STATISTICAL ANALYSIS PLAN

Protocol Title:	Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients With a Myocardial Infarction and Ischemic Left Ventricular Dysfunction
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Study Phase:	Phase 2
Product Name:	CAP-1002 Allogeneic Cardiosphere-Derived Cells
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CONFIDENTIALITY STATEMENT

REVISION HISTORY

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ABBREVIATIONS

Abbreviation	Definition
6MWT	Six-Minute Walk Test
AE	adverse event
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
CDC	cardiosphere derived cell
CEC	Clinical Events Committee
CI	confidence interval
CK-MB	creatine phosphokinase MB isoenzyme
CSR	Clinical Study Report
CT	computerized tomography
CTL	Cellular Technology Limited
CV	cardiovascular
DSMB	Data Safety Monitoring Board
DSA	donor specific antibodies
ECG	electrocardiogram
EDC	electronic data capture
ELISpot	enzyme-linked immunosorbent spot
EOS	end of study
FBS	fetal bovine serum
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICH	International Conference on Harmonisation
ICD	implantable cardioverter defibrillator
IP	investigational product
ITT	intent-to-treat
IWRS	interactive web-based system
LS	least-squares
LTFUP	Long-Term Follow-up
LV	left ventricular
LVAD	LV assist device
LVEDD	LV end diastolic diameter
LVEDV	LV end diastolic volume
LVEF	left ventricular ejection fraction
LVESD	LV end systolic diameter
LVESV	LV end systolic volume
M	million
MACE	major adverse cardiac event

MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescence intensity
MI	myocardial infarction
mITT	modified intent-to-treat
ML	maximum likelihood
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MNAR	missing not at random
MRI	magnetic resonance imaging
NIH	National Institutes of Health
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
NYHA	New York Heart Association
PGA	Patient Global Assessment
PHA	phytohemagglutinin
PT	Preferred Term
QoL	quality of life
SAB	single antigen bead
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDF1	stromal cell derived factor 1
SF-36	Short Form - 36 questions
SOC	System Organ Class
SPRO	serious procedure related outcomes
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
WHO-DD	World Health Organization Drug Dictionary
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem

PREFACE

The purpose of this statistical analysis plan (SAP) is to describe the planned statistical analyses and reporting for Capricor Protocol Number 1002-001. The planned analyses identified in this SAP may be included in future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in the Clinical Study Report (CSR) and manuscripts for publication.

The SAP is a supplement to the study protocol, which should be referred to for additional details on study design, study conduct, and other operational aspects of the study.

The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration and International Conference on Harmonisation (ICH) E9: Guidance on Statistical Principles in Clinical Trials.[1] All work planned and described in the SAP will follow internationally accepted guidelines published by the American Statistical Association. The following documents were also considered in preparation for writing this SAP:

- Clinical Research Protocol 1002-01 Amendment 8.1, February 22, 2017
- ICH E3 Guideline: Structure and Content of Clinical Study Reports[2]
- ICH E6 Guideline on Good Clinical Practice[3]
- ICH E8 General Considerations for Clinical Trials[4]

1. INTRODUCTION

The principal goal of the ALLSTAR Phase 2 trial is to establish the safety of intracoronary administration of allogeneic cardiosphere derived cells (CDCs) (CAP-1002) to shrink scar tissue 4 weeks to 12 months following myocardial infarction (MI). In parallel, signals of potential efficacy will also be evaluated. Phase 2 commenced after a Data Safety Monitoring Board had assessed one-month safety data from the Phase 1 Safety Cohort and recommended proceeding.

2. STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

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

The primary efficacy objective is to test the hypothesis that, in subjects with ischemic LV dysfunction and a previous MI, CAP-1002 by intracoronary infusion is superior to placebo in reducing infarct size, expressed as a percent of LV mass, 12 months after infusion, either in all subjects combined or in subjects with recent MI (<= 90 days before infusion).

2.1.2 Secondary Objectives

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

The secondary efficacy objective is to compare CAP-1002 and placebo treatment groups at 6 and 12 months post-infusion on endpoints related to LV function and structure, clinical function and status, and cardiac biomarkers.

2.2 Treatment Group Comparisons

Two treatment groups will be compared in the study:

- CAP-1002 (single administration of 25 M cells)
- Placebo

2.3 Study Endpoints and Hypotheses

2.3.1 Primary Safety Endpoint

The primary safety endpoint is whether or not any of the following adjudicated (see Section 12) events occur during the one month post intracoronary infusion:

1. Acute myocarditis possibly attributable to the investigational product (IP), diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to the IP, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo. See Section 12 for further information related to blinded adjudication by the Clinical Events Committee (CEC).

2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with electrocardiogram (ECG) documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting or during routine ECG monitoring while hospitalized.

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

4. Major adverse cardiac event (MACE), defined as the composite incidence of death, nonfatal recurrent MI, hospitalization with primary discharge diagnosis of heart failure, emergency room treatment for heart failure [N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) > 450 pg/mL or brain natriuretic peptide (BNP) >100 pg/ml, with treatment including intravenous diuretic administration], LV assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or creatine phosphokinase MB isoenzyme (CK-MB) levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

2.3.2 Primary Safety Endpoint Hypothesis

For the primary safety endpoint, the following hypothesis set will be tested:

$$H_o: \ p_c - p_p \geq 0.20$$

$$H_a: \ p_c - p_p < 0.20$$

where p_c and p_p are the proportions of subjects in the CAP-1002 and placebo treatment groups, respectively, who experienced the primary safety endpoint. H_o will be rejected if the upper limit of the 90% confidence interval (CI) for $p_c - p_p$ is less than 0.20.

2.3.3 Secondary Safety Endpoints

The following adjudicated (see Section 12) events will be evaluated as secondary safety endpoints over the twelve-month follow-up period:

1. Acute myocarditis possibly attributable to the IP, diagnosed with consideration of clinical

context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to the IP, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo. See Section 12 for further information related to blinded adjudication by the CEC.

2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with prior ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting or during routine ECG monitoring while hospitalized.

3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.

4. MACE, as defined above.

5. New cardiac tumor formation on magnetic resonance imaging (MRI).

6. Any hospitalization due to a cardiovascular (CV) cause or related to IP infusion.

7. Any inter-current CV illness, or one related to IP infusion, which prolongs hospitalization. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following IP administration. Troponin and CK-MB will be obtained approximately every 8 hours for the first 24 hours after infusion.

8. New TIMI flow ≤ 1 following IP infusion.

9. Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 30 beats or longer ascertained by periodic, protocol-mandated 24 hour ambulatory ECG monitoring.

10. Development of increased anti HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor. Elevation of donor-specific antibodies (DSA), using the LABScreen® single-antigen in vitro diagnostic assay that is a Luminex® based antibody detection assay designed to detect Class I or Class II HLA antibodies in human serum or plasma, is defined as mean fluorescence intensity (MFI) above a threshold of 5000; a threshold of 1000 MFI will also be used to evaluate elevation of DSA. See Section 12 for further information related to blinded adjudication by the CEC and Section 10.2 for details related to comparison to placebo.

2.3.4 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline in MRI assessment of infarct size as a percent of LV mass 12 months after IP administration.

2.3.5 Primary Efficacy Hypothesis

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

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

and

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

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

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

2.3.6 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated at 6 and 12 months post IP administration unless otherwise noted:

1. Absolute and relative change from baseline in global LV function measures:
   a) MRI assessment of LV ejection fraction (LVEF)
   b) MRI assessment of LV end diastolic volume (LVEDV) and end systolic volume (LVESV) indexed to body surface area (BSA)

2. Absolute and relative change from baseline in structural measures:
   a) MRI assessment of infarct size as a percent of LV mass
   b) MRI assessment of infarct size expressed in grams
   c) MRI assessment of viable mass expressed in grams
   d) MRI assessment of scar transmurality

3. Absolute and relative change from baseline in regional measures:

a) MRI assessment of function and structure by segment or groups of segments (e.g., region which received the IP)

4. Absolute change from baseline in clinical function/status measures:
   a) Distance covered in six minute walk test (6MWT)
   b) Minnesota Living with Heart Failure Questionnaire (MLHFQ) score
   c) Patient Global Assessment (PGA) score

5. Absolute and relative change from baseline in cardiac biomarkers:
   a) NT-proBNP

3. STUDY DESIGN AND SCHEDULE OF EVENTS

This is a randomized, double-blind, placebo-controlled phase 2 trial designed to evaluate the safety and efficacy of intracoronary delivery of CAP-1002 in subjects with ischemic LV dysfunction and a previous MI. Detailed inclusion and exclusion criteria are in Section 4 of the protocol.

Approximately 120 subjects with a previous anterior MI and resultant ischemic LV dysfunction who meet all inclusion and exclusion criteria will be enrolled into one of two cohorts: the Primary Randomized Cohort and the Exploratory Randomized Cohort. The Primary Randomized Cohort will include approximately 103 subjects who meet compatibility to receive IP from one or more donor(s). Compatibility is achieved when a subject is found at screening to have no pre-existing antibodies against a donor's HLA antigens (i.e., no DSA). The remaining subjects (approximately 17) who have pre-existing antibodies against all available donors will be enrolled in the Exploratory Randomized Cohort so that potential differences in safety and efficacy can be assessed. Each of the two cohorts will be randomized separately. Subjects will be randomized within strata defined by time since MI ("recent" or "chronic") to receive CAP-1002 or placebo in a 2:1 ratio favoring CAP-1002. "Recent" will be defined as more than 4 weeks but within 90 days prior to randomization and "chronic" will be defined as more than 90 days but less than 12 months prior to randomization. Enrollment in the study will end when approximately 130 subjects have been randomized.

Subjects will undergo protocol assessments through 12 months post infusion. Reviews by a Data Safety Monitoring Board (DSMB) will be done per charter at least semi-annually. The DSMB will review both safety and efficacy data after all subjects complete 6 months of follow-up or withdraw from the study. In addition, there will be one administrative interim efficacy analysis after Month 6 MRI measurements are available for all subjects. An additional administrative efficacy analyses may be done on an as-needed basis. Subjects will be followed annually for 5 years post infusion or reference date.

The Schedule of Events is shown in Appendix A.

4. SAMPLE SIZE AND POWER CALCULATIONS

Power calculations were done using Monte Carlo simulation based on observed data from two previous clinical trials in which subjects similar to those being enrolled in ALLSTAR Phase 2, i.e., with ischemic LV dysfunction, were treated with CDCs by intracoronary infusion: CADUCEUS, a phase 1 randomized, controlled trial, and ALLSTAR Phase 1, the open-label safety phase of the current trial. ALLSTAR Phase 1 was used for the assumed means and SDs and CADUCEUS was used for the treatment effect in Chronic MI patients relative to Recent MI. A simulation of the closed testing procedure to test the primary efficacy endpoint at the final analysis using parameters shown in Table 1 was done (see Section 2.3.5).

Table 1. Assumed Mean and Standard Deviation (SD) Percent Reduction in Scar Size at Months 6 and 12.

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

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

5. RANDOMIZATION AND BLINDING

The following are required for subject randomization to occur:

- Trigger from site via electronic data capture (EDC) that a subject is ready for randomization.
- Analysis of blood samples to determine cohort assignment (Primary or Exploratory) based on presence or absence of DSA to available donors.
- Identification of donor cell lines for which the subject is compatible.
- Strata membership: recent MI (“Recent”) or chronic MI (“Chronic”).

The Primary Randomized Cohort and the Exploratory Randomized Cohort will be randomized separately. Subjects will be randomized 2:1 CAP-1002:placebo within each stratum using random block sizes of 3 and 6 and institutional balancing in an interactive web-based system (IWRS). Notification that a subject has been randomized will be sent to an independent storage/distribution center (depot). The depot will have password protected access to the randomization assignment and will randomly assign subjects in the Primary Randomized Cohort to an appropriate donor (or placebo). Subjects in the Exploratory Randomized Cohort will be randomly assigned to one of the available donors regardless of compatibility (based upon available inventory).

Both investigators and subjects will be blinded to treatment assignment throughout the trial. Core and central laboratory personnel analyzing the MRI images and testing serum for serial donor specific antigen and whole blood for cellular immune response will also be blinded throughout the trial, as will the CEC adjudicating events, and all medical affairs and clinical operations staff, except as noted below. Personnel at the MRI core laboratory will be blinded to treatment assignment but not temporal order of the images; e.g., readers will have access to and will use baseline and Month 6 images when reading Month 12 images as part of the informed reading protocol. A member of the Sponsor staff will be unblinded if an emergency blind break is required at any time during the trial. Study sites will be trained regarding the emergency unblinding process. Should a medical event occur that necessitates unblinding, the process will be accessible to investigators 24 hours a day and will include an emergency Sponsor contact.

The distribution of IP will occur in validated dry vapor shippers allowing for consistent transportation and scheduling flexibility at all sites. Both CAP-1002 and placebo will be packaged in identical cryogenic bags with similar labels. At the clinical site, the IP is thawed to room temperature, prepared and drawn into masked (with amber/transparent tape) syringes. The amber/transparent tape will allow the treating physician to see air bubbles but obscure the clarity of the IP suspension. Specific instructions for use are provided to each investigative site for reference. Central laboratories will be used to assess sensitization to CAP-1002 [i.e., single antigen bead (SAB), enzyme-linked immunosorbent spot (ELISpot) assay]. Because these results may unblind, they will not be shared with investigators, subjects, site personnel, or Sponsor staff in order to preserve blinding.

The DSMB, including a statistician independent of the sponsor's clinical trial team, will have access to unblinded data and immunological test results. In addition, as a result of administrative interim efficacy analyses (see Section 13.2.2), a prespecified group of personnel from the Sponsor (the smallest group possible), as well as personnel from Janssen Biotech, Inc. ("Janssen") in order to comply with the terms of that certain Collaboration Agreement and License Option, will become unblinded and will have full access to the efficacy data.

A list will be maintained in the trial master file to track any persons unblinded during the trial.

6. ANALYSIS POPULATIONS

The following analysis populations are defined for the trial:

Primary Safety Population: All subjects in the Primary Randomization Cohort who received the IP. Subjects will be summarized and analyzed per treatment actually received, regardless of their randomization assignment.

Primary Intent-to-Treat (ITT) Population: All subjects in the Primary Randomization Cohort who were randomized. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

Primary Modified Intent-to-Treat (mITT) Population: For a given efficacy parameter, all subjects in the Primary Randomization Cohort who received the IP, had a baseline observation and at

least one post-baseline observation. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

Per Protocol Population: Subjects in the Primary Randomization Cohort with no major protocol violations at end of study (EOS). The list of subjects with major protocol violations will be compiled in a blinded fashion prior to database lock at EOS. For the analysis of the primary efficacy endpoint based on the per protocol population, a sensitivity analysis will be done to evaluate the effect of excluding subjects randomized in the wrong cohort or the wrong stratum from the per protocol population; i.e., subjects incorrectly randomized in the Exploratory Randomization Cohort would be excluded from the per-protocol sensitivity analysis, as would subjects randomized in the wrong stratum based on time since index MI (recent vs. chronic).

Exploratory Safety Population: All subjects in the Exploratory Randomization Cohort who received the IP. Subjects will be summarized and analyzed per treatment actually received, regardless of their randomization assignment.

Exploratory ITT Population: All subjects in the Exploratory Randomization Cohort who were randomized. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

Exploratory mITT Population: For a given parameter, all subjects in the Exploratory Randomization Cohort who received the IP, had a baseline observation and at least one post-baseline observation. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

7. DATA MANAGEMENT, PRESENTATION, AND ANALYSIS CONSIDERATIONS

7.1 Programming Environment

SAS® Version 9.2 or higher (SAS Institute, Cary, NC) will be used for statistical analyses and the production of tables, figures, and listings (TFLs).

7.2 Tables, Figures, and Listings

TFLs will be produced for the Primary Randomized Cohort; a subset of TFLs will also be produced for the Exploratory Randomized Cohort. Tables of contents for TFLs to be produced are shown in Appendix C. All TFLs will be appended to the final CSR.

7.2.1 Tables and Figures

- Tables and figures will present data summaries and/or analyses for the appropriate study population; e.g., summaries of safety parameters will be shown for the safety population only.
- Treatment group order in tables and figures will be Recent CAP-1002, Recent Placebo, Chronic CAP-1002, Chronic Placebo, Overall CAP-1002, Overall Placebo.

- Tables and figures will present summaries/analyses by study visit window (see Section 7.7).
- Table column headers and figure legends will include subgroup sample sizes.

7.2.2 Listings

- Listings will present all data collected for all subjects (i.e., the ITT populations) unless the listing applies only to a specific analysis population [e.g., listings of treatment-emergent adverse events (AEs) apply only to safety populations].
- Listings will be ordered by unique subject identifier, study visit window), date, and data collection time.

7.3 Data Analysis

- The reference date used for summaries and analyses will depend on the analysis population, as follows:
  - ITT population: randomization date
  - mITT population: IP administration date
  - Safety population: IP administration date
  - Per protocol population: IP administration date
- Categorical variables will be summarized as frequencies and percentages in each category. Percentages will be reported to one decimal place. Unless otherwise noted in Sections 8-10, categorical variables will be analyzed using chi square tests of association or, if any contingency table cell has less than 5 subjects, Fisher's exact test.
- Continuous variables will be summarized by numbers of subjects, means, standard deviations, medians, and ranges. The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one. The number of decimal places for measures of variance will be the same as the original data plus two. Unless otherwise noted in Sections 8-10, continuous variables will be analyzed using t-tests. Non-parametric tests and data transformations will be considered for variables with distributions that violate t-test assumptions.
- Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.
- P-values will be presented to two decimal places if > 0.01, to three places if < 0.01 but > 0.001, and to four places if < 0.001 but > 0.0001. P-values < 0.0001 will be presented as "< 0.0001."
- Statistical tests will be two-sided and tested at the 0.05 significance level unless otherwise noted in Sections 8-10.
- It is understood that statistical non-significance is not an indicator of equivalence.

7.4 Subgroups

- All TFLs will display data by recent vs. chronic MI. For most analyses, including analysis of the primary efficacy endpoint, subjects randomized in the wrong stratum will be analyzed according to time since the index MI, calculated as:

  time_since = infusion date – index MI date + 1

  If time_since is <= 90 days, the subject will be classified as "recent MI"; otherwise, as "chronic MI." For the analysis of the primary efficacy endpoint based on the per protocol population, a sensitivity analyses will be done to evaluate the effect of excluding subjects randomized in the wrong stratum from the per protocol population and the effect of analyzing subjects according to the strata in which they were randomized.

- Differences in safety and/or efficacy by subgroups defined by the following classifiers may be explored as part of the final analysis:
  - Demographics (age dichotomized by median, sex, race)
  - Baseline DSA mean fluorescence intensities < 500 vs. 500-1000 and/or DSA quartiles
  - Donor, stromal cell derived factor 1 (SDF1) level of lot received, master cell bank, and/or other identified measures of potential cell potency
  - CAP-1002 manufactured with a modified process ("P5")
  - With vs. without biventricular pacing initiated less than three months before the screening MRI or after the start of the study, the rationale being that this may confound functional and physiologic outcomes in patients with ischemic cardiomyopathy, and it can take up to 3 months post-implant for any effect to occur.
  - Baseline infarct size (≤ 20% vs. > 20% of LV mass)
  - Baseline LVEF (dichotomized by median)
  - Baseline weight (dichotomized by median)

7.5 Missing Data

- Listings will present data as reported.
- Missing or partially missing dates that are required for date-dependent definitions [e.g., treatment-emergent AEs (TEAEs), concomitant medications] will be assumed to be the most conservative date possible. For example, an AE with a completely missing start date will be considered treatment-emergent; similarly, an AE that started the same month and year as IP administration but with missing start day will be considered treatment-emergent.
- Handling of missing endpoint data in summaries and analyses for each endpoint is described in Sections 8-10.

7.6 Study Period and Time Point Definitions

The following study periods and time points are defined:

Screening Period: the 4-week time period before IP infusion.

Baseline: the last observation of a given parameter before IP infusion of a given subject.

Day 0: the day of planned IP infusion of a given subject.

(Nominal Visit) Analysis Time Point: analysis based on data collected at the *(nominal visit)* time point, where nominal visits are as shown in the table below.

EOS, Subject Level: subject-level EOS is reached after completion of the Month 12 visit or study or discontinuation for any reason.

EOS, Study-Level: study-level EOS is reached when all randomized subjects have either completed the Month 12 visit or have discontinued from the study for any reason.

Long-Term Follow-Up (LTFUP) Period, Subject-Level: the LTFUP period begins after completion of the Month 12 visit and continues until 4 more annual visits have been completed.

7.7 Visit Windows

Study visits will include Screening, Day 0, and nominal week or month indicated in the table below. Visit windows will be used in data listings, summaries and analyses and will be based on study day of the observation, defined as:

study day = date of observation – Day 0 date

Visit windows per protocol and to be used in listings, summaries and analyses are as follows:

Nominal Visit	Nominal Day	Min Day Per Protocol	Max Day Per Protocol	Min Day for Analyses	Max Day for Analyses
Week 2	14	11	17	1	22
Month 1	30	27	33	23	59
Month 3	90	84	96	60	135
Month 6	180	174	186	136	270
Month 12	360	354	366	271	426

where cell entries are study days as defined above. For example, per protocol the Month 1 visit will occur between 27 and 33 days post infusion (Day 0), but for purposes of listings, summaries and analysis all observations dated between 23 and 59 days post infusion will be included in the Month 1 visit window.

Efficacy assessments that occur too late to be included in the Month 12 analysis window will be included in "last observation" analyses (see Section 9).

For ITT summaries and analyses, study day will be defined as:

study day = date of observation – randomization date – X

where X is

- for treated subjects, the number of days between randomization and IP administration.
- for untreated subjects, the median of the number of days between randomization and IP administration among treated subjects.

For example, for a subject who received IP 5 days after randomization and who had an assessment 65 days after randomization, the study day for that assessment would be 60 and the assessment would therefore fall into the Month 3 analysis window.

In addition, visit windows based on time of data collection will be defined for cardiac biomarkers as follows:

Nominal Visit	Nominal Hour	Min Hour for Analyses	Max Hour for Analyses
8 Hours Post	8	0.01	12.00
16 Hours Post	16	12.01	20.00
24 Hours Post	24	20.01	28.00

If multiple valid, non-missing observations exist within a given window, the observation to be used will be:

1. the observation closest to the nominal visit day/time in question, or
2. the latest observation if the multiple observations are equidistant from the nominal visit day/time, or
3. the average (arithmetic or geometric, as appropriate) of the observations if the multiple observations have the same actual time point.

8. STUDY POPULATION PARAMETERS

Listings of all study population parameters will be done for the primary and exploratory ITT populations and summaries will be done for the primary mITT population. Some summaries may also be done for other analysis populations defined in Section 6. Study population parameters to be listed and summarized are described below.

8.1 Analysis Populations

The analysis populations defined in Section 6 will be described in terms of the identification of subjects in each population and the frequency distribution of each population.

8.2 Eligibility and Informed Consent

Eligibility and informed consent parameters will be listed and will include protocol version and dates of informed consents (general, biomarkers). Inclusion and/or exclusion criteria that were not met will be listed, as will details on any waivers granted. Satisfaction of inclusion/exclusion criteria will be summarized.

8.3 Demographics

Subject demographic parameters will be study site, age, sex, race, and ethnicity and will be listed and summarized. Summary tables will include p-values for treatment group differences. Age will be computed in SAS as follows:

AGE = floor((intck('MONTH', bdt, rdt) - (day(rdt) < day(bdt))) / 12)

where bdt = birth date in SAS date format and rdt = reference date in SAS date format.

8.4 Medical History

General medical history and cardiac history will be listed and summarized separately. Summaries will include frequencies and percentages of subjects with each condition. Differences in medical and cardiac history by treatment group will be analyzed and p-values (for frequencies only) will be included in the summary table.

8.5 Computerized Tomography of the Chest, Abdomen and Pelvis

A computerized tomography (CT) of the chest, abdomen and pelvis is performed at the screening visit to ensure that there are no clinically significant pre-existing abnormalities to internal organs or presence of tumors or cancer. Parameters will be listed and will include whether or not the CT was done, date of the CT, and the result (normal, abnormal not clinically significant, abnormal clinically significant).

8.6 Laboratory Screens and Immunogenicity Testing (HLA)

Laboratory screens will include human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), glycosylated hemoglobin (HbA1c), and serum pregnancy. Laboratory screens and HLA will be listed and summarized.

8.7 IP Administration

Details of IP administration will be listed. Parameters to be summarized will include successful completion of IP administration, reason for non-completion, total volume infused, whether or not the full dose was administered, final TIMI flow score per artery infused, and indicators for a series of events occurring during IP administration and a series of events within 24 hours of IP administration. Such events will also be recorded as AEs and will also appear in AE listings and summaries.

8.8 Subject Study Progress

A listing of subject study progress will show dates of screening, informed consent, randomization, IP administration, study visits, and EOS. Number of subjects who completed each visit will be summarized.

8.9 Subject Disposition

A listing of subject disposition will include dates of randomization and IP administration (or attempt), whether or not the subject completed the Month 12 visit, subject-level EOS date, reason for study discontinuation (if applicable), and whether or not the subject consented to annual LTFUP. Frequencies and percentages of subjects who discontinued and reasons for discontinuation as well as duration of follow-up will be summarized. Duration of follow-up will be calculated as:

$$\text{duration} = \text{date of last known status} - \text{date of infusion} + 1$$

where date of last known status is the maximum date among AE start and end dates, concomitant medication start and stop dates, visit dates (including unscheduled visits), and EOS date.

The summary table will include a p-value for treatment group comparison of discontinuation for any reason and, if appropriate, for duration of follow-up based on a log rank test.

9. EFFICACY ANALYSIS

All efficacy parameters will be listed for the primary ITT population and summarized for the mITT population. The primary analysis of primary and secondary efficacy endpoints will be done using the primary mITT population. Secondary analyses may be done using the other analysis populations defined in Section 6 or in subgroups defined in Section 7.4. In addition, "last observation" analyses will be done for certain parameters for which some subjects' final assessments were done too late to be included in the Month 12 analysis window.

Analyses of changes from baseline will be done using general linear models with baseline values as covariates. Analyses of the effect of treatment group, analysis window (e.g., baseline, Month 6, Month 12), and their interaction will be done using mixed effects linear regression, with subject as a random effect, analysis window, and treatment group as fixed effects, and baseline as a fixed-effect covariate. For "last observation" analyses, "time" as a continuous covariate will be substituted for analysis window. Study site may also be included as a random effect if there is evidence of correlation within study sites (per the interclass correlation coefficient from the unconditional model) and/or if doing so appreciably improves the model fit (e.g., per Akaike's Information Criterion). Other covariates that may be considered include age (< 65 vs. ≥ 65 years), sex, race (African-American vs. other), baseline 6MWT, baseline LVESV, baseline NT-proBNP, and DSA (as an indicator variable). Residuals will be evaluated for substantial departure from normality and independent and constant variance and appropriate remedies (e.g., data transformations, detecting and assessing the influence of outliers, alternative analytical approaches) will be attempted when necessary. An unstructured covariance will be the default covariance structure but other structures (e.g., compound symmetry) may be used to evaluate sensitivity to the choice of structure or, if study site is included as a random effect, to achieve convergence.

Assuming missing observations are "missing at random" (MAR), i.e., the fact that they are missing is unrelated to the missing variable but can be related to another variable on which data have been collected, the maximum likelihood (ML) approach is able to handle subjects with

either Month 6 or Month 12 changes from baseline missing, but not both. Therefore, for analyses based on the mITT population, missing data will be addressed using ML. For analyses based on the ITT population, in which some subjects may have both Month 6 and Month 12 changes from baseline missing, multiple imputation will be used based on all observations and will use a fully conditional specification method with 20 burn-in iterations and the regression method of imputation. Variables in the imputer's model will be baseline observation (because baseline is used as a covariate in analyses), Month 6 change from baseline, Month 12 change from baseline, and treatment group. Because the MAR assumption is not testable, and because it seems possible that subjects with poorer outcome may be more likely to miss trial assessments, a sensitivity analysis under a "missing not at random" (MNAR) assumption will be done (for the final analysis only) of the primary efficacy endpoint in which multiple imputation will use the pattern-mixture model approach to address missing values; i.e., the imputation will be based on a pre-specified subset of subjects. For this MNAR analysis, only those subjects who had implantable cardioverter defibrillators (ICDs) inserted during the trial. Because very few missing observations are expected in this trial, 5 imputed data sets will be used for all analyses using multiple imputation.

A closed testing procedure will be used for the primary efficacy analysis only (see Section 2.3.5) and will be done as follows:[6]

1. Let p_f and p_s be the p-values from the tests of the individual null hypotheses involving the full group and the subgroup, respectively; tests will be based on least squares (LS) means comparisons.

2. Let $t_{max} = \max(t_f, t_s)$, where t_f and t_s are the t-statistics from the full group and subgroup analyses in (1) above.

3. Let r = the correlation between t_f and t_s, estimated by the ratio of SDs of the treatment effect estimates in the full group and subgroup.

4. Let p_{inter} be the p-value from the test of the intersection hypothesis using Dunnett's test; specifically, $p_{inter} = 1 - \text{probnorm}(t_{max}, t_{max}, r)$.

Then, if $p_{inter} < 0.025$ and either $p_f < 0.025$ or $p_s < 0.025$ (with treatment effect favoring CAP-1002), the test of treatment effect for the primary efficacy endpoint will be considered statistically significant.

For all non-primary efficacy analyses, tests of treatment effect will be based on comparisons of LS means with no adjustment for multiple comparisons.

A descriptive correlation analysis will be done for all pairs of tissue-based and functional efficacy endpoints (i.e., MRI outcomes) using Pearson's or Spearman's correlation coefficient.

Efficacy parameters are described below.

9.1 MRI Parameters

MRI data will be delivered in a raw file provided by the MRI Core Lab and will include the following parameters:

- LVEF
- LVESV, LVEDV indexed to BSA
- Infarct size as a percent of LV mass (primary efficacy endpoint)
- Infarct size in grams
- Viable mass in grams, equal to total LV mass minus non-viable mass
- Regional wall motion

Regional wall motion will be analyzed using average (over slices) percent scar tissue (i.e., scar size), percent non-viable tissue, end diastolic wall thickness, end systolic wall thickness, and wall thickening. The region of IP administration will be assumed to be the region of the index MI. Sixteen-segment data correspond to region as follows:

- Left anterior descending artery = segments 1, 2, 7, 8, 13, and 14
- Left circumflex artery = segments 5, 6, 11, 12, and 16
- Right coronary artery = 3, 4, 9, 10, and 15

Index MI locations reported for subjects with different coronary anatomy will be associated with specific segments on a case-by-case basis. Analysis parameters will be observations averaged over the involved segments for the index location. For example, if the index location is the right coronary artery, wall thickening for the index location will be the mean "average" wall thickening over segments 3, 4, 9, 10, and 15.

Regional wall motion will also be analyzed within the following locations:

- Anterior = 1, 7, and 13
- Lateral = 5, 6, 11, 12 and 16
- Inferior = 4, 10, and 15
- Septal = 2, 3, 8, 9, and 14

Of note, segments 2 and 3 will be excluded for wall thickness and wall thickening analyses.

Scar transmurality will be defined as number of segments with > 0% non-viable tissue.

For each parameter, the observed value, absolute change from baseline, and percent change from baseline (except for scar transmurality) will be listed and summarized. Summary tables will include p-values for treatment group comparisons of changes from baseline. For the primary efficacy endpoint, p-values for the intersection hypothesis as well as the subgroup hypotheses (see Section 2.3.5) will be presented.

Details from the MRI procedure collected on the CRF will be listed.

9.2 6MWT

Observed, absolute change from baseline, and percent change from baseline in distance walked in the 6MWT will be listed and summarized. Summary tables will include p-values for treatment group comparisons of changes from baseline. Because of potential differences in 6MWT administration procedures across study sites, "site" will be carefully considered as a potential source of excess variation and will be included in the statistical model as a random effect if warranted. Details from the 6MWT collected on the CRF will be listed.

9.3 NYHA Class

Observed values of New York Heart Association (NYHA) class will be listed and the distribution of change from baseline will be summarized. The summary table will include p-values for treatment group comparisons of distribution.

9.4 Quality of Life

9.4.1 MLHFQ

The MLHFQ was designed to measure physical, emotional, social, and mental quality of life (QoL) dimensions. Subjects are asked to provide a score on a scale from 0 to 5 as to how much each of 21 facets prevented them from living as they desired (0 = "no," 5 = "very much"). The sum of the 21 scores reflects overall QoL. Although the MLHFQ was not designed to measure any particular dimension separately, two dimensions will be derived: Physical (sum of items 2-7, 12, 13) and Emotional (sum of items 17-21). All 21 items as well as the total score and scores for Physical and Emotional dimensions will be listed. Only the total score and Physical and Emotional dimension scores will be summarized. The summary table will include observed values and changes from baseline and p-values for treatment group comparisons of change from baseline.

Missing values for a given individual score will be imputed as the visit-specific worst observed score among all subjects in the given cohort/stratum if the missing value is in the CAP-1002 group and as the best observed score in the given cohort/stratum among all subjects if the missing value is in the placebo group.

9.4.2 SF-36 Health Survey (v1.0)

The Short Form 36 (SF-36) Health Survey consists of subject responses to 36 questions which are used to derive 8 summary scores, or "scales": physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. Therefore, while all 36 questions will be listed, only these 8 scales will be summarized. Summary tables will include observed values, changes from baseline and p-values for treatment group comparisons of change from baseline. The RAND scoring system will be used.[5] In this system, scores from individual questions are averaged to derive scores for the 8 scales; therefore, missing responses to individual questions are ignored.

9.4.3 WPAI:SPH Questionnaire

The Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SPH) questionnaire was designed to measure work and activity impairment due to the specific health problem (for this trial, heart condition) during the past seven days. The instrument yields four types of scores:

1. Absenteeism (work time missed) =

$$\frac{100 \times \#\ hours\ missed\ due\ to\ heart\ condition\ (Q2)}{Q2 + \#\ hours\ missed\ due\ to\ other\ reasons\ (Q3) + \#\ of\ hours\ actually\ worked\ (Q4)}$$

2. Presenteeism (impairment at work / reduced on-the-job effectiveness) =

$$\frac{100 \times how\ much\ did\ your\ heart\ condition\ affect\ your\ productivity\ while\ working\ (Q5)}{10}$$

3. Work productivity loss (overall work impairment / absenteeism plus presenteeism) =

$$100\ x\ (Absenteeism + (1 - Absenteeism)\ \text{x}\ Presenteeism)$$

4. Activity Impairment =

$$\frac{100 \times how\ much\ did\ your\ heart\ condition\ affect\ your\ ability\ to\ do\ regular\ daily\ activities\ (Q6)}{10}$$

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The first 3 summary scores are calculated only for those currently employed.

Each of the 6 WPAI questions will be listed, but only the 4 summary scores detailed above will be summarized. Summary tables will include observed values, changes from baseline and p-values for treatment group comparisons of change from baseline.

9.4.4 PGA

PGA consists of a single question, “Considering all the ways that your heart condition affects you, what is your assessment of how much your heart condition is impacting your life today?” Possible responses are “no impact,” “mild impact,” “moderate impact,” and “severe impact.” PGA will be listed and summarized. The summary table will include p-values for treatment group comparison of improvement or no change from baseline vs. worsening from baseline, analyzed using generalized estimating equations with the sandwich variance estimator for correlated (longitudinal) data.

9.5 NT-proBNP

Observed, absolute change from baseline, and percent change from baseline in NT-proBNP will be listed and summarized. Summary tables will include p-values for treatment group comparisons of changes from baseline.

10. SAFETY ANALYSES

Safety parameters will be listed and summarized for the primary safety population. The primary analysis of primary and secondary safety endpoints will be done using the primary safety population. Secondary analyses may be done using the other analysis populations defined in Section 6 or in subgroups defined in Section 7.4. Safety parameters are described below.

10.1 Primary Safety Endpoint

The primary safety endpoint is a composite indicator variable, as described in Section 2.3.1. The primary safety endpoint listing will include indicators for each component of the endpoint and for the endpoint itself; similarly, each component and the endpoint itself will be summarized as frequency and percentage of subjects, 90% CIs for both treatment groups, a 90% CI for the difference in proportions between treatment groups, and the p-value from an equivalence Wald test of H_o.

Since the primary safety endpoint is based on events that occur immediately after IP infusion and safety analyses are done only in subjects who were infused, handling of missing data is not applicable.

10.2 Secondary Safety Endpoints

The secondary safety endpoints include clinical events, as described in Section 2.3.3. The secondary safety endpoint listing will include indicators for each event, study day of the event, and total days of follow-up. Each endpoint will be summarized as frequency of subjects who experienced the endpoint and event rate per 100 subject-years. The summary table of the clinical event endpoints will also include a p-value for the comparison of event rate between treatment groups based on negative binomial regression with an offset for days of follow-up (log transformed). If the dispersion parameter is not significantly different from zero, Poisson regression will be used instead. Since the clinical event endpoints account for differential length of follow-up, handling of missing data is not applicable.

For the analysis of the secondary safety endpoint of development of increased HLA antibody levels to HLA antigens specific to the CAP-1002 CDC donor, incidence of increased HLA antibody levels, specific to the donor, will be summarized and analyzed; for placebo subjects, a random donor will be selected from those that were matched to the subject during screening. Elevated levels of DSA will also be summarized and analyzed by time point for all nominal time points at which samples were collected for DSA testing. Analyses will be performed using both 5000 and 1000 MFI as the threshold for defining increased HLA antibodies.

One secondary safety endpoint, new TIMI flow $\leq$ 1, would only occur intra-procedurally and will be analyzed using a chi square or Fisher's exact test instead of negative binomial or Poisson regression.

10.3 AEs

AEs reported from screening through EOS will be coded according to MedDRA® (Medical Dictionary for Regulatory Activities) version 18.1. Each reported AE will be mapped to a Preferred Term (PT) and a System Organ Class (SOC). A subset of AEs (indicated below) will be adjudicated by the independent CEC.

A TEAE will be defined as an AE that began or worsened after the time of vascular access. AEs with insufficient date or time information to determine whether or not they were treatment-emergent will be considered treatment-emergent and the ambiguity regarding start time/date for these AEs will be footnoted in summary tables.

All reported TEAEs will be listed. Separate listings will be done for deaths, non-treatment-emergent AEs and serious AEs (SAEs), treatment-emergent SAEs, TEAEs within 24 hours of IP administration (adjudicated if related to IP or procedure), and TEAEs that resulted in study discontinuation (excluding deaths). Treatment-emergent SAEs will be adjudicated. The listing of deaths will include most appropriate category of death (e.g., CV, cerebrovascular, infection, malignancy, trauma/accident) and whether or not an autopsy was performed.

Incidence and number of TEAEs will be summarized by SOC and PTs within SOCs, both overall and by relationship to IP, relationship to IP administration, and severity. Relationship status "possibly," "probably," or "definitely" will be considered related and will be adjudicated. Missing relationship will be considered related and missing severity will be considered severe; the lack of assigned relationships for these AEs will be footnoted in summary tables. Only the most related TEAE per subject for a given PT will be counted in summaries by relationship; similarly, only the most severe TEAE will be counted in summaries by severity. Separate summaries will be done for TEAEs within 24 hours of IP administration (adjudicated if related to IP or procedure), treatment-emergent SAEs, treatment-emergent deaths, and TEAEs resulting in study discontinuation (excluding deaths). Each summary table will include a p-value for the comparison of incidence for each SOC and PT, as well as overall, between treatment groups. Product limit estimates of median time to death and 95% CIs will be calculated.

10.4 Concomitant Medications

Both general and cardiac medication use from 30 days pre infusion through EOS will be coded to generic terms using the World Health Organization Drug Dictionary (WHO-DD) version 2015:1. Listings will include IP administration date, WHO-DD drug class, WHO-DD preferred drug name, generic/trade drug name, start and stop dates, dose, route, frequency, and indication. Frequencies and percentages of subjects reporting or receiving each medication will be summarized by WHO-DD drug class and preferred name within drug class. Any pre-infusion medications reported will be listed and summarized separately from concomitant medications. Medications that were stopped no later than the day before IP administration will be considered "pre-infusion." All other medications will be considered "concomitant." Medications recorded

with insufficient exposure dates to determine whether or not they were concomitant will be considered concomitant.

10.5 Laboratory Evaluations

Listings of laboratory evaluations will include study visit, date and time of collection, normal ranges, and observed values with out-of-range values flagged. Separate series of listings will show out-of-range observations.

Observed values and changes from baseline will be summarized by study visit. Separate series of summaries will show incidence of out-of-range observations by study visit. Shift tables will summarize shifts from one out-of-range category at baseline to another out-of-range category at each subsequent study visit and will include p-values for treatment group differences.

Because local laboratories will be used for this study, units for some parameters may not be consistent across all laboratories; therefore, laboratory observations will be converted to standard units, if necessary, for summaries. Appendix B lists all clinical laboratory evaluations that will be done for this study and the corresponding standard units (evaluations listed without units are unitless).

Listings and summaries will be done separately for each of the following laboratory evaluations or groups of evaluations:

- Serum chemistry
- Hematology
- Urinalysis
- Coagulation (infusion visit only)
- Cardiac biomarkers (troponin I or troponin T, NT-proBNP)
- DSA monitoring
- ELISpot in a subset of subjects

For ELISpot, Cellular Technology Limited (CTL) will provide assay results for cells from test antigen cardiac cell lines in fetal bovine serum (FBS) containing medium, cells in serum-free medium, each in triplicate, and the positive control [phytohemagglutinin (PHA)] in a single well. Let X = average spot number to the given antigen (cells and antigen), SD(X) = SD of the three values for the antigen, Y = average spot number in the FBS-medium control (cells and no antigen), and SD(Y) = SD of the three values for the FBS-medium control. Then, the antigen specific value is:

$$X - SD(X) - [Y + 2SD(Y)]$$

A positive antigen specific response is defined as an antigen specific value > 3.[7-9] All negative antigen specific values will be reported as 0 spot values since negative values are biologically irrelevant. The values of X, SD(X), Y, SD(Y), antigen specific value, and antigen specific response will also be provided by CTL.

10.6 CV Physical Examination

CV physical examination findings will be listed and summarized. Summaries will show the number of subjects with each condition and other condition-specific details, if applicable. Shifts from baseline in present/absent indicators will also be summarized, if appropriate.

10.7 Vital Signs, Height, Weight, and Body Mass Index (BMI)

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Listings of vital signs, height, weight, and BMI will include study visit, date and time of collection, and observed values. Observed values and changes from baseline will be summarized. BMI will be calculated as:

$$BMI = \frac{weight\ (kg)}{(height\ (m))^2}$$

using baseline height.

Prior to summarizing, unit standardization may be required and will be done as follows:

- Temperature recorded in degrees F will be converted to degrees C as C = 5(F-32)/9.
- Height recorded in inches will be converted to centimeters by multiplying by 2.54.
- Weight recorded in pounds will be converted to kilograms by multiplying by 0.454.

10.8 12-Lead ECG

Listings of 12-lead ECG parameters will include study visit, date and time of ECG, and observed values. Observed values and changes from baseline in ventricular rate and interval parameters (QRS, PR, QT, QTcB, QTcF) will be summarized.

Bazett's correction (QTcB) will be calculated as:

$$QTcB = QT/\sqrt{60/HR}\ ,$$

and Fridericia's correction (QTcF) as:

$$QTcF = QT/\sqrt[3]{60/HR}$$

where HR = ventricular rate.

Summaries of 12-lead ECG parameters will also include normal sinus rhythm indicator, specific rhythms, premature atrial contractions indicator, details of premature ventricular contractions and heart block and conduction abnormalities, and overall interpretation.

10.9 24-Hour Ambulatory ECG Monitoring

Listings of 24-hour ambulatory ECG parameters will include study visit, start and end dates and times, and observed values. Observed values and changes from baseline in heart rate (mean, minimum, maximum) number of premature atrial contractions over 24 hours, and number of premature ventricular contractions over 24 hours will be summarized. Summaries will also include indicators for sinus rhythm (normal sinus, sinus bradycardia, sinus tachycardia), atrial fibrillation, atrial flutter, junctional rhythm, heart block abnormalities, conduction defects, asystole, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, and overall interpretation. Other details regarding the presence of these events will be included in the listings.

10.10 Echocardiography

An echocardiogram will be performed at screening and Month 1 only. Echocardiography will be performed to measure the size and shape of the heart, its chambers and blood flow as well as valvular structure and function. Additionally, the echocardiogram will be used for detection of new abnormalities that may be indicative of myocarditis.

The following echocardiographic indices will be listed and summarized:

- LVEDV
- LVESV
- LV end diastolic diameter (LVEDD)
- LV end systolic diameter (LVESD)
- LVEF
- LV fractional shortening, calculated as 100 x (LVEDD-LVESD)/LVEDD.

11. OTHER DATA COLLECTED

11.1 Missed Visits and Assessments

A listing will be provided of missed visits and assessments.

11.2 Protocol Violations/Deviations

Protocol discrepancies will be classified as either violations or deviations. Per ICH E3 (Structure and Content of Clinical Study Reports),[2] violations will be defined as:

- Enrolling into the trial without meeting all inclusion/exclusion criteria and without obtaining a waiver for any deviations from the protocol-defined entry criteria;
- Continuing in the trial after developing a withdrawal criterion (see Protocol Section 7.5);
- Receiving an incorrect dose or incorrect treatment; or
- Taking a prohibited concomitant medication (see Protocol Section 5.4).

Subjects with protocol violations will be excluded from the per protocol population. All other protocol discrepancies will be considered deviations and will be categorized for purposes of

summarization. Some protocol deviations may prohibit subjects from being in the per protocol population; this will be determined before database lock.

In addition to the listings of inclusion/exclusion criteria detailed in Section 8.2 and missed visits and assessments detailed in Section 11.1, a separate listing will show all other protocol violations/deviations and will include protocol version, the category of the violation/deviation (to be determined), a description of the violation/deviation, and an indicator for per protocol exclusion (to be determined). Frequency and percentage of subjects by classification and category will be summarized.

12. CLINICAL EVENTS COMMITTEE

In order to apply some level of consistency and standardization, the following will be adjudicated by a CEC:

- Primary and secondary safety endpoints with the following exceptions:
  - The CEC will refer any potential case of acute myocarditis to the DSMB in order to make a final ruling on whether the clinical event meets the protocol-defined definition of acute myocarditis. The DSMB will be unblinded to humoral and cellular immunology data.
  - Development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor. The DSMB clinical immunologist will be unblinded to all available DSA data during the conduct of the trial.
- AEs occurring within 24 hours of IP administration.
- AEs judged by the investigator as possibly, probably or definitely related to the IP or IP administration procedure, reported at any time.
- Treatment-emergent SAEs.

The CEC will follow consensus definitions of CV endpoint events.[10] In the case where the protocol explicitly provides an endpoint definition, the CEC will adjudicate the clinical event according to the protocol definition and then, separately, according to the consensus definition. In the case where the protocol provides only a partial definition (e.g., “emergency room treatment for heart failure”) or is silent on the definition of the endpoint, the consensus definition, if it exists, will be used.

For safety endpoints, a hierarchy will be applied for a clinical event that could be adjudicated in multiple categories so that a clinical event is counted only once. The hierarchy, from highest severity to lowest, will be death > heart failure hospitalization > CV-related hospitalization. Any adjudicated event not otherwise named in the consensus definitions will be MedDRA-coded.

13. SEQUENCE OF PLANNED ANALYSES

13.1 Interim Safety Reviews

An independent DSMB appointed by the Sponsor, separate from the National Institutes of Health (NIH) DSMB used for ALLSTAR Phase 1, will oversee ALLSTAR Phase 2. Interim safety reviews will be conducted at intervals not to exceed 6 months apart. The DSMB will evaluate unblinded safety data in the form of TFLs and/or narratives.

Data on the following will be provided to the DSMB for review:

- Subject disposition
- Demographic and other baseline characteristics
- IP administration details
- Primary and secondary safety endpoints
- TEAEs and SAEs
- Safety laboratory evaluations
- Concomitant cardiac medications

13.2 Interim Analyses

13.2.1 DSMB Safety

Periodic safety reviews of the safety population will be overseen by the DSMB. Analyses of the primary safety endpoint will include tests of the one-sided hypothesis that the difference in rates between the CAP-1002 and placebo treatment groups is no greater than 20% (see Section 2.3.2). In addition, the proportion of subjects experiencing serious procedure-related outcomes (SPROs) will be monitored. A series of charts are provided in the protocol to assist with this oversight. These “stopping” guidelines will serve as a trigger for consultation with the DSMB for additional review and do not mandate automatic closure of study enrollment. Stopping will be at the discretion of the Sponsor, after consideration of DSMB recommendations.

13.2.2 Administrative Safety and Efficacy

An administrative interim safety and efficacy analyses will be performed when all subjects in the primary mITT population have completed the Month 6 visit or have discontinued from the study. An additional administrative interim analyses may be conducted on an as-needed basis. Results from interim efficacy analyses will be used for business planning activities and will have no effect on the conduct of Phase 2. As such, there will be no statistical penalty applied to the final efficacy analysis as a result of interim efficacy analyses.

13.3 Final Analysis

The final analysis will occur when all subjects have reached EOS (completed the Month 12 visit or discontinued), all clinical data have been entered into the data capture system, AE and concomitant medication data have been coded, quality control checks have been completed, all

data queries have been resolved, protocol violations/deviations have been identified, and the database has been locked.

14. DEVIATIONS FROM STATISTICAL METHODS IN THE PROTOCOL

None.

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APPENDIX A: SCHEDULE OF EVENTS

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

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

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

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

[4] On day of discharge.

[5] Urinalysis only.

[6] For subjects on anticoagulation therapy only.

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

[8] Non-postmenopausal females only.

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

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

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

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

APPENDIX B: LABORATORY EVALUATIONS

Hematology:
Hematocrit (Hct; %)
Hemoglobin (Hgb; g/dL)
Mean corpuscular hemoglobin (MCH; pg)
Mean corpuscular hemoglobin concentration (MCHC; g/dL)
Mean corpuscular volume (MCV; FL) Platelet count (K/μL)
Red blood cell (RBC) count (M/μL)
White blood cell (WBC) count with differential (K/μL)

Urinalysis:
Appearance
Bilirubin
Color
Glucose
Ketones
Microscopic examination of sediment
Nitrite
Occult blood
pH

Protein

Specific gravity
Urobilinogen

Serum beta human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)
Single antigen bead (SAB) assay , Human Leukocyte Antigen (HLA) and anti-HLA antibodies assays

ELISpot assay

Serum Chemistry:
Albumin (ALB; g/dL)
Aspartate aminotransferase (AST [SGOT]; U/L)
Alkaline phosphatase (ALK-P; U/L)
Alanine aminotransferase (ALT [SGPT];U/L)

Blood urea nitrogen (BUN; mg/dL)

Creatinine (mg/dL)
Creatine kinase and subtypes (Ng/ml)
Glucose (mg/dL)
Lactate dehydrogenase (LDH; U/L)
Potassium (K; mmol/L)
Sodium (Na; mmol/L)
Total bilirubin (mg/dL)
Direct bilirubin (mg/dL)
Total protein (G/dL)

Hemaglobin A1c (HbA1c;%) (screening only)

Troponin I (preferable) or Troponin T if Troponin I is not available (ng/ml)
N-terminal pro-hormone brain natriuretic peptide (NT-proBNP; pg/ml)

Coagulation: (Infusion Visit only - for patients taking Coumadin)
Activated partial thromboplastin time (PTT; sec)

International Normalized Ratio (INR)
Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus (HCV)
Human Immunodeficiency Virus (HIV)

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