' or 'not met' for the surrogate and primary endpoints. This communication will not include any numeric results; rather, it will consist of two binary responses: one corresponding to whether the threshold has been met for the left ventricular (LV) surrogate endpoints and the other for whether the threshold has been met for HF-MACE. See the sample reporting form for IA1 in Section 5 of the document.

SCI will provide a copy of this communication, along with the numeric results described in Table 1, in the subsequent DMC safety report. The DMC is not involved in the conduct of IA1 and is not responsible for conveying a recommendation to the ESC based on its results.

Table 1. Decision rules for surrogate and primary endpoints based on observed interim data

	Group A (sham)		*Group B (rexlemestrocel-L)*
LVEF (%)			
N with baseline and Month 6 echocardiogram data	xx		xx
Mean (SD) at baseline (M_0)	xx (xx)		xx (xx)
Mean (SD) at Month 6 (M_6)[a]	xx (xx)		xx (xx)
Mean (SD) change (Δ=M_6 – M_0)[a]	xx (xx)		xx (xx)
Difference in mean change between treatment groups ($\delta = \Delta_B - \Delta_A$)		xx	
δ < +2.5%		Yes/No	
LVESV (mL)			
N with baseline and Month 6 echocardiogram data	xx		xx
Mean value at baseline (M_0)	xx (xx)		xx (xx)
Mean value at Month 6 (M_6)[a]	xx (xx)		xx (xx)
Mean change (Δ=M_6 – M_0)[a]	xx (xx)		xx (xx)
Difference in mean change between treatment groups ($\delta = \Delta_B - \Delta_A$)		xx	
δ > –5mL		Yes/No	
LVEDV (mL)			
N with baseline and Month 6 echocardiogram data	xx		xx
Mean value at baseline (M_0)	xx (xx)		xx (xx)
Mean value at Month 6 (M_6)[a]	xx (xx)		xx (xx)
Mean change (Δ=M_6 – M_0)[a]	xx (xx)		xx (xx)
Difference in mean change between treatment groups ($\delta = \Delta_B - \Delta_A$)		xx	
δ > –5mL		Yes/No	
HF-MACE			
N	xx		xx
n (%) with HF-MACE	x (x)		x (x)
Unstratified HR (95% CI)[b]		x.x (x.x, x.x)	
Log-rank statistic (Z)		0.xx	
Z < c^*		Yes/No	

Table includes all randomized subjects who underwent index cardiac catheterization on or before ddmmmyyyy.
a. Subjects missing data at Month 6 are excluded.
b. Hazard ratio of Group B/Group A. Calculations in this mock table assume Group B corresponds to the active arm.
c. Critical value derived under the Hwang, Shih, and DeCani beta-spending function (γ=–2).

Data received: SDTM ddMMMyyyy, IRT ddMMMyyyy
E:\Proj\Teva\Programs\xxx.sas v.xxx (last run: ddMMMyy, hh:mm) xxx.rtf

3.1. Left ventricular surrogate endpoints

The analysis of the LV surrogate endpoints will include only patients who underwent index cardiac catheterization on or before the IA1 cutoff date and have baseline and Month 6 measurements made through 2D echocardiography as determined by the core echocardiographic reading center. SCI will provide the sponsor and ESC with a single "yes/no" response as to whether the LV threshold has been met on the basis of the three LV surrogate endpoints as shown in Table 2. A response of "yes" indicates an unfavorable finding for rexlemestrocel-L relative to sham patients.

Table 2. Possible outcomes of LV surrogate endpoint decision criteria

LV threshold met (Answer given to ESC)	*LVEF* $\delta < +2.5\%$	*LVESV* $\delta > -5$ *mL*	*LVEDV* $\delta > -5$ *mL*
Yes	Yes	Yes	Yes
	Yes	Yes	No
	Yes	No	Yes
	Yes	No	No
	No	Yes	Yes
No	No	No	No
	No	Yes	No
	No	No	Yes

For each scenario in Table 2, Table 3 shows an example of the scenario using differences between the mean change for each LV surrogate endpoint ($\bar{\delta} = \Delta_B - \Delta_A$) and the binary response that SCI would provide to the sponsor and ESC if these results were obtained at IA1.

Table 3. Examples of scenarios at IA1 and the corresponding binary response communicated to the ESC

LV threshold met (Answer given to ESC)	*LVEF* $\delta < +2.5\%$	*LVESV* $\delta > -5$ *mL*	*LVEDV* $\delta > -5$ *mL*
Yes	1.4	-3.2	0
	2.4	-1.4	-5.2
	-1.0	-8.4	-3.2
	0	-7.2	-12
	4.6	1.5	0.5
No	3.5	-5.2	-6.4
	2.6	-4.7	-7.8
	4.7	-6.4	-2.1

3.2. HF-MACE

An independent Clinical Endpoints Committee (CEC), which will be blinded to treatment assignment for the duration of the study, will review and determine the onset of HF-MACE events. In preparation for IA1, the CEC will adjudicate all investigator-reported HF-MACE events that have been reported up to that point. The HF-MACE analysis will include only events for the subset of patients who underwent Day 0 index cardiac catheterization on or prior to the cutoff date for IA1. All events for such patients will be incorporated in the analysis, including events which occurred after the first six months of follow-up (i.e., no events will be censored). Teva estimates that roughly 20 to 30 HF-MACE events will have occurred and have been positively adjudicated at the time of IA1. Assuming observation of 314 events at the conclusion of the study, this would represent an information fraction of roughly 6 to 10% (i.e., 20/314 to 30/314).

With an information fraction of 7%, the critical value derived under the Hwang, Shih, and DeCani beta spending function (γ=–2) would be a z-score of -1.85 (with negative z-scores corresponding to an increased hazard rate in the rexlemestrocel-L group relative to sham patients). Hence, SCI would report "yes" to the sponsor and ESC if the z-score is less

than -1.85. As with the LV threshold, a response of "yes" indicates an unfavorable finding for rexlemestrocel-L relative to sham patients.

At the time of IA1, SCI will calculate the critical value in East according to the actual number of observed events out of the planned 314 events at the final analysis. Because the DMC will not review the HF-MACE data at IA1, and because stopping for superiority is not a potential outcome of the review (i.e., no alpha spending will be involved), the HF-MACE information fraction at IA1 is not relevant in determining the stopping boundaries for IA2.

4. Interim Analysis (IA) 2

The DMC will review IA2 after the CEC's confirmation of approximately the first 50% (~157) of the pre-planned 314 HF-MACE events. The goal of IA2 is to consider early discontinuation of the trial either due to superiority or the potential lack of efficacy (i.e., futility). If neither superiority nor futility is concluded, IA2 involves recalculation of the sample size based on a conditional power of 80% assuming the observed hazard ratio and control event rate for the future. Recalculation will be constrained so that the minimum number of events remains at 314 and the maximum cannot exceed 471. The DMC will communicate recommendations from IA2 to the ESC, which includes a member of the sponsor.

4.1. Superiority and futility

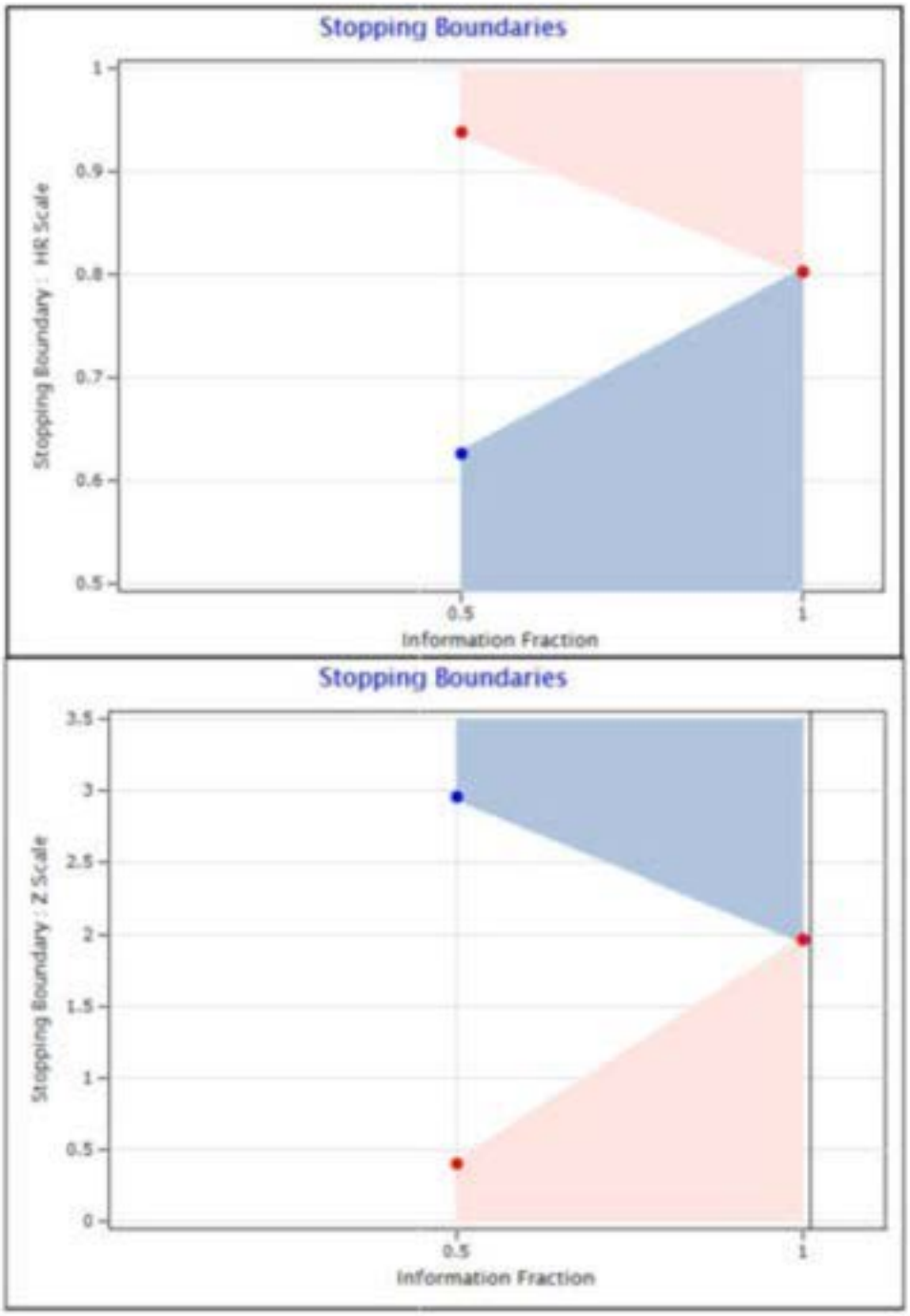
The DMC may recommend termination of the trial because of convincing benefit if the log-rank statistic for HF-MACE is greater than the O'Brien-Fleming boundary as implemented using a Lan-DeMets alpha-spending function. Assuming that IA2 occurs at exactly an information fraction of 0.5, Figure 1 shows that superiority could be declared if the observed observed $HR_{active/sham}$ were roughly 0.63 or lower (equivalent to $z > 2.96$).

The DMC has the option to recommend termination of the trial due to futility if the log-rank statistic for HF-MACE is less than the critical value derived under the Hwang, Shih, and DeCani beta-spending function ($\gamma = -2$). As shown in Figure 1, futility could be declared if the observed $HR_{active/sham}$ were roughly 0.94 or greater at an information fraction of 0.5 (equivalent

to $z < 0.41$). At the time of IA2, SCI will calculate the critical values for superiority and futility in East according to the actual number of observed events out of the planned 314 events at the final analysis.

In addition to the primary analysis, the DMC will have available various supportive analyses of HF-MACE as well as analyses of the trial's secondary endpoints for consideration in its recommendation. Section 3.3 outlines the efficacy presentations from the report template prepared by SCI for the DMC's reports.

Figure 1. Superiority (blue) and futility (red) boundaries at IA2 expressed on the HR and *z*-score scales



4.2. Sample size recalculation

If neither superiority nor futility is concluded at IA2, conditional power corresponding to the protocol-specified two-sided Type I error rate of 0.05 will be estimated by simulation under

the currently observed trend at IA2 and the current accrual rate for projection of entry of new patients. The simulation, which will use a fixed seed to allow replication, will involve 10,000 simulations per estimate. A Weibull distribution will be fit to the observed data to estimate, by maximum likelihood methods, the scale and shape parameters for each group, which will be used in simulations for the second stage of the trial. Simulations that use these estimates will randomly assign a future event time for currently enrolled and future patients. SCI will use the inverse normal p-value combination method for the two stages of the trial that Teva specifies in its statistical analysis plan in estimating conditional power.

In the conditional power estimates, the first stage of the trial will use the treatment effect from the 157 observed events for IA2 for all simulations. For the second stage, SCI will simulate conditional power ranging from the observation of 157 further HF-MACE events (for the pre-planned total of 314 events) to 314 (for the maximum allowed number of events of 471 under the protocol). For each simulation, the conditional power will be the proportion of simulated test statistics with a two-sided p-value of 0.05 or less when combining the data from the two stages of the trial.

On the basis of the pooled event rate, Teva will inform SCI roughly four months before IA2 of how it would intend to observe 157 to 314 events in the second stage of the trial. This could be achieved through an increase in follow-up time, an increase in sample size, or some combination of the two. SCI will then use this proposed strategy in its simulations.

The final analysis will use a proportional hazards model to estimate the treatment effect with adjustment for NYHA Class (Functional Class II versus Class III), geographic region (US versus ex-US), and presence of epicardial CAD (ischemic versus nonischemic). The simulated conditional powers at IA2 will not use adjusted test statistics, however, because:

- Current estimates of the treatment effect for each of the 8 combinations of covariates would be imprecise at the time of IA2, and
- Adjusted estimates for use in conditional power simulations would require assumptions about the future accrual rate for patients within each level of the covariates.

SCI will present results of the simulated conditional powers to the DMC for consideration in recommending a sample size increase. At the DMC's request, SCI may also simulate conditional powers based on other assumed future trends aside from the currently observed treatment effect.

Teva and the DMC are currently determining the process for communicating any recommendation to increase the trial's sample size at IA2 such that insight into the interim treatment effect is limited to SCI, the DMC, and those from the ESC and Sponsor on a need-to-know basis. The group is also considering what recommendation should be made should a simulated conditional power of 80% not be achieved at the maximum of 471 events. For example, should the conditional power with 471 events be below a certain threshold, Teva might prefer that the DMC recommend discontinuation of the trial because of futility, rather than to recommend an increase of the trial to its maximum size with suboptimal power. SCI will update this document once these guidelines have been determined.

4.3. Efficacy presentations at IA2 for review by the DMC

A separate report template contains mock-ups of the efficacy presentations that the DMC will review at IA2. Currently planned presentations are included below. The DMC has the ability to add or modify the presentations for IA2 as it sees fit.

- HF-MACE
  - Table: HF-MACE (CEC-confirmed)
  - Table: Subgroup analyses of HF-MACE (CEC-confirmed)
  - Figure: Time to first CEC-confirmed HF-MACE event
  - Table: Adjudication status of CV endpoint events flagged for adjudication as HF-MACE
  - Table: HF-MACE (Best available data)

- Secondary endpoints
  - Table: Hospitalizations for decompensated HF
  - Table: Fatal events (all cause) by investigator-reported term

- Table: CEC-confirmed underlying causes of cardiovascular death
- Table: MACE-Plus (CEC-confirmed)
- Table: Subgroup analyses of MACE-Plus (CEC-confirmed)
- Figure: Time to first CEC-confirmed MACE Plus event
- Table: MACE-Plus (Best available data)

5. Sample reporting form for IA 1

TEVA C41750/3100
Interim Analysis #1
Predefined threshold outcome report

Date: May 10, 2016
Recipients: [redacted], MD ([redacted])
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Answers of 'yes' indicate an unfavorable finding for rexlemestrocel-L relative to sham patients that a threshold has been met.

Left ventricular surrogate endpoints threshold:

Absolute mean change from baseline at Month 6 in LVEF is not at least 2.5% greater in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm < +2.5%)

OR

Absolute mean change from baseline at Month 6 in LVESV and LVEDV is not at least 5 mL lower in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm > –5 mL)

Left ventricular surrogate endpoint threshold met?

☐ Yes ☐ No

(See Tables 2 and 3 in the interim analysis statistical plan for example scenarios and responses for the LVEF threshold.)

HF-MACE threshold:

The log-rank statistic for HF-MACE is less than the critical value derived under the Hwang, Shih, and DeCani beta-spending function (γ=–2).

HF-MACE threshold met?

☐ Yes ☐ No

Appendix 3: TEVA C4175/3100 Interim Analysis #1 Predefined Threshold Outcome Report

TEVA C41750/3100
Interim Analysis #1
Predefined threshold outcome report

Date: May 10, 2016

Recipients: [redacted], MD ([redacted])
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Answers of 'yes' indicate an unfavorable finding for rexlemestrocel-L relative to sham patients that a threshold has been met.

Left ventricular surrogate endpoints threshold:

Absolute mean change from baseline at Month 6 in LVEF is not at least 2.5% greater in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm < +2.5%)

OR

Absolute mean change from baseline at Month 6 in LVESV and LVEDV is not at least 5 mL lower in the active group compared to the control group (i.e., mean absolute Δ in active arm – mean absolute Δ in sham arm > –5 mL)

Left ventricular surrogate endpoint threshold met?

[X] Yes [ ] No

(See Tables 2 and 3 in the interim analysis statistical plan for example scenarios and responses for the LVEF threshold.)

HF-MACE threshold:

The log-rank statistic for HF-MACE is less than the critical value derived under the Hwang, Shih, and DeCani beta-spending function (γ=–2).

HF-MACE threshold met?

[ ] Yes [X] No

Appendix 4: MSB-MPC-CHF001 (Dream-HF #1) Interim Analysis #2 (IA2) – Design and Results as Reported by the Independent Data Monitoring Committee on 8 April 2017

MSB-MPC-CHF001 (DREAM-HF #1) Interim Analysis #2 (IA2) Design and Results as Reported by the Independent Data Monitoring Committee on 8 April 2017

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Interim Analysis 2 (IA2) based on the evaluation of non-fatal recurrent heart failure events MACE [non-fatal recurrent (multiple events per patient) decompensated HF events or successfully resuscitated cardiac death events] and correlated terminal cardiac events [i.e., cardiac death, heart transplant, artificial heart placement or left ventricular assist device (LVAD) placement]. These are the same clinical events that will be incorporated into the trial's primary endpoint at completion of the DREAM-HF #1 study (MSB-MPC-CHF001).

IA2 will be performed using the Joint Frailty Model (JFM) approach which is designed to avoid the introduction of bias due to dependent censoring associated with mortality or other terminal clinical events. By design, approximately 250 randomized patients having a minimum of 3-months follow-up data will be included in IA2. It is anticipated that ~106-122 positively adjudicated non-fatal recurrent HF-MACE will be included in IA2. This would represent ~20-23% of the 531 non-fatal recurrent HF-MACE expected at the end-of-the-trial. An independent unblinded statistician will perform the IA2 data evaluation. This individual will review the results and inform the Sponsor and the trial's Executive Steering Committee (ESC) of its findings relating to pre-defined hazard ratio thresholds. Throughout the IA2 process, Mesoblast will remain fully blinded to the quantitative results and will be informed only if the pre-defined hazard ratio (HR) thresholds have been achieved. The IA2 output will not include an analysis for superiority or any other early stopping of the trial for success. Rather, it will include three components:

- The **first component** is a **futility analysis** with a stopping rule threshold for **non-fatal recurrent HF-MACE** at HR $\geq$0.92. calculated for drug vs. placebo using JFM. The specific question that the independent statistician will address will be "Using the JFM analysis, is the HR <0.92?". The response from the independent statistician will be a YES or NO answer to the following sub-category questions:
  - ✓ Using the JFM analysis, is the HR for recurrent non-fatal HF-MACE <0.92 for rexlemestrocel-L therapy vs. sham groups for the aggregated NYHA Class II plus NYHA class III patients?
  - ✓ Using the JFM analysis, is the HR for recurrent non-fatal HF-MACE <0.92 for rexlemestrocel-L therapy vs. sham groups for the NYHA Class II patients alone?
  - ✓ Using the JFM analysis, is the HR for recurrent non-fatal HF-MACE <0.92 for rexlemestrocel-L therapy vs. sham groups for the NYHA Class III patients alone?

  If the response to any of these three sub-category questions is that the HR <0.92 then crossing the futility boundary will be rejected as an outcome and the study will continue. The study will be stopped for futility if all three HR $\geq$0.92.

Since the study may be stopped for futility if the pre-defined HR threshold is achieved (or crossed) and since the study will not be stopped for superiority of the test treatment to placebo and since the number of non-fatal recurrent HF-MACE will not be changed based on the IA2 results, a significance level adjustment at the time of final analysis will not be performed.

1.0 Design of Interim Analysis #2 (IA2)

1.1 Background

- There was uncertainty as to how to best statistically conduct an interim analysis (IA) for the Phase 3 MSB-MPC-CHF001. This trial is designed to evaluate event outcomes in patients with advanced chronic heart failure (HF) associated with reduced left ventricular ejection fraction (LVEF). The issue is how to best evaluate and interpret the results of the IA2 in a patient population with the potential for dependent censoring due to mortality or other terminal clinical events (e.g., cardiac death, heart transplant, left ventricular assist device (LVAD) placement, placement of an artificial heart).[1-3]
- The specific question focuses on the amount of interaction (co-dependency) of non-fatal recurrent HF-MACE and terminal events in the initial ~250 Randomized patients with advanced heart failure in DREAM-HF #1 who would be included in the proposed IA2 that was incorporated into the trial's Protocol Amendment 06.

Several aspects of the moderate-to-advanced HF patient population may complicate the determination of the treatment effect on disease-related events. This patient population is characterized by frequent HF-related hospitalizations and other recurrent non-fatal HF-MACE, high mortality and continued worsening of the disease, often leading to surgical interventions such as LVAD implantation, placement of an artificial heart implantation, and/or heart transplant. Patients who are hospitalized or experience other non-fatal HF-MACE, may be at an increased risk of additional HF-MACE.[4-6] Therefore, recurrent non-fatal HF-MACE within a patient may not be independent.[3,6] Patients with a high rate of recurrent non-fatal HF-MACE may also have an increased risk of terminal cardiac events[4] (TCE: cardiac death, LVAD implantation, heart transplant, placement of an artificial heart or), and therefore the risks of recurrent non-fatal HF-MACE and cardiac terminal events are likely to be correlated and may need to be jointly estimated to avoid any substantial bias.[6,7] Other challenges include the possibility that the impact of a treatment on the risk of recurrent non-fatal HF-MACE may be different than on the risk of a terminal cardiac event, and random between-patient variations (unobserved covariates) may impact treatment outcomes.

The evaluation of effect of the therapy on reducing both recurrent non-fatal and terminal cardiac events is important.[5] However, the unbiased assessment of the impact of therapy on recurrent clinical events can be confounded by the competing risk of terminal cardiac events such as death, LVAD implant, artificial heart implant, or heart transplant and the differential follow-up times between treatment groups. To address these challenges, the joint frailty model, a semi-parametric analysis that accounts for recurrent clinical events, unequal follow-up times between treatment groups and terminal events as a competing risk, will be used for the study primary analysis as well as for interim analysis. The joint frailty model provides a quantified measure of comparison between treatment groups (hazard ratio), taking into account the risk of recurrent clinical events confounded by the competing risk of terminal events.[7] Specifically, this model:

- Takes into account the differences in follow-up times due to terminal events and their impact on recurrent event rates: when terminal events occur relatively early, the follow-up time is shorter and the likelihood of recurrent clinical events is lower.
- Accounts for the impact of random between-subject differences on the risk of both terminal and recurrent clinical events.

- Accounts for and quantifies the substantially increased risk of a terminal event (cardiac death, heart transplant, artificial heart, LVAD implantation) due to recurrent HF-MACE.
- Takes into account a possibility of a differential treatment effect for recurrent HF-related hospitalizations and terminal events; risks of recurrent and terminal events are jointly estimated preventing possible bias due to independent analyses of related processes.

1.1.1 Model Assumptions

The model assumptions are as follows:

A. If terminal and recurrent event(s) occur on the same day only the terminal cardiac event counts
B. If two recurrent (non-terminal) events occur on the same day, only one event counts
C. If any events occurs after admission date on different days they will count as separate events.
D. LVAD, heart transplant and artificial heart subjects who are alive at the Interim Analysis Data Cutoff will be censored.
E. Subjects lost to follow-up will be censored at the time of last contact.
F. Terminal cardiac events preclude the observation of further recurrent events for the purpose of the interim analysis.
G. Any non-cardiac or unknown cause of death would be treated as a censoring event, not a terminal cardiac event.

- In the past, clinical trials for chronic heart failure have traditionally used a time-to-first event (TTFE) composite outcome (e.g. cardiovascular death or HF hospitalization) as the primary endpoint.[1] This approach has the advantage that it combines fatal and non-fatal events, which increases the event rate and avoids multiplicity issues.[2] However, it has the limitation that it only considers the first event while ignoring recurrent HF hospitalizations or major HF-MACE that allow the patient to survive with their native heart intact while be vulnerable to a subsequent decompensated HF event (e.g., successfully resuscitated cardiac arrest). Furthermore, it ignores a key characteristic of *advanced heart failure* which is that an increase in "hospitalizations for worsening condition" is associated with an increased risk of CV death or other terminal events for the native heart (e.g., placement of a LV assist device, heart transplantation, or placement of an artificial heart) and so any censoring due to one of these events may not be independent of the recurrent event process.[3] This is an important issue since recurrent HF hospitalizations are an indication of worsening disease state and are therefore, within individuals, likely to be related to each other. By ignoring these repeat events, the true burden of the disease as well as the potential overall health-economic impact of the recurrent events is significantly underestimated.[4] As such, it is important that the analyses used in IA2 of DREAM-HF #1's Protocol Amendment 06 consider how recurrent HF hospitalizations are impacted by the competing risk of cardiac terminal events. Traditional methods for handling competing risks in the analysis of time-to-event data do not account for recurrent events of the same type within individuals.
- There are numerous statistical models that have been suggested to address the problem of how to best analyze recurrent events. However, each model carries its own advantages and disadvantages. Three validated statistical models were assessed with specific interest in the advantages and limitations of each.[5-7]
    - The Poisson Model
    - The Negative Binomial Model

- The Joint Frailty Model

1.1.2 The POISSON Model

- The Poisson model is one of the least robust approaches to evaluating clinical event rates. It simply considers the total number of events per a fixed period of time, ignoring the time between repeated occurrences. It cannot identify whether the effect of exposures changes the rate of occurrence across the time period being evaluated. Its output provides a rate ratio for recurrent events while assuming all events are independent of each other. Of note, in the Poisson model, an increase in the mortality rate for the sham arm in DREAM-HF #1 will result in a decrease in the expected number of heart failure hospitalizations for a given individual.
- Use of the Poisson model for DREAM-HF #1 would assume that the underlying event rate for terminal and recurrent HF events is the same in all subjects. This does not hold in the case of HF hospitalizations where the observed distribution of the number of events is markedly more skewed than the Poisson distribution. In HF, some patients are inherently more (less) frail than others, subsequently presenting with increased (fewer) hospitalizations, respectively. If this wide intra-population variability (i.e., over dispersion) is ignored, standard errors are likely to be too small resulting in confidence intervals that are too narrow and an increase in the type I error rate.[5]

- The Poisson method does not, in general, incorporate competing risks into the analysis of recurrent events. Rather, it assumes that the chance of having a HF hospitalization or terminal event is randomly distributed with all individuals having an equal chance, of experiencing one, two or more events. One simple strategy for incorporating CV terminal events into analyses of recurrent HF hospitalizations is to consider a CV terminal event to be merely an additional event in the recurrent event process. The events endpoint then incorporates all CV terminal events and recurrent HF hospitalizations. This is the approach that was used to evaluate clinical outcomes in the ixCELL-DCM trial.[6]

- Because of all of the above reasons, the Poisson model is inappropriate for use in DREAM-HF #1's Interim Analysis 2. Finally, the CBER statistical reviewer had previously stated that if a recurrent events analysis is used, the correlation between recurrent and terminal events will need to be ascertained. This is not possible using the Poisson method.

1.1.3 The NEGATIVE BINOMIAL Model

- The Negative Binomial model is an extension of the Poisson model which evaluates recurrent events which induces an association between repeat events within individuals through a random effect term. This allows for greater variability due to population heterogeneity in a data set than would be expected from standard analytic models (i.e., overdispersion). This is accomplished using an ancillary parameter that is directly related to the amount of expected variability (overdispersion) in the study population.
- The Negative Binomial's assumptions for individual-specific event rates are conditional on a random effect for each patient's true underlying rate. The larger this value is the more overdispersion; values typically range from 0 to about 4. Given that overdispersion is the norm, the Negative Binomial model has more generality than the Poisson model.[7] The

Negative Binomial distribution does not assume randomness: there is a possibility of 'proneness' (i.e., certain groups of individuals in the population have a higher chance of having HF hospitalization or terminal events than others). The variance introduced by the "ancillary parameter' can be interpreted as a factor that expresses the level of 'proneness'. The larger the variance is relative to the mean, the higher the level of 'proneness' in the population. Note that this variance factor is an expectation value, it is related to the expected value and must be estimated as part of the evaluative process.

- In summary, the Negative Binomial model for evaluating recurrent events incorporates a factor that accounts for heterogeneity from patient-to-patient. This factor reflects the fact that the value for recurrent HF hospitalization can vary widely across the DREAM-HF #1 patient population. In situations when terminal events are at least moderately correlated with recurrent events, this model may generate a substantial bias in recurrent events hazard ratio. However, if the terminal event rate is small or terminal events and recurrent events are weakly correlated, this model is acceptable and provides reliable estimates

1.1.4 The JOINT FRAILTY Model (JFM)

- A joint frailty model (JFM) simultaneously analyses recurrent events and an associated time to terminal event while accounting for the relationship between the two processes.[8] In the analysis of HF hospitalizations and CV terminal events, the random effects approach used in the JFM introduces a random covariate into the model that induces dependence among the recurrent event times. The concept is that the random effect describes excess risk or frailty for distinct individuals, taking into account unmeasured heterogeneity that cannot be explained by observed covariates alone. The JFM treats CV death or terminal events (LVAD, heart transplantation, artificial heart) as a competing risk with patients then being censored from further repeat HF hospitalizations. Hospitalizations that patients would have experienced had they not died are treated as missing data, and the JFM captures this 'lost information' in the estimation of underlying event rates and treatment effects. Of note, any non-CV deaths are handled as non-informative censoring.
- The net result is the ability to simultaneously estimate the effect of treatment on HF hospitalizations and CV terminal events under the assumption that the two are independent of one another after conditioning on an individual specific random effect term in which each patient has his/her own independent frailty factor. It also proportionately adjusts heart failure hospitalization rate and time to death. Research of this model is based on simulations. The JFM-based analysis and parameter estimates are based on the algorithm as described by Lei Liu.[8]

Table 1: Comparison of Statistical Models

	Types of Events Assessed in the Model	Takes into Account Correlation	
		Between Recurrent HF Events	Between Recurrent HF and Terminal Events
Poisson Model	Treats terminal and recurrent HF events similarly. Does not allow subject-to-subject variability.	No	No
Negative Binomial Model	Treats all events similarly but accounts for different patient-specific event rates. As such, does handle some heterogeneity across subjects.	Yes	No
Joint Frailty Model	Treats terminal and recurrent HF events differently. Models different kinds of events separately with an assumed weighting factor for terminal events. Incorporates the exposure time for a given subject.	Yes	Yes

1.1.5 Approach to Avoid Statistical Analysis Bias Between Recurrent Non-fatal Decompensated HF Events and Terminal Events

- If non-fatal HF-MACE and terminal events are weakly correlated, one can treat the terminal events as the last recurrent event for the patient and hazard ratio (HR) bias is likely to be small. In this case, the Negative Binomial model can be used. In general, if the terminal event rate is <10% (as calculated as the percent of the study population) then the JFM results and other appropriate models (e.g., Negative Binomial) are likely to give similar results. In this case, treatment of a terminal event for a patient as the last recurrent event would be expected to result in a small bias. The empirical threshold of 10% is based on experience rather than on calculations and simulations.
- If recurrent non-fatal decompensated HF events and terminal events are strongly correlated, it is necessary to use JFM in order to prevent the bias (potentially in the unfavorable direction) from being introduced by the analysis. Indeed, if the terminal event rate is high, the hazard ratio bias caused by mixing correlated recurrent HF hospitalization and terminal events can be large.
- Thus, the stronger the correlation between recurrent non-fatal decompensated HF events and terminal events, the larger the difference between estimated treatment effects as determined by the Negative Binomial and the JFM.
- It was estimated that by February 2017 approximately 33 terminal events will have occurred in the 250 randomized patients evaluated at that time. The terminal event rate is estimated to be 33/250 = 13.2%. With a value that is >10%, it is likely that the recurrent non-fatal decompensated HF events and terminal events are substantially correlated. Ignoring medium to strong correlation between recurrent and terminal events may lead to an importantly biased hazard ratio (HR) estimate for recurrent events.[5]
- At the time of DREAM-HF #1's Interim Analysis 2, there would be the opportunity to obtain the terminal cardiac event HR based on a time-to-first event analysis. This is potentially important since FDA is interested in knowing whether the trial's success based on JFM is accompanied by demonstrated non-inferiority-to-control using

analyses based on terminal cardiac events. It is anticipated that a demonstration of at least numerical non-inferiority (HR<1.0) of MPCs to sham for terminal events accompanied by substantial and statistically significant risk reduction in recurrent events would be looked upon favorably by the FDA during the review process. Alternatively, the non-inferiority to sham for terminal events may be demonstrated in meta-analysis of two Phase 3 trials (if FDA agrees).

- *Accordingly, it is recommended to perform the* DREAM-HF #1's *Interim Analysis 2 using the JFM as the primary analysis to avoid important bias.*

1.1.6 Recurrent Non-fatal HF-MACE for the MSB-MPC-CHF001 Trial: Definition

The primary efficacy measure and endpoint for this study will remain the time-to-recurrent non-fatal HF-MACE in the presence of terminal cardiac events. The following two components apply to 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 outpatient visit;
- **Successfully resuscitated cardiac arrest (RCD)** will be adjudicated when a subject experiences sudden death or cardiac arrest and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Patients who have loss of consciousness and receive a successful appropriate shock from an implantable cardioverter-defibrillator with meaningful recovery will also be designated as RCD.

1.1.7 Terminal Cardiac Events for the MSB-MPC-CHF001 Trial: Definition

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 correlated with recurrent non-fatal HF-MACE within the Joint Frailty Model analysis.

1.1.8 Non-fatal HF-MACE and Terminal Cardiac Events: Clarifications

- It is the intent that a terminal cardiac event occurs when the LV is no longer functioning as an independent viable pumping chamber that provides pulsatile blood flow to the systemic circulation.
- Only the first terminal cardiac event is accounted for in this analysis. However, all terminal cardiac events will be collected and adjudicated for sensitivity analyses.
- Adjudication of all potential HF-MACE and terminal cardiac events will be performed by an independent, blinded CEC. For details on the role and responsibilities of the CEC, please see the CEC Manual of Operations.

1.1.9 Successfully Resuscitated Cardiac Death (RCD): Definition

- **Positive Adjudication for Resuscitated Cardiac Death (RCD)**

- ✓ **Ventricular Fibrillation or Flutter (VF)**
  - ➢ VF is defined as ventricular rate greater 250 beats/min with disorganized ventricular activity (or as set up by treating physician). Resuscitation measures for VF will be tracked whether it is CPR or includes ICD firing.
  - ➢ Ventricular fibrillation or flutter accompanied by appropriate ICD shock will be adjudicated as RCD.
- ✓ **Ventricular Tachycardia (VT)**
  - ➢ VT is defined with a ventricular rate between 180 beats/min up to 250 beats per minutes (or as set up by treating physician), with ventricular rate greater than atrial rate, and if ventricular rate is similar to atrial rate then changes in ventricular rate drive changes in atrial rate.
  - ➢ If the VT event is long enough that it triggers an appropriate ICD shock and is associated with documented LOC or syncope, it will be adjudicated as a RCD.

1.2 Design: Recommendations for Establishment of an IA2 Futility Boundary for the MSB-MPC-CHF001 Trial (DREAM-HF #1)

Presently, there are no publications that provide a specific set of criteria using the Joint Frailty Model that are applicable for use during an interim analysis. However, several approaches using a combination of statistical and other data sources could be utilized to provide guidelines for estimation of lower limit boundaries. For the purposes of the IA2, the methodology for selection of a boundary that will be used as a futility/stopping criterion will be described.

As a reference point, DREAM-HF #1 was originally powered for a RRR of 25% (HR = 0.75) using a TTFE analysis of HF-MACE. Recently, analyses have become available in which HF-MACE outcomes data from previously completed clinical heart failure trials were re-evaluated in order to quantify the impact of using a non-fatal recurrent HF-MACE approach rather than a TTFE analysis. The following table summarizes the differences in HR values for active treatment versus control data.

Table 2: Hazard ratio comparisons for multiple global heart failure trials – TTFE vs. Recurrent Events analyses

Clinical Trial, product	HR for TTFE Analysis	Recurrent Event Analysis	HR Difference (Recurrent Events Minus TTFE)	Model Used (Publication ref.)
Charm Added (candesartan)	0.83	0.65	-0.18	Joint Frailty Model – (Rogers, Yaroshinsky, et al, Stat in Med, 2016) [9]
Charm Alter (candesartan)	0.77	0.61	-0.16	Joint Frailty Model - (Rogers, Yaroshinsky, et al, Stat in Med, 2016) [9]
Emphasis (eplerenone)	0.68	0.53	-0.15	Negative Binomial Model – (Rogers, et al. Circulation, 2012) [10]
CUPID-1 (mydicar)	0.32	0.18	-0.14	Joint Frailty Model – (Zsebo, Yaroshinsky, et al, Circulation Research, 2014) [11]
Mean Value	0.65	0.49	-0.16	

For these four heart failure trials, the average HR difference was 0.16 lower (i.e., -0.16) for recurrent events analyses compared with TTFE analyses. Based on these data, the expected joint frailty model HR in DREAM-HF #1 was established as follows:

Expected JFM Hazard Ratio =

[0.75 (assumed TTFE value)] – [0.16 (expected difference: Recurrent Events minus TTFE value)]

HR = 0.59

Accordingly, the HR that was used in the power and sample size calculations for the revised DREAM-HF #1 Study using recurrent non-fatal HF-MACE (analyzed using JFM approach) was changed to HR = 0.60. This value was used to calculate the trial's 93.5% statistical power at the 2-sided 0.05 level of significance as well as the 531 positively adjudicated non-fatal recurrent HF-MACE required at completion of the study. Of note, HR = 0.68 (risk reduction vs. Placebo of 32%) for the study would still have 80% power for this treatment effect.

1.2.1 Rationale for the Boundary to be Used as a Futility/Stopping Criterion

In DREAM-HF #1's Protocol Amendment 04, it was stated that Interim Analysis 2 would be based on a time-to-first event (TTFE) HF-MACE approach utilizing TTFE analysis methodology. According to Protocol Amendment 04, IA2 was to be conducted when approximately 157 of the anticipated 314 TTFE at completion of the study had occurred and were positively adjudicated. At 157 positively adjudicated events, the futility boundary would be HR = 0.92.

Since the time that Protocol Amendment 04 was operationalized, data became available demonstrating the relationship between TTFE and non-fatal recurrent events analyses. As shown previously in Table 2, when the same study data are analyzed, the Joint Frailty Model appears to produce much lower hazard ratios than the respective TTFE analyses. As such, approximately **106-122 positively adjudicated recurrent non-fatal HF-MACE will be included in the analysis. This represents approximately 73% of the number of positively adjudicated events that were estimated to be required for the futility analysis in Protocol Amendment 04.** This small difference in the number of events to be evaluated between TTFE and JFM was assumed to be counter-balanced by the more robust impact of the JFM on the hazard ratio estimation as compared to the TTFE analysis. In order to be appropriately conservative in our conduct of the revised IA2 futility analysis, it was decided that the prior futility boundary estimate of HR = 0.92 would be an appropriate threshold for the current futility analysis to be conducted using the Joint Frailty Model. This seems reasonable with the caveat that it appears highly unlikely that the HR=0.60 can be reached at the time of final analysis if a hazard ratio based on the JFM at the time of IA2 exceeds 0.92.

Accordingly, **Mesoblast proposed using a HR = 0.92 threshold as part of a Go-No vs. Go (Futility) analysis**. As such, if the actual IA2 hazard ratio for DREAM-HF #1 using the JFM is >0.92 then the study would be stopped for futility. If the hazard ratio is $\leq$0.92 then the study would continue to completion. The Negative Binomial model estimation of hazard ratio for recurrent events would be used for sensitivity analysis purposes. Similarly, an analysis of terminal events would be performed for sensitivity purposes to demonstrate numerical non-inferiority to the sham study arm (i.e., a hazard ratio <1.0).

1.3 Overview of the Conduct of the Revised IA2

Mesoblast planned to conduct DREAM-HF #1's Interim Analysis 2 (IA2) based on the evaluation of non-fatal recurrent heart failure (HF) events. This is the same clinical endpoint that is being used as the trial's primary efficacy endpoint at completion of the study. IA2 will be performed using the Joint Frailty Model approach which is designed to avoid the introduction of bias due to dependent censoring associated with mortality or other terminal clinical events [e.g., cardiac death, heart transplant, artificial heart placement or left ventricular assist device (LVAD) placement].

It was expected that approximately 244 randomized patients having a minimum of 6-months follow-up data would be included in IA2. **An independent unblinded statistician performed the IA2 data evaluation.** This individual reviewed the results and informed the Sponsor and the trial's Executive Steering Committee (ESC) of its findings relating to pre-defined hazard ratio thresholds. Throughout the IA2 process, Mesoblast remained fully blinded to the quantitative results other than whether the pre-defined hazard ratio thresholds have been achieved.

The IA2 output included a futility analysis with a stopping rule threshold at HR >0.92. The response from the independent statistician was a YES or NO or INDETERMINATE answer to the following sub-category questions:

- ✓ Using the JFM analysis, is the **HR ≤0.92 for therapy vs. sham groups** for the **aggregated NYHA Class II plus NYHA Class III patients**?
- ✓ Using the JFM analysis, is the **HR ≤0.92 for therapy vs. sham groups** for the **NYHA class II patients alone**?
- ✓ Using the JFM analysis, is the **HR ≤0.92 for therapy vs. sham groups** for the **NYHA class III patients alone**?

Assumptions supporting DREAM-HF #1's Interim Analysis 2:

- ✓ Interim Analysis #2 would be conducted during the first calendar quarter of 2017.
- ✓ 250 subjects randomized in a 1:1 manner to either MPC therapy or sham control.
- ✓ Minimum exposure of 6 months per patient
- ✓ Estimated mean exposure of approximately 14-months
- ✓ Estimated events to be included in IA2 would include:
  - ❖ Recurrent non-fatal HF-MACE = 106-122
  - ❖ Terminal events = 33
  - ❖ Total number of recurrent non-fatal HF-MACE plus TCEs = 139-155

1.3.1 Primary and Interim Analysis Data Cutoff

The Study Primary Analysis Data Cutoff was based on a minimum length of time and cumulative total number of clinical events. Unless discontinued for a terminal event, all subjects must have completed the minimum of 6-Month Active Observation Period and a total of at least 531 positively adjudicated recurrent HF-MACE have occurred. The Primary Analysis Data Cutoff will occur when both conditions have been met, whichever comes later. The Primary Analysis Data Cutoff is the trigger for locking the clinical database, unblinding the treatment assignment and performing all the planned analyses.

For IA2, the analysis data cut-off date was December 31, 2016. All recurrent non-fatal HF-MACE and all terminal cardiac events that occurred on or before this date were be included in IA2. The subjects with less than 3 months of follow-up were excluded from IA2.

The full analysis set (FAS) for Interim Analysis 2 included all patients in the ITT population 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. All patients must have had follow-up of at least 3 months as calculated using the Interim Analysis Data Cutoff date of December 31, 2016. The only exception is patients who experienced a terminal cardiac event that occurred prior to three months of follow-up.

All recurrent non-fatal HF-MACE and all terminal cardiac events included in the analysis needed to be positively adjudicated by the CEC prior to database lock for IA2. In this Interim Analysis, no efficacy analyses are planned on any follow-up data collected after the Interim Analysis Data Cutoff.

If a discrepancy is noted in the final database for any subject such that the actual investigational study product received differs from the randomized treatment assignment, analyses will be performed with the subject analyzed according to the actual treatment received.

An independent unblinded statistician performed the IA2 data evaluation. This individual reviewed the results and informed the Sponsor, the DMC and the trial's Executive Steering Committee of its findings relating to pre-defined hazard ratio thresholds. Throughout the IA2 process, Mesoblast remained fully blinded to the quantitative results and was informed only if the pre-defined hazard ratio (HR) thresholds had been achieved, not achieved or indeterminate. The IA2 output did not include an analysis for superiority or any other early stopping of the trial for success.

The **futility analysis** had a stopping rule threshold for **recurrent non-fatal HF events** at HR >0.92 calculated for MPC therapy vs. sham control using JFM. The specific question that the independent statistician addressed was "Using the JFM analysis, is the HR <0.92?". The response from the independent statistician will be a YES or NO or INDETERMINATE answer to the following sub-category questions:

- Aggregated NYHA Class II plus NYHA class III patients?
- NYHA Class II patients alone?
- NYHA Class III patients alone?

<u>Action planned</u>: If the response to any of these three sub-category questions was HR <0.92 then crossing the futility boundary will be rejected as an outcome and the study will continue. The study will be stopped for futility if all HR <u>≥</u>0.92.

2.0 Interim Analysis #2 (IA2) Results

Table 3: Pre-specified targeted values for IA2 data compared to actual IA2 data

	Pre-specified Targeted Values for IA2 Data	Actual IA2 Data
# randomized patients with a minimum of 6 months follow-up data	250 unique patients	270 unique patients
CEC Positively adjudicated recurrent non-fatal HF-MACE	106-122 (20.0 – 23.0% of the minimum of 531 required recurrent non-fatal HF-MACE at end-of-study)	123 (23.1% of the minimum of 531 required recurrent non-fatal HF-MACE at end-of-study)
CEC Positively adjudicated TCEs	33	28
Total # of recurrent non-fatal HF-MACE + TCEs	139-155	151
Mean exposure in the DREAM HF-1 trial	14 months	15.4 months

Table 4: Results of sub-group futility analyses for IA2

SUB-GROUP ANALYSES	RESULTS
Using the JFM analysis, is the Hazard Ratio (HR) for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. sham groups for the aggregated NYHA Class II plus NYHA Class III Patients?	Question: Using the JFM analysis, is the HR <0.92? Answer: NO
Using the JFM analysis, is the HR for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. sham groups for the NYHA Class II Patients Alone? This analysis may not be feasible due to small number of recurrent events.	Using the JFM analysis, is the HR <0.92? Answer: INDETERMINATE
Using the JFM analysis, is the HR for recurrent non-fatal HF events <0.92 for rexlemestrocel-L therapy vs. sham groups for the NYHA Class III Patients Alone? This analysis may not be feasible due to small number of recurrent events.	Using the JFM analysis, is the HR <0.92? Answer: YES

CONCLUSION: Since the response to the "NYHA Class III Patients Alone" sub-category question was YES (i.e., <0.92), crossing the futility boundary was rejected.

Figure 1: Correspondence from the DMC Chairperson to the DREAM-HF #1 Executive Steering Committee (April 8, 2017): IA2 Results and Associated Study Recommendations

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

April 8th, 2017

Dear Drs [redacted]

The DREAM-HF DMC met by teleconference on April 8th, 2017, and reviewed the data for the DREAM-HF interim analysis-2 for futility. The results are as follows:

1) **For ALL SUBJECTS**: Using the Joint Frailty Model analysis, the HR for recurrent non-fatal HF events was <0.92 for nelaxonestrocel-L therapy vs. the sham group.

2) **For NYHA-2 SUBJECTS ONLY**: Using the Joint Frailty Model analysis, the HR for recurrent non-fatal HF events the result was indeterminate for nelaxonestrocel-L therapy vs. the sham group.

3) **For NYHA-3 SUBJECTS ONLY**: Using the Joint Frailty Model analysis, the HR for recurrent non-fatal HF events was <0.92 for nelaxonestrocel-L therapy vs. the sham group.

[redacted]
MD, FRCPC, FACC
For the DREAM-HF DMC

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

April 8th, 2017

Dear Drs [redacted]

The DREAM-HF DMC met by teleconference on March 22nd and again on April 8th, 2017, and after reviewing the data recommend that the trial continue as planned.

[redacted]
MD, FRCPC, FACC
For the DREAM-HF DMC

Thus, a pre-specified interim futility analysis of the recurrent non-fatal HF-MACE efficacy endpoint in DREAM-HF #1's first 270 patients was performed by the trial's Independent DMC. According to the pre-specified futility guidelines for this analysis, the trial met the criteria for continuation.

3.0 References

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Appendix 5: SAP Addendum for Two Patients from Site # [redacted] who were Randomized Twice: Patient # [redacted] and Patient # [redacted]

Appendix 5: SAP Addendum for Two Patients from Site # [redacted] who were Randomized Twice: Patient # [redacted] and Patient # [redacted]

Only the DREAM HF-1 blinded team was involved in the development of a feasible solution regarding the efficacy and safety evaluations of these two patients' data. The following personnel were involved in creating this addendum:

[redacted]
and [redacted]

Two patients at Site # [redacted] were randomized twice and assigned two different patients identification numbers.

1. Patient [redacted] was originally randomized to the study on [redacted]. Due to an administrative error, the patient's treatment assignment was disclosed to the blinded sponsor project manager and this was reported as an unblinding event. The sponsor approved that the patient be deactivated and re-randomized as patient [redacted]. The patient was re-randomized on [redacted] and subsequently treated in the cardiac catheterization lab.
2. Patient [redacted] after enrollment and before randomization asked to be withdrawn from the study. Subsequent to this request, the patient was mistakenly randomized two weeks later. The patient withdrew from the trial and was considered a screen failure. Thirty-four (34) months later the patient enrolled again, was randomized (patient number [redacted]) and received trial treatment in the cardiac catheterization lab.

The following decisions were made relating to these two unique individuals:

- All available data for these patients will be included in the patient narratives.
- Since both patients had the trial procedure (index cardiac catheterization) performed after their second randomization, Day 0 would be defined as the date of the index cardiac catheterization. Therefore, for the primary efficacy analysis it was decided to use the second randomization date for both patients and treat all events prior to the second randomization date as prior medical history.
- If a patient was randomized to two different treatments at the first and second randomizations, then the following sensitivity analysis will be performed in addition to the primary analysis.
  - The first randomization will be honored and the patient will be censored at the time of the trial treatment procedure based on the second randomization. In this case, the Day 0 visit will be defined as the date of the disqualifying event.
  - For patient [redacted] and patient [redacted] the date of second randomization will be used as a new Day 0.

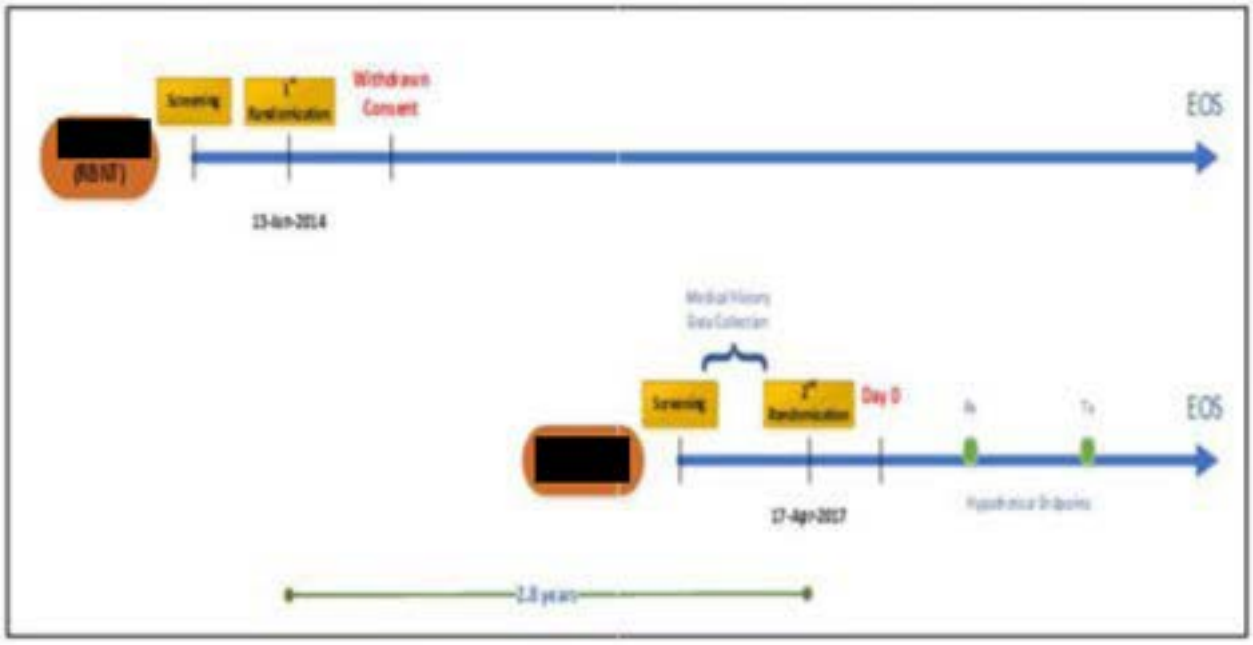
The data collection and analysis procedures for the two patients (Patient [redacted] and [redacted]) who were randomized twice are summarized below. The reconciliation procedures as described above will be applied to both of these patients.

Patient [redacted] and [redacted] (same patient; randomized twice with 6 days between randomizations). The time between the 1st and 2nd randomization in this case was only 6 days. Since the patient was clinically stable during this time period, it is expected that minimal differences in efficacy events or safety events will occur regardless of which date is used for Day 0.

Patient [redacted] and [redacted] (same patient; randomized twice with 34 months between randomizations) – see Figure 1.

- Patient [redacted]
  - This patient will be censored using the time of 2nd randomization. Entered endpoints for this patient will be used for the sensitivity analysis if randomization assignments differ between 1st and 2nd randomization.
  - All potential endpoints events including primary, terminal cardiac events and/or events of special interest that occurred between 1st and 2nd randomization (2.8 years) will be collected and entered as an AE and checked as potential endpoints.
  - Once endpoints are entered as an AE, the medical source documentation will be requested by the site so that endpoints can be submitted to the CEC.
- Patient [redacted]
  - For this patient, medical records and the entered medical history will be reviewed by the blinded CRA to find potential endpoints. These endpoints will be entered into the AE eCRF page of patient [redacted]. If potential endpoints are found in the medical records that were not entered into the Medical History eCRF page of patient [redacted] then they will be entered there.

Figure 1: Patient [redacted] and [redacted] (Same Patient who was Randomized Twice)



Appendix 6: Missing Data Handling for Efficacy Endpoints Other Than Time-to-Event for Secondary Biomarkers or Other Non-clinical Event Measurements That are Missing Due to Absence of Follow-Up Visits and/or Terminal Events

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Appendix 6: Missing Data Handling for Efficacy Endpoints Other Than Time-to-Event for Secondary Biomarkers or Other Non-clinical Event Measurements That are Missing Due to Absence of Follow-Up Visits and/or Terminal Events

Considerations and review of the following statistical approach were the result of a series of discussions with an external consultant biostatistician, Dr. [redacted] Dr. [redacted] is Distinguished [redacted] Previously, [redacted] was the [redacted] of the National Research Center's (NRC) "Panel on Handling Missing Data in Clinical Trials". [redacted] is the primary author of a major textbook in biostatistics [redacted]. At [redacted] strong recommendation, the following statistical section and its methodology is based on the 2017 publication by Permutt and Li. [1]

BACKGROUND INFORMATION

This summary is based on the Permutt and Li 2017 publication in Pharmaceutical Statistics.[1] The goal of the statistical analyses is to establish a systematic and pre-specified set of rules for handling of missing secondary biomarkers or other non-clinical event data that allow for inclusion of all patients who are randomized (1:1) to either active treatment or sham control treatment in the DREAM HF-1 trial, and have a baseline value for the measurement of interest. This includes patients who have missing data due to (1) a Terminal Event (TE) defined as first occurrence of LVAD implantation, heart transplant, placement of an artificial heart or (2) all-cause death including death as determined by vital status at the end of study. (Note: Vital status [alive or dead] was established at the end of the trial for 100% of the randomized patients).

Analyses of interest for potentially important measurements are based on change from baseline to a pre-defined time-point(s) of interest post Day 0. Only patients with a baseline value for the measurement will be included in the analyses. DREAM HF-1 data handling conventions for missing biomarkers or other non-clinical event measurements at timepoints of interest will be based on one of two different statistical considerations, described as "Missing-at-Random" (MAR) or "Negative Clinical Outcomes" (NCO).

Below we assume that:

- a patient has a baseline value for the measurement of interest,
- a patient missing clinic visit at the time point of interest with missing data for a measurement of interest.

Of note, in these analyses, death of any cause includes death as determined by vital status at the end of the study.

1. ANALYSES AS "MISSING-AT-RANDOM" (MAR)

If a randomized patient in the DREAM HF-1 trial:

- has not experienced a Terminal Event (i.e., death of any cause, LVAD implantation, heart transplant or placement of an artificial heart) at or prior to the timepoint of interest, and
  - has at least one known clinic visit or telephonic visit after the timepoint of interest and/or has vital status of "alive" at the end of study or
  - has not been treated and has vital status of "alive" at the end of study
  - then this missing data point will be considered as *"Missing-at-Random" (MAR)*. The value for this type of missing data point will be handled as an imputed value using multiple imputations technique (described in Section 8.3 in the Statistical Analysis Plan). Analyses that assume "missing at random" will be conditional on available post-treatment information, including vital status at the end of study.

2. ANALYSES AS "NEGATIVE CLINICAL OUTCOMES" (NCO)

A. Patients who experienced a Terminal Event at or prior to the timepoint of interest

Patients who experience a Terminal Event at or prior to the timepoint of interest for the measurement of interest will have Terminal Event induced missing data at the timepoint of interest. These missing data, if not included in the analyses, may introduce a substantial bias. Permutt and Li [1] proposed an approach to patients with this type of missing data that we would characterize as:

- has experienced a Terminal Event at or before timepoint of interest (i.e., first occurrence of death of any cause, LVAD implantation, heart transplant or placement of an artificial heart at or prior to the timepoint of interest). In the DREAM HF-1 trial, these patients will be considered as having *a "Negative Clinical Outcome"*.

B. Patients who experienced a Terminal Event after the timepoint of interest

Patients who experience a Terminal Event after the timepoint of interest for the measurement of interest and who have no clinic or telephonic visit between the missed timepoint of interest and the Terminal Event are at a high probability of having a bad clinical outcome. Permutt and Li [1] proposed an approach to patients with this type of missing data that we would characterize as:

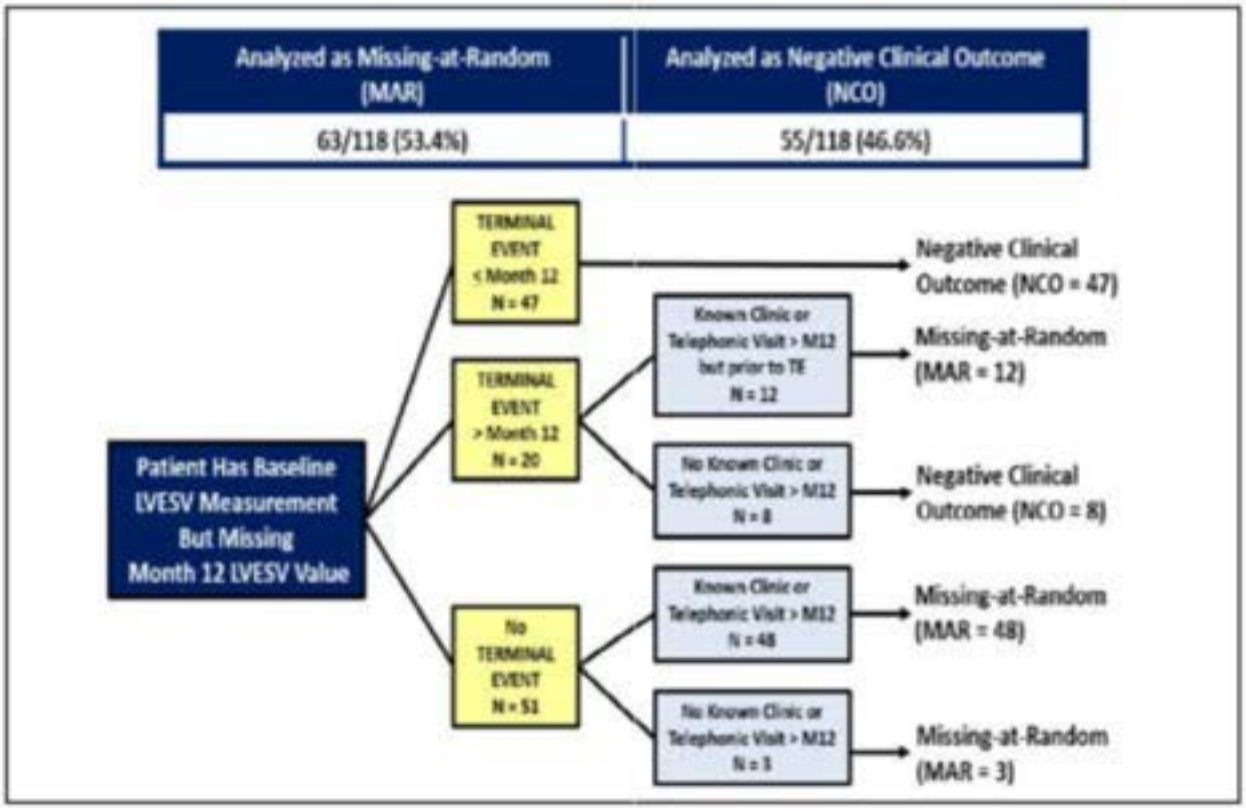
- has experienced a Terminal Event after the timepoint of interest (i.e., first occurrence of death of any cause, including death as a vital status at the end of study, LVAD implantation, heart transplant or placement of an artificial heart after the time point of interest), and

- has no known clinic visit or telephonic visit after the timepoint of interest and prior to Terminal Event or
- has been randomized but not treated and has vital status of "dead" at the end of study

In the DREAM HF-1 trial, these patients will be considered as having a "Negative Clinical Outcome" (NCO).

The following figure illustrates the application of these missing data procedures in the DREAM HF-1 trial for a particular secondary biomarker or other non-clinical event measurement, left ventricular end-systolic volume (LVESV). For this analysis, all randomized patients with a baseline LVESV value will be accounted for whether or not they experienced a Terminal Event prior to, at, or after Month 12 of follow-up. It is based on the 537 randomized patients who have a baseline LVESV value. A preliminary blinded listing of the DREAM HF-1 study data set showed that 118 of the 537 patients (22.0%) have a missing LVESV value at the Month 12 clinic visit. Using the definitions and rules discussed above, 60/118 (50.8%) patients would have their missing Month 12 data point be considered as "Missing-at-Random". These data points would be handled as an imputed value (per Section 8.3 in the Statistical Analysis Plan). The remaining patients (58/118, 49.2%) would have their missing Month 12 data handled as "Negative Clinical Outcomes" using the Permutt and Li [1] approach further described below.

Figure 1: Dream HF-1: Data Handing Rules for 118 Patients with Baseline LVESV Measurement And Missing LVEVS Value at Timepoint of Interest = Month 12 (M12)



3. COMPARISON BASED ON TRIMMED MEANS

This trimmed mean statistical analysis, as proposed by Permutt and Li [1], will be described using LVESV at Month 12 as a representative secondary biomarker or other non-clinical event measurement measurement. We first calculate change from baseline to Month 12 for all patients with a baseline LVESV value. An increase in LVESV compared to baseline is considered a "bad" outcome. If a patient experienced a Terminal Event at or prior to Month 12, the change from baseline value to 12 months will be missing. However, we do KNOW that if a value is missing due to a Terminal Event, it is a "bad" (i.e., negative) clinical outcome. So clinically the change from baseline to Month 12, if missing due to a Terminal Event, is not really a missing data point. Rather, it has a non-numeric value of "NEGATIVE CLINICAL OUTCOME". Ignoring this value may lead to substantial treatment bias. For example, if active treatment works, then ignoring patients who experienced a Terminal Event (i.e., excluding non-responders) may give unfair advantage in the analysis of a measurement of interest to the sham-control group due to removal of patients with the worst outcome (for example death) from the analysis.

We assume for this example that the total cohort of randomized patients in the DREAM HF-1 trial has a Terminal Event rate of 20% at or prior to Month 12. If we assume in our 1:1 randomized trial that 15% of the active treatment group and 25% of the sham-control group patients experienced a Terminal Event at or prior to Month 12 then the active treatment patients compared to the sham-control patients will have a ~40% smaller number of "NEGATIVE CLINICAL OUTCOME" values at Month 12 while having a larger number of numeric values.

Next we exclude from the analysis the percentage of patients in each treatment group equal to the higher percentage of non-numeric "NEGATIVE CLINICAL OUTCOME" across the two treatment groups. In this example, 25% of the "worst outcomes" will be excluded from each treatment group, accounting for the non-numeric "NEGATIVE CLINICAL OUTCOME" values in each treatment group. This equates to all of the sham-control group's non-numeric values being removed (25% of the total group). In the active treatment group, we also exclude 25% of the patients (i.e., 15% of non-numeric values and 10% of the worst numeric values). This approach allows for a subsequent comparison of the remaining "best" 75% of the randomized patients in each treatment group. Next, calculate the mean LVESV change from baseline by treatment group for these 75% of patients. Those are **trimmed means** which reflect the fact that the missing observations due to Terminal Events are "NEGATIVE CLINICAL OUTCOME". The comparison of trimmed means is the comparison between treatment groups for "completers" (i.e., patients who did not have a Terminal Event at or prior to Month 12).

If there are more "completers" on active treatment than in the sham-control group then the sham-control "completers" are compared with the best of the active treatment "completers". The active trimmed mean will therefore be better than the sham control trimmed mean. As noted by Permutt and Li [1], more "completers" (i.e., less Terminal Events) are an effect of the active treatment and since a Terminal Event is a "bad outcome", having more "completers" is a good effect. The comparison of trimmed means gives the active treatment group credit for this effect. Comparison of trimmed means may be performed using the permutation test.

This statistical approach, which is systematic and pre-specified, can be applied to any change from baseline missing data point for any potentially important secondary biomarker or other non-clinical event measurement (e.g., LVESV, LVEDV, LVEF, [redacted], 6MWT). Standard errors will be computed using bootstrapping method.

[redacted]

5. PERMUTATION TEST

The first step of permutation test is to calculate the difference between the trimmed means as calculated above (accounting for non-numeric worst possible values). Let's call this difference between means "the observed difference" equal to D1. The permutation test is designed to determine whether the observed difference D1 between treatment group means is large enough to reject at the 0.025 one-sided significance level the Null Hypothesis of no difference between two means.

As step two, let's re-randomize all originally randomized patients into "active treatment" and "sham control" groups so that some of the latter patients will be assigned an "active treatment" label and vice versa. Further, let's calculate the difference between trimmed means as described in step one for this iteration.

If we repeat step two 10,000 times; the difference between trimmed means for the "active" and "sham control" treatment groups under the null hypothesis is expected to be zero. Under these settings the difference between trimmed means ≥D1 may have occurred only by chance alone. Count the number of iterations (n) with the difference between trimmed means ≥D1. Proportion of these iterations n/10,000 is the one-sided p-value. If it is <0.025, the observed difference between trimmed means is statistically significant at the 0.025 one-sided level.

The procedure to determine significance of the difference between trimmed medians is exactly the same.

6. REFERENCES

1. Permutt T and Li F. Trimmed means for symptom trials with dropouts. Pharmaceut. Statist. 2017;16:20-8.

Appendix 7: Visit Windows

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Appendix 7: Visit Windows

The by-visit analysis windows for this study were constructed with a medians-based approach around the protocol-specified visit. Data collection schedules varied from one data domain to the next, necessitating a distinct set of windows for each domain. The following tables describe the windows for each data domain using target study days and with upper and lower bounds for the data to be included in each window. In cases where multiple assessments fall into a window, the latter assessment will be selected for the by-visit analysis.

Table 1: General Mapping for AVISIT and AVISITN

AVISIT	AVISITN	AVISIT	AVISITN	AVISIT	AVISITN
Baseline	0	Month 12	16	Month 44	32
Day 0, Mid	1	Month 14	17	Month 46	33
Day 0, Post	2	Month 16	18	Month 48	34
Day 1	3	Month 18	19	Month 50	35
Day 10	4	Month 20	20	Month 52	36
Month 1	5	Month 22	21	Month 54	37
Month 2	6	Month 24	22	Month 56	38
Month 3	7	Month 26	23	Month 58	39
Month 4	8	Month 28	24	Month 60	40
Month 5	9	Month 30	25	Month 62	41
Month 6	10	Month 32	26	Month 64	42
Month 7	11	Month 34	27	Month 66	43
Month 8	12	Month 36	28	Month 68	44
Month 9	13	Month 38	29	Month 70	45
Month 10	14	Month 40	30	Month 72	46
Month 11	15	Month 42	31		

For visits with hour-based time points (ex. Day 0, 8 Hours Post), AVISITN will be modified to include decimals (ex. AVISIT = Day 0, 8 Hours Post, AVISITN=2.08).

1. CLINICAL CHEMISTRY/HEMATOLOGY

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Day 10	10	2	20
Month 1	30	21	60
Month 3	91	61	136
Month 6	182	137	273
Month 12	365	274	456
Month 18	548	457	639
Month 24	730	640	821
Month 30	913	822	1004
Month 36	1095	1005	1186
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

2. VITAL SIGNS

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, 2 Hours Post" to the SDTM records at "VISIT 2 DAY 0 POST" and "2 HOURS POST".
- Assign "Day 0, 4 Hours Post" to the SDTM records at "VISIT 2 DAY 0 POST" and "4 HOURS POST".
- Assign "Day 0, 8 Hours Post" to the SDTM records at "VISIT 2 DAY 0 POST" and "8 HOURS POST".
- Assign "Day 0, 12 Hours Post" to the SDTM records at "VISIT 2 DAY 0 POST" and "12 HOURS POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Day 1	1	1	5
Day 10	10	6	20
Month 1	30	21	60
Month 3	91	61	136
Month 6	182	137	273
Month 12	365	274	456
Month 18	548	457	639
Month 24	730	640	821
Month 30	913	822	1004
Month 36	1095	1005	1186

AVISIT	ATARGET	AWLO	AWHI
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

3. ECG

Telemetry will be windowed with other imaging.

Electrocardiogram

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Day 1	1	1	5
Day 10	10	6	20
Month 1	30	21	60
Month 3	91	61	136
Month 6	182	137	273
Month 12	365	274	456
Month 18	548	457	639
Month 24	730	640	821
Month 30	913	822	1004
Month 36	1095	1005	1186
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

4. HOLTOR MONITOR

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Day 10	10	1	20
Month 1	30	21	60
Month 3	91	61	136
Month 6	182	137	273

5. PHYSICAL EXAMINATION

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Day 10	10	1	20
Month 1	30	21	60
Month 3	91	61	136
Month 6	182	137	273
Month 12	365	274	456
Month 18	548	457	639
Month 24	730	640	821
Month 30	913	822	1004
Month 36	1095	1005	1186
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

5.1 Echocardiography (LVESV, LVEDV, LVEF) and [redacted]

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Month 3	91	2	136
Month 6	182	137	273
Month 12	365	274	547
Month 24	730	548	912
Month 36	1095	913	1277
Month 48	1460	1278	1642
Month 60	1825	1643	2007
Month 72	2190	2008	

6. NYHA CLASSIFICATION

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Month 3	91	2	136
Month 6	182	137	273
Month 12	365	274	547
Month 24	730	548	821
Month 30	913	822	1004
Month 36	1095	1005	1186
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

6.1 MLHF, EQ-5D, and 6 Minute Walk Test

- Assign "Baseline" for all pre-treatment records.
- Assign "Day 0, Post" to the SDTM records at "VISIT 2 DAY 0 POST".
- Assign all other AVISIT values based on the following windows.

AVISIT	ATARGET	AWLO	AWHI
Month 3	91	2	136
Month 6	182	137	273
Month 12	365	274	456
Month 18	548	457	639
Month 24	730	640	821
Month 30	913	822	1004
Month 36	1095	1005	1186
Month 42	1278	1187	1369
Month 48	1460	1370	1551
Month 54	1643	1552	1734
Month 60	1825	1735	1916
Month 66	2008	1917	2099
Month 72	2190	2100	2281

Appendix 8: Review of Concomitant Medications by ATC Classification

Appendix 8: Review of Concomitant Medications by ATC Classification

DREAM-HF Study - Sept-2020 - Review of Concomitant Medications by ATC Classification			Results at Baseline	
Concomitant Medication Categories	**WHODRUG ATC *Classification**	**Comment**	**(Unique Patients) Number**	**Percent (%)**
ACE INHIBITORS AND/OR ANGIOTENSIN II ANTAGONISTS **including Entresto**	**TOTAL** (unique patients including Entresto)		**469**	**83.8%**
	ACE INHIBITORS AND DIURETICS	Lisinopril-HCTZ (Zestoretic)	1	0.2%
	ACE INHIBITORS, PLAIN	Lisinopril, Enalapril, Enalapril Maleate, Vasotec, Ramipril, Lotensin, Lotensin(Benazepril), Benazepril Hydrochloride, Monopril(Fosinopril Sodium), Prinivil(Lisinopril Dihydrate), Lisinopril(Prinivil, Zestril), Quinapril, Perindopril(Coversyl), Trandolapril, Captopril	225	40.2%
	ANGIOTENSIN II ANTAGONISTS AND DIURETICS	Hyzaar, Losartan Potassium/HCTZ	2	0.4%
	ANGIOTENSIN II ANTAGONISTS, PLAIN	Losartan, Losartan Potassium, Valsartan, Diovan, Cozaar, Irbesartan, Losartan(COZAAR), Candesartan, Micardis(Telmisartan), Atacand(Candesartan Cilexetil), Olmesartan, Avapro(Irbesartan), Valsartan	121	21.6%
SACUBITRIL/VALSARTAN (Entresto™)	ANGIOTENSIN II ANTAGONISTS, OTHER COMBINATIONS		125	22.3%
MINERALOCORTICOID ANTAGONIST	ALDOSTERONE ANTAGONISTS	Aldactone (Spironolactone),Eplerenone(INSPRA)	**339**	**60.5%**
DIURETICS **(includes Lasix /Furosemide)**	**TOTAL** (unique patients)		**542**	**96.8%**
	THIAZIDES, PLAIN	Hydrochlorothiazide, chlorothiazide (DIURIL)	9	1.6%
	SULFONAMIDES, PLAIN	Bumetanide, Furosemide, Lasix, Metolazone (Zaroxolyn), Torsemide	492	87.9%
	ALDOSTERONE ANTAGONISTS	Aldactone (Spironolactone), Eplerenone(INSPRA)	339	60.5%

DREAM-HF Study - Sept-2020 - Review of Concomitant Medications by ATC Classification			Results at Baseline	
Concomitant Medication Categories	**WHODRUG ATC *Classification**	**Comment**	**(Unique Patients) Number**	**Percent (%)**
	THIAZIDES, COMBINATIONS (1.Ace Inhibitors & Diuretics, 2.Angiotensin II Antagonists & Diuretics, 3.Beta Blocking Agents, Selective, and Thiazides)	1. Lisinopril-HCTZ (ZESTORETIC) 2. Hyzaar, Losartan potassium HCTZ 3. Bisoprolol-hydrochlorothiazide	4	0.7%
DIGITALIS	DIGITALIS GLYCOSIDES	Digoxin(DIGOX), Lanoxin	**145**	**25.9%**
STATINS	HMG COA REDUCTASE INHIBITORS	Atorvastatin, Lipitor(Atorvastatin Calcium), Crestor (Rosuvastatin Calcium), Rosuvastatin, Lovastatin, Livalo(Pitavastatin Calcium), Pravastatin, Zocor(Simvastatin), Vytorin(Inegy), Pravachol (Pravastatin Sodium)	**381**	**68.0%**
ORAL ANTICOAGULATION	**TOTAL** (unique patients)		**122**	**21.8%**
	DIRECT THROMBIN INHIBITORS	Pradaxa (Dabigatran Etexilate Mesilate), Dabigatran	9	1.6%
	DIRECT FACTOR XA INHIBITORS	Apixaban, Eliquis, Xarelto, Rivaroxaban, Savayasa (Edoxaban)	114	20.4%
ANTI-PLATELET AGENTS (including ASA)	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	Aspirin, ASA, Brilinta, Clopidogrel, Clopidogrel Bisulfate, Ecotrin, Effient, Prasugrel HCL, Plavix, Prasugrel, Ticagrelor	**389**	**69.5%**
HEPARIN	HEPARIN GROUP	heparin as a separate category (Heparin, Enoxaparin, Lovenox, Tinzaparin)	**12**	**2.1%**
TYPE II DIABETES MEDICATIONS OF SPECIAL INTEREST			**23**	**4.1%**
(SGLT2 Inhibitor)	OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULIN	Farxiga (Dapagliflozin), Invokana (Canagliflozin), Jardiance (Empagliflozin)	**23**	**4.1%**

DREAM-HF Study - Sept-2020 - Review of Concomitant Medications by ATC Classification			Results at Baseline	
Concomitant Medication Categories	**WHODRUG ATC [a] Classification**	**Comment**	**(Unique Patients) Number**	**Percent (%)**
(GLP1 Receptor agonists)	OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULIN	Victoza (Liraglutide), Nateglinide, Trulicity (Dulaglutide), Trulicity/Dulaglutide, Byetta, Albiglutide, Bydureon, Repaglinide, Empagliflozin,	**0**	**0%**
BETA BLOCKERS	**TOTAL** (unique patients)		**535**	**95.5%**
	Alpha and Beta Blocking Agents	Carvedilol, COREG	359	64.1%
	1. BETA BLOCKING AGENTS + 2. BETA BLOCKING AGENTS SELECTIVE	1. Combigan (0.2%/0.5%), Dorzolamide HCL/Timolol Maleat (COSOPT), Timoptic (Timolol Maleate), Timolol 2. Bisopreolol, Bisopreolol Fumarate, Bystolic (Nebivolol Hydrochloride), Lopressor(Metoprolol Tartrate), Metoprolol, Metoprolol Succinate ER, Metoprolol XL, TOPROL-XL, Toprol, atenolol, bisoprolol	179	32.0%
	BETA BLOCKING AGENTS, SELECTIVE, AND THIAZIDES	Bisoprolol-hydrochlorothiazide	1	0.2%
	BETA BLOCKING AGENTS, NON-SELECTIVE	Sotalol, Sotalol (Betapace) (Sotalol Hydrochloride), Betapace	24	4.3%

a. Anatomical Therapeutic Chemical (ATC).

Appendix 9: Review of Adverse Events of Interest

Appendix 9: Review of Adverse Events of Interest

Adverse Event Preferred Term
Abdominal abscess
Abdominal discomfort
Abdominal pain
Abdominal pain lower
Abdominal pain upper
Acquired Von Willebrand's disease
Acute interstitial pneumonitis
Acute myocardial infarction
Acute respiratory distress syndrome
Acute respiratory failure
Adrenal insufficiency
Altered state of consciousness
Anaemia
Anaemia postoperative
Angina pectoris
Anticoagulation drug level below therapeutic
Anxiety
Arrhythmia
Ascites
Aspiration
Asthenia
Asthma
Atelectasis
Atrial fibrillation
Atrial flutter
Atrial tachycardia
Bacteraemia
Balance disorder
Balanitis candida
Bladder dilatation
Blister
Blood albumin decreased
Blood bilirubin increased
Blood creatinine increased
Blood glucose increased
Blood lactic acid increased
Blood magnesium decreased
Blood magnesium increased
Blood phosphorus decreased
Blood potassium increased
Blood urea increased
Blood uric acid increased
Brain natriuretic peptide increased
Bronchitis
Bundle branch block left
C-reactive protein increased
Cardiac failure chronic

Adverse Event Preferred Term
Cardiac failure congestive
Cardiac perforation
Cardiac tamponade
Cardiogenic shock
Cardiomyopathy
Cardiorenal syndrome
Cardiovascular deconditioning
Catheter site erythema
Catheter site haematoma
Catheter site haemorrhage
Catheter site inflammation
Cellulitis
Cerebrovascular accident
Chest discomfort
Chills
Chronic obstructive pulmonary disease
Clostridium difficile infection
Clostridium test positive
Coagulation factor deficiency
Coagulopathy
Cognitive disorder
Complications of transplanted heart
Confusional state
Constipation
Convulsion
Corona virus infection
Cough
Creatinine renal clearance decreased
Cystitis
Cytomegalovirus colitis
Cytomegalovirus viraemia
Death
Deep vein thrombosis
Dehydration
Delirium
Depression
Dermatitis contact
Device failure
Device leakage
Device related infection
Diabetes mellitus
Diabetic neuropathy
Diarrhoea
Dilatation ventricular
Diplopia
Dizziness
Dizziness postural
Dry gangrene
Dyspepsia

Adverse Event Preferred Term
Dysphonia
Dyspnoea
Dyspnoea exertional
Electrocardiogram QT prolonged
Electrolyte imbalance
Emphysema
Encephalopathy
Epistaxis
Erectile dysfunction
Erysipelas
Escherichia urinary tract infection
Fall
Fatigue
Feeding disorder
Fluid overload
Fluid retention
Fungal sepsis
Gamma-glutamyltransferase increased
Gastritis erosive
Gastroenteritis
Gastrointestinal haemorrhage
Glucose urine present
Glycosylated haemoglobin increased
Haemarthrosis
Haematemesis
Haematochezia
Haematoma
Haematuria
Haemoglobin decreased
Haemorrhagic anaemia
Headache
Heart rate increased
Heart transplant rejection
Heparin-induced thrombocytopenia
Herpes zoster
Hyperglycaemia
Hyperhidrosis
Hyperkalaemia
Hyperlipidaemia
Hypernatraemia
Hypertension
Hyperthyroidism
Hyperuricaemia
Hypervolaemia
Hypoalbuminaemia
Hypocalcaemia
Hypoglycaemia
Hypokalaemia
Hypomagnesaemia

Adverse Event Preferred Term
Hyponatraemia
Hypophosphataemia
Hypotension
Hypothermia
Hypothyroidism
Hypovolaemia
Hypoxia
Ileus
Impaired gastric emptying
Impaired healing
Implant site inflammation
Incision site haemorrhage
Incision site infection
Incision site pain
Infection
Infectious pleural effusion
Influenza
Insomnia
Intermittent claudication
International normalised ratio increased
Intra-abdominal haematoma
Iron deficiency anaemia
Ischaemic cardiomyopathy
Ischaemic hepatitis
Ischaemic stroke
Jugular vein thrombosis
Lactic acidosis
Large intestinal ulcer haemorrhage
Left atrial dilatation
Leukocytosis
Liver function test abnormal
Local swelling
Localised oedema
Low cardiac output syndrome
Lower gastrointestinal haemorrhage
Lower respiratory tract infection
Lung consolidation
Lymphadenopathy
Malaise
Malnutrition
Melaena
Memory impairment
Mental status changes
Metabolic acidosis
Metabolic encephalopathy
Mitral valve incompetence
Monocyte count increased
Muscle spasms
Muscle tightness

Adverse Event Preferred Term
Muscular weakness
Musculoskeletal chest pain
Musculoskeletal pain
Myalgia
Myocardial infarction
N-terminal prohormone brain natriuretic peptide increased
Nasopharyngitis
Nausea
Nephrolithiasis
Nerve injury
Neuropathy peripheral
Neutropenia
Neutrophil count increased
Nodal rhythm
Non-cardiac chest pain
Normochromic normocytic anaemia
Oedema
Oedema peripheral
Oliguria
Oral candidiasis
Oropharyngeal pain
Orthostatic hypotension
Osteopenia
Osteoporosis
Pain in extremity
Palpitations
Paraesthesia
Pericardial effusion
Perinephric effusion
Peripheral arterial occlusive disease
Peripheral ischaemia
Peritoneal haemorrhage
Pharyngeal oedema
Platelet count decreased
Platelet count increased
Pleural effusion
Pneumonia
Pneumothorax
Pneumothorax traumatic
Post procedural constipation
Post procedural haemorrhage
Postoperative ileus
Postoperative respiratory failure
Postpericardiotomy syndrome
Presyncope
Procalcitonin increased
Procedural hypertension
Procedural hypotension
Procedural nausea

Adverse Event Preferred Term
Procedural pain
Productive cough
Protein urine present
Pruritus
Pseudomonal bacteraemia
Pseudomonas infection
Pulmonary arterial hypertension
Pulmonary embolism
Pulmonary hypertension
Pulmonary toxicity
Pyrexia
Rales
Rash
Rash erythematous
Rash generalised
Renal disorder
Renal failure
Renal failure acute
Renal failure chronic
Renal impairment
Renal infarct
Renal ischaemia
Respiratory alkalosis
Respiratory failure
Respiratory syncytial virus infection
Respiratory tract congestion
Retroperitoneal haematoma
Rib fracture
Scab
Sepsis
Septic shock
Shock
Sick sinus syndrome
Sinus arrest
Sinus bradycardia
Skin irritation
Skin lesion
Sleep disorder
Soft tissue infection
Staphylococcal bacteraemia
Staphylococcal infection
Subarachnoid haemorrhage
Subdural haematoma
Subdural haemorrhage
Syncope
Systemic inflammatory response syndrome
Tachycardia
Throat irritation
Thrombocytopenia

Adverse Event Preferred Term
Tooth fracture
Toxicity to various agents
Transaminases increased
Transplant failure
Transplant rejection
Tremor
Tricuspid valve incompetence
Troponin increased
Upper respiratory tract infection
Upper-airway cough syndrome
Urethral injury
Urinary casts present
Urinary retention
Urinary tract infection
Urinary tract infection fungal
Urinary tract obstruction
Urine ketone body present
Urine output decreased
Vascular graft complication
Venous stenosis
Venous thrombosis
Ventricular extrasystoles
Ventricular fibrillation
Ventricular tachycardia
Vertigo
Vertigo positional
Viral infection
Vision blurred
Visual impairment
Vomiting
Weight increased
White blood cell count increased
White blood cells urine positive
Wound
Wound infection