Clinical Trial Protocol: CAP-1002-DMD-01 (HOPE)

Study Title:	A Randomized, Open-label Study of the Safety and Efficacy of Multi-Vessel Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with Cardiomyopathy Secondary to Duchenne Muscular Dystrophy [HOPE-Duchenne (Halt cardiomyOPathy progrEssion in Duchenne)]
Study Number:	CAP-1002-DMD-01
Study Phase:	Phase II
Product Name:	CAP-1002 Allogeneic Cardiosphere-Derived Cells
IND Number:	CCI
Indication:	Cardiomyopathy in DMD
Investigators:	Multicenter Study Principal Investigator: PPD, MD, MPH
Sponsor:	Capricor, Inc. 8840 Wilshire Blvd. 2nd floor Beverly Hills, CA 90211
Sponsor Contact & Medical Monitor:	PPD, MD PPD, Capricor, Inc. PPD PPD

Original Protocol:	01 May 2015
Amendment 1.0:	27 January 2016
Amendment 2.0:	29 February 2016
Amendment 3.0:	18 July 2016

SYNOPSIS

Sponsor:

Capricor, Inc.

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

Name of Active Ingredient:

Cardiosphere-Derived Cells

Study Title:
A Randomized, Open-label Study of the Safety and Efficacy of Multi-Vessel Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with Cardiomyopathy Secondary to Duchenne Muscular Dystrophy [**HOPE-Duchenne** (**Halt** cardiomyOPathy progrEssion in **Duchenne**)]

Study Number:
CAP-1002-DMD-01

Study Phase: Phase II

Primary Objective(s):
To assess the safety and tolerability of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to Duchenne muscular dystrophy (DMD).

Secondary Objective(s):
To assess efficacy of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to DMD by stabilizing or improving cardiac structure, by evaluating functional status, and by assessment of quality of life.

Study Design:
Male subjects at least 12 years of age, with cardiomyopathy secondary to DMD, and meeting all inclusion and no exclusion criteria, will be randomized. Each subject that meets all eligibility criteria will be randomized in a 1:1 manner to either investigational product (CAP-1002) or usual care.

If randomized to investigational product, a subject will receive an intracoronary infusion of CAP-1002 (intended total dose of 75 million [75M] cells) in three coronary arteries supplying the three major cardiac territories of the left ventricle of the heart (anterior, lateral, inferior/posterior). All three major cardiac territories will be treated (infused) during a single procedure in an open-label fashion.

Subjects randomized to receive usual care will not receive an infusion. They will continue to be cared for and treated in whatever manner the investigator deems most appropriate for the subject on an ongoing basis, except that usual care cannot include treatment with CAP-1002 or other investigational treatments.

Approximately 24, and not more than 30, subjects will be randomized into the study in two sequential enrollment groups. Safety data from Group 1 will undergo a Data Safety Monitoring Board (DSMB) review prior to initiation of enrollment for Group 2.

The first 6-8 randomized subjects will comprise Group 1, and will include a minimum of 3 subjects completing intracoronary infusion with CAP-1002. The DSMB will conduct a review of interim safety data through 72 hours post -Day 0 for at least 3 infused subjects and for at least 6 subjects overall.

Enrollment of Group 2 will begin per DSMB recommendations following their review of the 72 hour safety data from Group 1. Group 2 will include approximately 18 subjects. Screening and randomization will continue until at total of 12 subjects are infused with CAP-1002 or 30 subjects are randomized into the study, whichever comes first.

CCI

Subject infusions will be staggered by at least three days to allow for detection of acute procedure-related complications should they occur. Additionally, subject infusions in Group 2 will not begin until at least two weeks after the final infusion occurs in Group 1, to allow for completion of the Group 1 safety data review through 72 hours post Day 0.

No screening procedures will take place until the subject is fully informed of the research and signs the informed consent or provides assent. Subjects 18 years of age or older must have the ability to provide informed consent and follow up with protocol procedures. Subjects at least 12 years of age but younger than 18 years of age must have the ability to provide assent

along with the subject's parent or guardian providing permission for study participation.

Randomization will take place within 30 days of the first screening procedure. After completion of the screening procedures, eligible subjects randomized to active treatment arm will receive CAP-1002 administered via intracoronary infusion on Day 0. Day 0 for eligible subjects randomized to the usual care arm will occur 7 days after the date of randomization. All randomized subjects will have study visits at Day 3, Weeks 2 and 6, and Months 3, 6 and 12 post Day 0. Key safety assessments such as sudden unexpected death, and other major adverse cardiac events (MACE), will be assessed for all subjects, with the exception of those only relevant to subjects assigned to the active treatment arm, such as new TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2 (persisting >3 minutes after termination of cell infusion).Since CAP-1002 is grown from donors unrelated to recipients, humoral and cellular immune responses will also be evaluated.

DSMB Oversight:

The Data and Safety Monitoring Board (DSMB) will meet per charter, at least semiannually to review available data, and will conduct an interim review of safety data for Group 1 subjects through 72 hours post-day 0. They will review both safety and efficacy data after all subjects have completed 6 months of follow-up.

Study Population and Rationale:

Approximately twenty-four (24), and not more than 30, male subjects at least 12 years of age, with cardiomyopathy secondary to DMD and left ventricular scar as assessed by late gadolinium enhancement (LGE) cardiac MRI in at least 4 segments, will be considered for enrollment in the study. This sample size is adequate to support an assessment of safety and tolerability of intracoronary infusion of CAP-1002 in this disease population, as well as an exploratory assessment of efficacy. Enrollment will continue until 12 subjects have completed infusion with CAP-1002 or 30 subjects have been randomized, whichever occurs first.

Cardiomyopathy is currently the leading cause of death in DMD patients (Spurney 2011, Passamano, Taglia et al. 2012), having recently supplanted respiratory causes as a result of treatment improvements for that aspect of the disease. Afflicted patients lack a functional dystrophin protein and experience progressive muscle weakness starting at an early age and ultimately an abbreviated lifespan. Given the global and progressive nature of the disease, rarely are these patients considered for heart transplant, use of mechanical cardiac assist devices is largely experimental (Ryan, Jefferies et al. 2014), and the effectiveness of the therapies in use or in development for DMD on the cardiac manifestations of the disease is generally a secondary consideration. CAP-1002 is intended to target the cardiomyopathy in DMD as opposed to the skeletal myopathy.

CCI [redacted]

CCI [redacted]

Inclusion Criteria:

Each subject must meet all of the following inclusion criteria to be randomized in the study:

1. Male subjects 18 years of age or older must be able to provide informed consent and follow up with protocol procedures. Male subjects at least 12 years of age but younger than 18 years of age must be able to provide assent with parent or guardian providing permission for study participation. Only male subjects will be randomized into this study.
2. Documented diagnosis of Duchenne Muscular Dystrophy by genetic mutation analysis.
3. Cardiomyopathy with left ventricular scar by LGE in at least 4 segments as assessed by contrast-enhanced MRI and EF >35% at the time of screening.
4. Use of evidence based medical-therapy in accordance with the "DMD Care Considerations Working Group" guidelines for the management of DMD (Bushby, Finkel et al. 2010a, Bushby, Finkel et al. 2010b), for at least three months prior to signing the consent form (or, providing assent) or documented contraindication or intolerance or patient preference.
5. Subjects must be taking systemic glucocorticoids for at least six months prior to screening.
6. Subjects must be 12 years of age or older at time of screening
7. Subjects must be appropriate candidates for cardiac catheterization and intracoronary infusion of CAP-1002, in the judgement of the site's interventional cardiologist.

Exclusion Criteria:

Subjects that meet any of the following exclusion criteria will not be permitted to enroll into the study:

1. Therapy with intravenous inotropic or vasoactive medications at the time of screening.
2. Inability to undergo cardiac catheterization and/or MRI without general anesthesia.
3. Immunologic incompatibility with all available Master Cell Banks (MCBs) by single-antigen bead (SAB) serum antibody profiling.
4. Planned or likely major surgery in the next 12 months after planned randomization.
5. Left Ventricular Assist Devices (LVAD) or those subjects actively in the process of acquiring a LVAD.
6. Contraindication to cardiac MRI.
7. Known hypersensitivity to contrast agents.
8. Estimated glomerular filtration rate (GFR) <60 mL/min, as calculated by the CKD-EPI cystatin C equation (Inker, Schmid et al. 2012).

9. Active infection not responsive to treatment.
10. Active systemic allergic reaction(s), connective tissue disease or autoimmune disorder(s).
11. History of cardiac tumor or cardiac tumor demonstrated on screening MRI.
12. History of previous stem cell therapy.
13. History of use of medications listed in Appendix 3 within 3 months prior to signing the ICF / Assent through completion of the study infusion.
14. Known moderate-to-severe aortic stenosis/insufficiency or severe mitral stenosis/regurgitation.
15. Current active alcohol or drug abuse.
16. Known history of Human Immunodeficiency Virus (HIV) infection.
17. Known history of chronic viral hepatitis.
18. Abnormal liver function (ALT/AST >10 times the upper reference range) and/or abnormal hematology (hematocrit <25%, WBC <3000 µl, platelets <100,000 µl) studies without a reversible, identifiable cause.
19. Known hypersensitivity to bovine products.
20. Known hypersensitivity to dimethyl sulfoxide (DMSO).
21. Uncontrolled diabetes (HbA1c >9.0).
22. Inability to comply with protocol-related procedures, including required study visits.
23. Any condition or other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for the study.
24. Currently receiving investigational treatment on another clinical study or expanded access protocol, including any of the following:
    - Received investigational intervention within 30 days prior to randomization
    - Treatment and/or an incomplete follow-up to treatment with any investigational cell based therapy within 6 months prior to randomization
    - Active participation in other research therapy for cardiovascular repair/regeneration

Test Product, Dose, and Mode of Administration:

CAP-1002 is an investigational product consisting of allogeneic cardiosphere-derived cells (CDCs). Each dose of CAP-1002 is supplied as a concentrated suspension of 25 million CDCs [redacted] In cases where a dose of 12.5 million CDCs is utilized, the half dose is administered in a half volume.

All subjects (Groups 1 and 2) assigned to the active treatment arm will receive a protocol-defined total dose of CAP-1002 cells infused to the left ventricle cardiac territories (anterior, lateral, inferior/posterior). A single maximum dose administration of 25M CAP-1002 cells or 12.5M CAP-1002 cells will be delivered with a TERUMO Finecross™ MG guiding catheter to each cardiac territory (intended total dose to all three territories is 75 M cells). Additionally, an intermediate wash solution is administered to each subject between boluses of CAP-1002.

Usual Care:

Subjects randomized to usual care will receive optimal medical therapy according to the treatment plan of their primary DMD doctor and site investigator, informed by the evidence based medical-therapy in accordance with the "DMD Care Considerations Working Group" guidelines for the management of DMD (Bushby, Finkel et al. 2010a, Bushby, Finkel et al. 2010b). Usual care should not include other investigational therapies until the Month 12 study visit is completed.

Duration of Follow-Up:

All randomized subjects will be followed out to one year post-Day 0. Annual follow-up phone calls will be conducted for an additional four years after this time for subjects that provide consent and/or assent. These annual follow-up phone calls will continue in concert with a subject's normal, annual clinical follow-up which may include annual cardiac MRI where clinically indicated.

Due to the small size of the trial population, continued participation for all subjects is crucial to data quality. Therefore, no subject will be assessed as "Lost to Follow-Up" unless the site has attempted to contact the subject (or parent/guardian) by phone (or email or other subject-preferred method of communication) on at least 3 different days, plus an attempt to contact the subject (or parent/guardian) by certified mail.

Efficacy Assessments:
The following will be evaluated as exploratory efficacy endpoints at six- and twelve-month follow-up visits:

1. Cardiac Structural: Absolute and relative change in parameters measured by cardiac MRI, including:
    a. Left ventricular EF (%);
    b. Left ventricular end-diastolic volume and end-systolic volume;
    c. Left ventricular stroke volume;
    d. Regional left ventricular function assessment;
    e. Left ventricular LGE expressed as a percent of left ventricular mass;
    f. Left ventricular LGE expressed in grams;
    g. Left ventricular viable mass expressed in grams;
    h. Left ventricular circumferential strain;
    i. Number of left ventricular segments with LGE.
2. Functional: Serial changes in Performance of Upper Limb (PUL) scale, spirometry, and 6-minute walk test (6MWT) when deemed appropriate by the Investigator.
3. Quality of Life: Change in PedsQL (Pediatric Quality of Life Inventory), including the cardiac module, and PODCI Adolescent Questionnaire.
4. Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3; for subjects providing consent/assent, additional samples for exploratory analyses will be collected, archived, and available for future testing.

Safety Assessments:
The study will monitor the proportion of subjects experiencing any of the following events during or post intracoronary infusion delivery. For comparison, these same events, as applicable, will be monitored in usual care subjects on or after Day 0, using 9:00 am on Day 0 as the reference time point:

1. New TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2, noted immediately following intracoronary infusion of CAP-1002 and persisting >3 min after cell infusion, despite intracoronary vasodilator administration.
2. Sudden unexpected death within 72 hours of intracoronary infusion 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.
3. Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002. Troponin and CK-MB will be obtained every 8 hours (±30 minutes) at minimum for 20-24 hours after CAP-1002 infusion.

The study will evaluate the following during the six and twelve month follow-up period:

1. 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.
2. Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations), emergency room treatment for heart failure (including outpatient infusion), left ventricular assist device or heart transplant.
3. Any hospitalization due to a cardiovascular cause.
4. Any inter-current cardiovascular illness which prolongs hospitalization.
5. Development of, or an increase in, the frequency of VT with duration of 30 seconds or longer ascertained by continuous cardiac rhythm monitoring.
6. Development of increased anti-Human Leukocyte Antigen (HLA) antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor at immunologically significant titers.
7. Peak change from baseline in troponin and CK-MB levels following CAP-1002 infusion.

Usual Care Subjects – CAP-1002 Access Post-Study:

If the available evidence suggests an appropriate risk/benefit profile for this product, Capricor may (with DSMB agreement) open an open-label extension protocol to make CAP-1002 available for Usual Care subjects after they complete the 12-month study assessment period.

Statistical Methods:

Randomization: A randomization allocation algorithm will be applied by subject so that the treatment allocation of CAP-1002:placebo is 1:1.

Analysis Populations:

- *Intent to Treat (ITT) Population*: All subjects randomized. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment (CAP-1002 or usual care) actually received.
- *Modified ITT (mITT) Population*: Subjects in the CAP-1002 treatment group who received the IP, and all subjects in the usual care treatment group who remain on study as of 9:00 am (subject's time zone) on Day 0. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment (CAP-1002 or usual care) actually received.
- *Per Protocol Population*: Subjects with no major protocol violations. The list of subjects with major protocol violations will be compiled prior to database lock.
- *Safety Population*: Subjects randomized to CAP-1002 treatment who received the IP, and all subjects in the usual care treatment group who remain on study as of 9:00 am (subject's time zone) on Day 0. Subjects will be summarized and analyzed per treatment

actually received, regardless of their randomization assignment.

Efficacy Analyses:

The primary analysis of efficacy will be performed for the mITT Population as defined above. Additional analyses will be defined in the Statistical Analysis Plan (SAP).

- Cardiac structural results will be summarized for the intervention and control groups for each visit at which they are performed. Absolute and relative changes compared to baseline will be summarized using descriptive statistics.
- Functional and mobility values will be summarized using descriptive statistics and changes from baseline will be compared between groups.
- Improvements in quality of life parameters will be listed and summarized using descriptive statistics and compared between groups.
- Biomarker results for Osteopontin, ST2, IL-10, and Galectin-3 will be listed and summarized using descriptive statistics.

Safety Analysis:

- The primary analysis of safety will be performed on the Safety Population as defined above. Additional analyses will be defined in the SAP.Safety and tolerability of intracoronary infusion of CAP-1002 will be evaluated by the occurrence of reduction in TIMI flow and major cardiac events, frequency and severity of adverse events, and by changes from baseline in laboratory assessments, vital signs, physical examination, and ECG.

Missing Data:

Handling of missing data will be detailed in the SAP.

Date of Original Approved Protocol: 01 May 2015

Date of Most Recent Protocol Amendment (if applicable): 29 February 2016

Prepared in: Microsoft Word 2010

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

6MWT	6-Minute Walk Test
µl	Microliter
ADC	Adipose-Derived Cell
AE	Adverse Event
AF	Assent Form
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (same as SGPT)
AMI	Acute Myocardial Infarction
AST	Aspartate aminotransferase (same as SGOT)
Atm	Atmospheres
BP	Blood Pressure
BMMNC	Bone Marrow Mononuclear Cell
BUN	Blood urea nitrogen
C	Celsius
CCU	Critical (or Coronary) Care Unit
CDC	Cardiosphere Derived Cell
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CK-MB	Creatine phosphokinase MB isoenzyme
CMV	Cytomegalovirus
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSC	Cardiac Stem Cell
CT	Computerized Tomography
DCM	Dilated Cardiomyopathy

DMD	Duchenne Muscular Dystrophy
DMSO	Dimethyl Sulfoxide
DSA	Donor-Specific Antibody
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDV	End-Diastolic Volume
EF	Ejection Fraction
ELISpot	Enzyme-Linked Immunosorbent Spot
ESR	Expedited Safety Report
ESV	End-Systolic Volume
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus
HF	Heart Failure
Hgb	Hemoglobin
HbA1c	Glycosylated Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Heart Rate
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-10	Interleukin 10
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
iPSCs	Induced pluripotent stem cells
IRB	Institutional Review Board
IS	Infarct Size
ITT	Intent-to-Treat (randomized population)
K	Potassium
Kg	Kilogram
LAD	Left Anterior Descending
LCX	Left Circumflex
LDH	Lactate dehydrogenase
LGE	Late gadolinium enhancement
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
M	Million
MACE	Major Adverse Cardiac Event
MCB	Master cell bank
Mcg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity

MI	Myocardial Infarction
Min	Minute
mL	Milliliter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
Mm	Millimeters
mmol	Millimole
MoA	Mechanism of Action
MOP	Manual of Procedures (??)
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
Na	Sodium
NCS	Not Clinically Significant
NHLBI	National Heart, Lung and Blood Institute
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
NYHA	New York Heart Association
OCR	Oxygen Consumption Rate
OTW	Over The Wire
P	Probability
PCI	Percutaneous Coronary Intervention
PedsQL	Pediatric Quality of Life Inventory
PGA	Patient Global Assessment
PODCI	Pediatric Outcomes Data Collection Instrument
PRA	Panel Reactive Antibodies
PSP	Patient Specific Probability
PTT	Activated Partial Thromboplastin Time
PUL	Performance of Upper Limb
QoL	Quality of Life
RBC	Red blood cell
RCA	Right Coronary Artery

RNA	Ribonucleic Acid
RR	Respiration Rate
SAB	Single-antigen bead
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SF-36	Short Form (health survey) - 36 questions
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPRO	Serious Procedure Related Outcome
ST2	Cardiac Stress Biomarker (IL-1 Receptor Family; binds IL-33)
TEAE	Treatment-Emergent Adverse Event
TIMI	Thrombolysis In Myocardial Infarction
TMPG	TIMI Myocardial Perfusion Grade
TnI	Troponin I
UA	Urinalysis
VF	Ventricular Fibrillation
VGEF	Vascular Endothelial Growth Factor
VT	Ventricular Tachycardia
WBC	White Blood Cell
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1 INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is a pediatric onset, genetic disease in which patients lack dystrophin, a protein critical for stabilizing muscle cell membranes. Affecting 1 in 3,500-5,500 male births, DMD accounts for 80% of all cases of muscular dystrophy. Patients experience progressive skeletal muscle weakness and loss of ambulation by age 15, eventual respiratory and cardiac failure, and an abbreviated lifespan averaging only three decades (Bushby, Finkel et al. 2010a, Bushby, Finkel et al. 2010b). With corticosteroids and non-invasive ventilation, heart failure has emerged as the main cause of death. Yet the overwhelming majority of clinical trials in DMD have focused on skeletal rather than cardiac muscle disease. Without any functional dystrophin protein, cardiomyocytes experience a disruption of membrane integrity, leading to an overload of intracellular calcium, leading to cardiomyocyte death. Cell death is accompanied by local inflammation which serves as a source of oxidative stress for the remaining cardiomyocytes (Shirokova and Niggli 2013). These foci of cell death are often experienced by patients as microinfarcts, and accompanied by chest pain and the release of cardiac enzymes, clinical hallmarks of MI. This amplifying process triggers progressive scar tissue deposition and leads eventually to heart failure. Improvements in the treatment of respiratory muscle disease have elevated the inevitable cardiomyopathy to the leading cause of death in DMD patients (Spurney 2011, Passamano, Taglia et al. 2012).

No specific therapies currently exist to treat DMD cardiomyopathy. Given the global and progressive nature of the disease, rarely are these patients considered for heart transplant, use of mechanical cardiac assist devices is largely experimental (Ryan, Jefferies et al. 2014), and the effectiveness of the therapies in use or in development for DMD on the cardiac manifestations of the disease is generally a secondary consideration. Standard of care corticosteroid use in DMD patients, aimed at prolonging ambulation, has been shown to delay the progression of heart disease when its use is initiated prior to the onset of cardiac dysfunction (Markham, Kinnett et al. 2008). However, definitive evidence for this and the optimal steroid dosing regimen are still under investigation (e.g. NCT01603407). The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers on top of steroids has become standard therapy for these patients once cardiac dysfunction has set in (Jefferies, Eidem et al. 2005, Allen, Flanigan et al. 2013). However, progressive decline of cardiac function still occurs in the face of what can be considered current maximal medical management (Hor, Mazur et al. 2011). Most novel DMD therapies have been advanced in development on the basis of skeletal muscle effects, and have a reduced or uncharacterized effect on cardiac muscle. Of the dozens of recently completed or active DMD clinical trials, very few have a primary cardiac endpoint.

CAP-1002 is an investigational product consisting of allogeneic cardiosphere-derived cells (CDCs). CCI

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The HOPE-Duchene Phase II study will be the first investigation of CAP-1002 in male subjects with cardiomyopathy secondary to DMD and the first trial of the product not conducted exclusively in adults. CCI [redacted]

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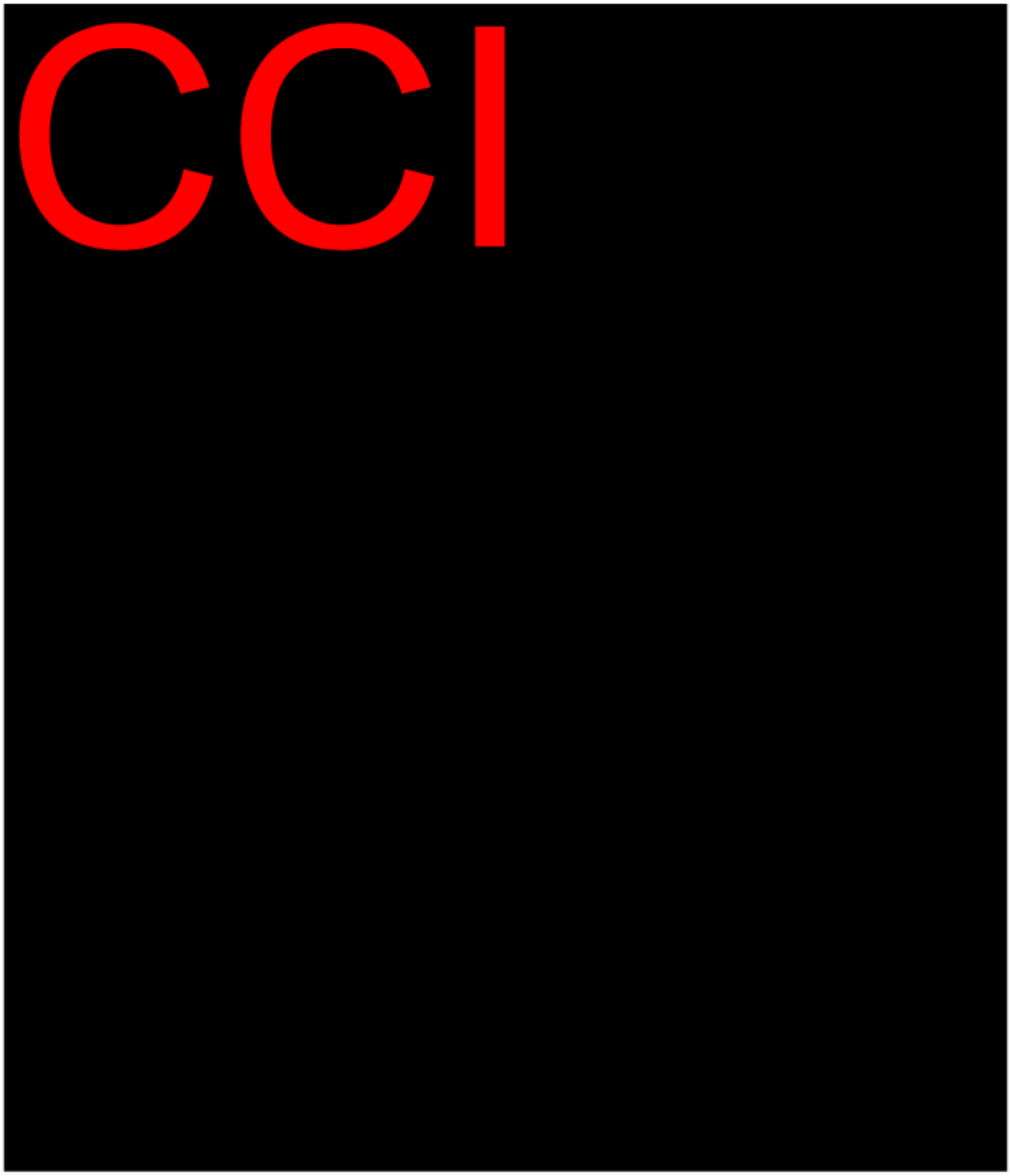
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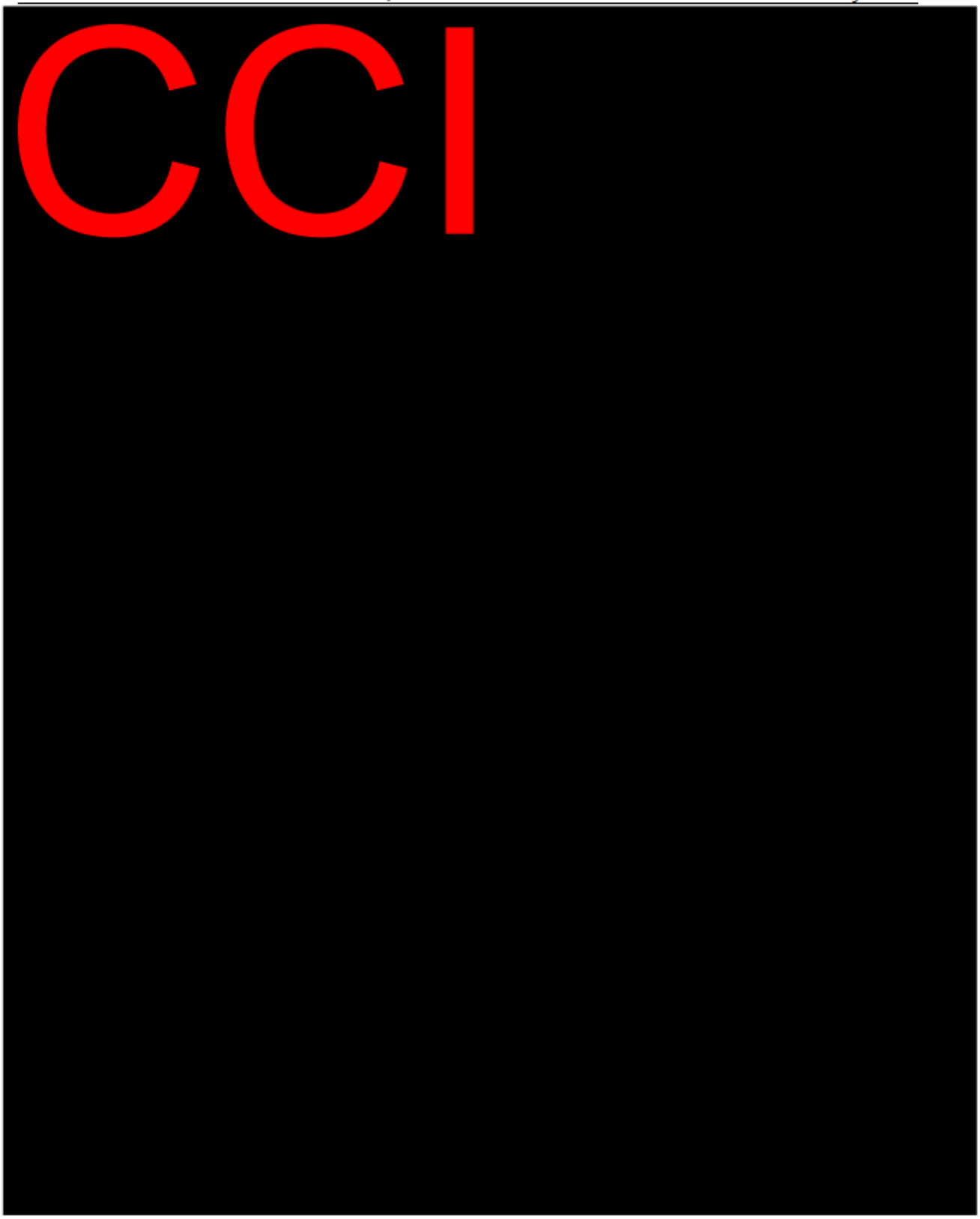
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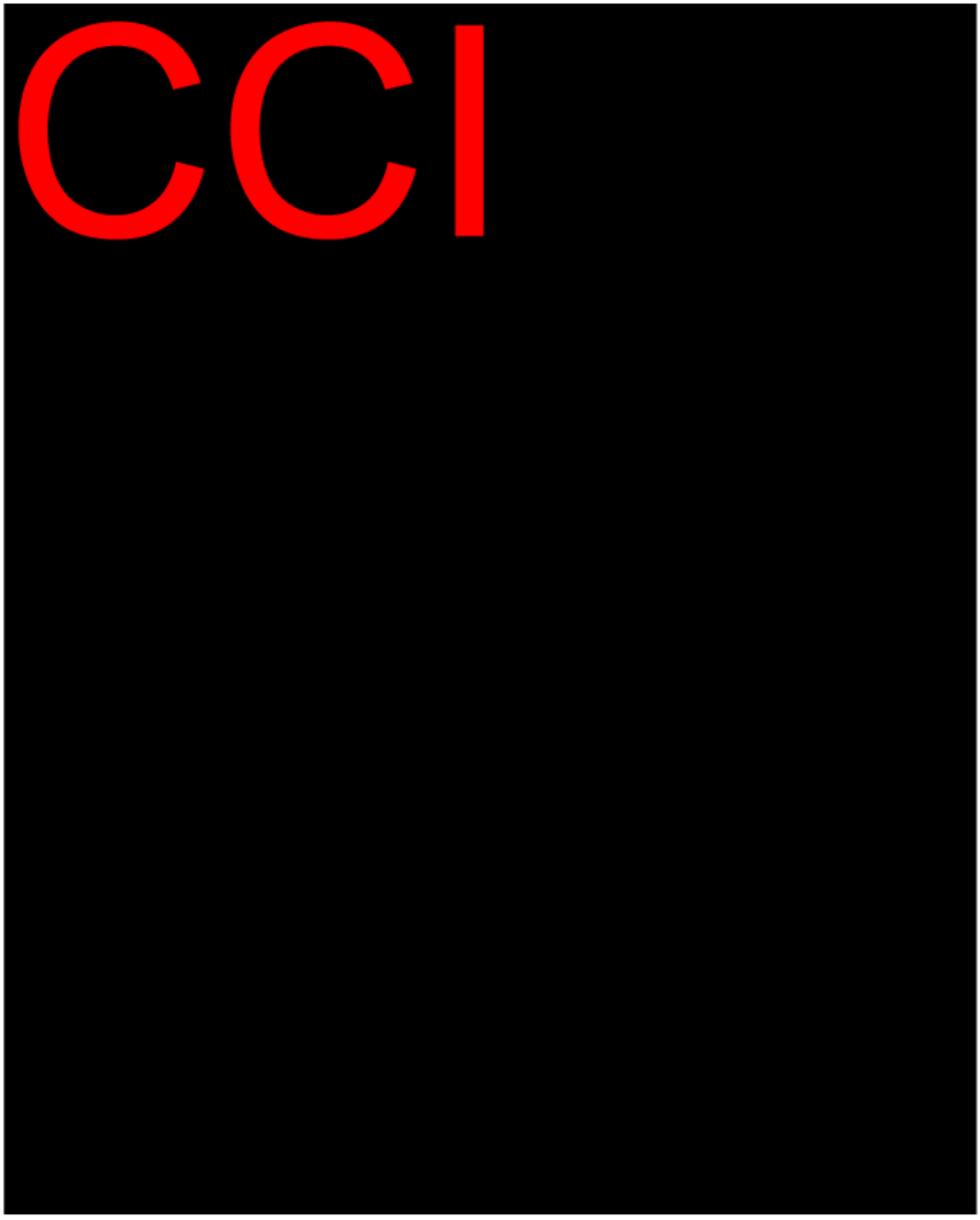
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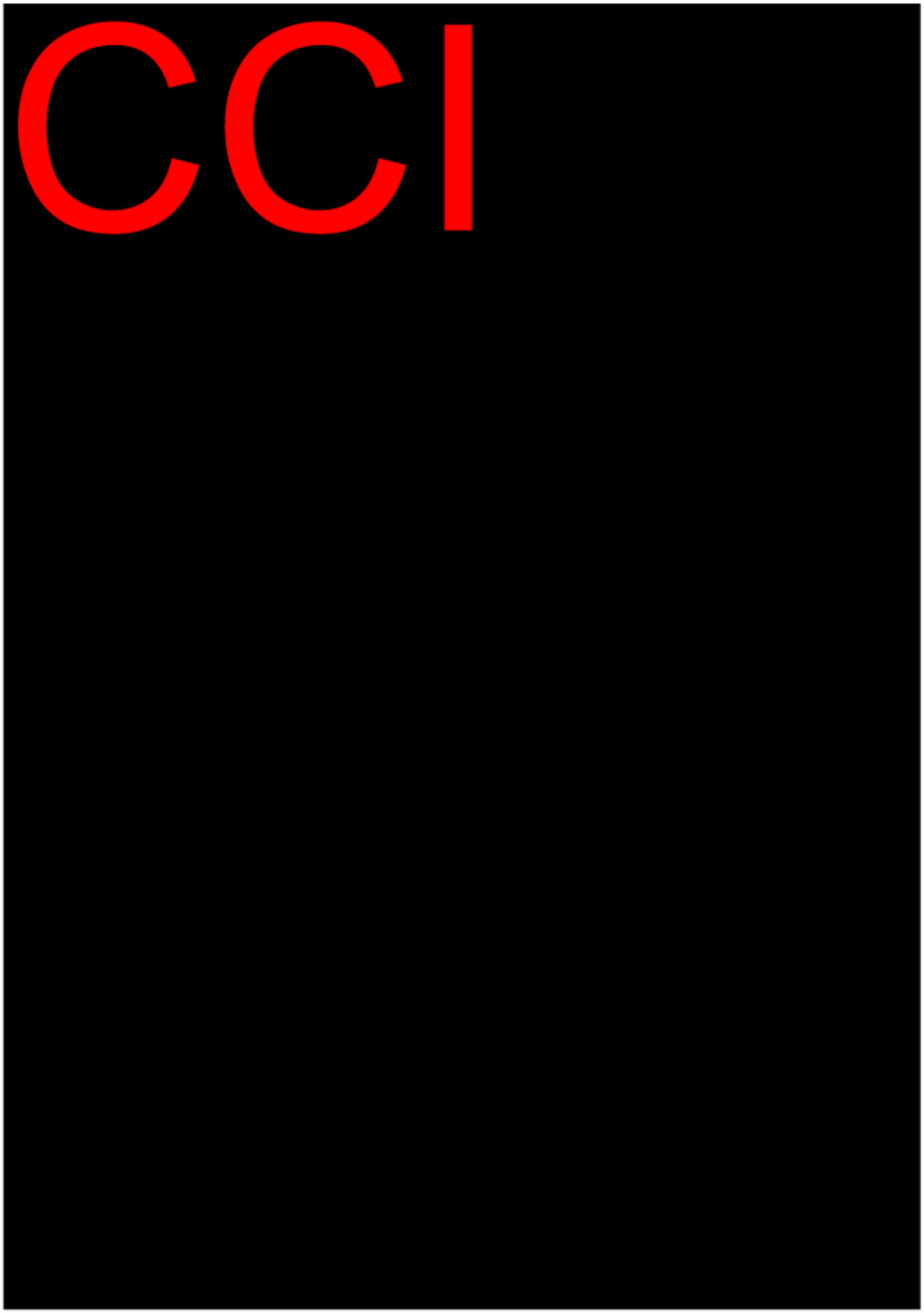
1.3 Information on CAP-1002

CAP-1002 CDCs are grown from donors unrelated to treatment recipients. Human Leukocyte Antigen (HLA) matching of the donors and the subjects will not be performed. Subjects will be assessed for anti-HLA antibodies at screening. Subjects who can be matched (in the sense that no DSAs are present to one or more donors) will be randomized into the study. Subjects who are mismatched against all available donors, because they harbor one or more anti-HLA antibodies against each donor, will be screen failures and not randomized into this study.

All randomized subjects will be monitored for development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 donor (i.e. DSAs).

CAP-1002 is administered as a dose of 25 million cells CCI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1.5 Study Population

Cardiomyopathy is currently the leading cause of death in DMD patients (Spurney 2011, Passamano, Taglia et al. 2012), having recently supplanted respiratory causes as a result of treatment improvements for that aspect of the disease. Afflicted patients lack a functional dystrophin protein and experience progressive muscle weakness starting at an early age and ultimately an abbreviated lifespan. Given the global and progressive nature of the disease, rarely are these patients considered for heart transplant, use of mechanical cardiac assist devices is largely experimental (Ryan, Jefferies et al. 2014), and the effectiveness of the therapies in use or in development for DMD on the cardiac manifestations of the disease is generally a secondary consideration. CAP-1002 is intended to target the cardiomyopathy in DMD as opposed to the skeletal myopathy.

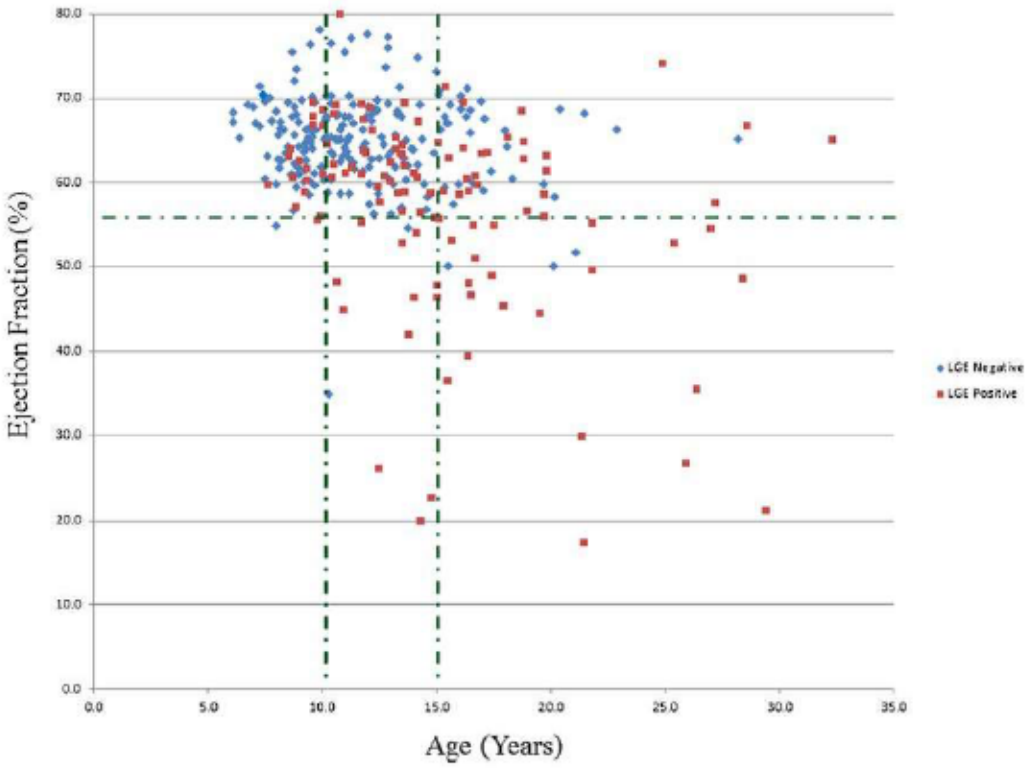
1.6 Cardiac Magnetic Resonance Imaging

MRI will be used to assess numerous efficacy endpoints in the HOPE-Duchenne study. Cardiac MRI is proving to have great prognostic and diagnostic value for DMD cardiomyopathy, and its use has revealed several hallmarks of the disease previously undetectable by standard echocardiography.

Circumferential strain (ε_{cc}), assessed via an MRI tagging protocol, has been shown to be abnormal in young DMD patients with still normal ejection fraction (EF) and no signs of myocardial fibrosis, and to worsen with age and alongside a decline in EF and the emergence of myocardial fibrosis (Hor, Wansapura et al. 2009). Furthermore, a recently completed trial of a mineralocorticoid receptor antagonist used in conjunction with maximal medical management showed that the worsening in ε_{cc} experienced by subjects with some degree of myocardial fibrosis pre-existing at baseline could be attenuated with intervention, and that improvements in ε_{cc} were accompanied by improvements in EF and preceded by reductions in the degree of myocardial fibrosis present (Raman, Hor et al. 2014).

Myocardial fibrosis, assessed as late gadolinium enhancement (LGE) on MRI and quantified either on the basis of segmental involvement or in absolute terms, has also been shown to be prevalent in DMD patients, to increase with age, and to correlate negatively with EF (Hor, Taylor et al. 2013). Data illustrating this relationship is shown in Figure 9.

Figure 9. Relationship between myocardial fibrosis, ejection fraction, and age in DMD patients



The LVEF of LGE negative (blue diamonds) and LGE positive (red square) patients are plotted against age demonstrating LGE was associated with older age and lower LVEF. From (Hor, Taylor et al. 2013).

1.7 Potential Risks and Benefits

Risks associated with administration of the study agent are primarily related to placing a guidewire down the coronary arteries in order to position the infusion catheter. The risk of coronary dissection is estimated to be less than 1% in this setting (Janssens, Dubois et al. 2006, Schachinger, Erbs et al. 2006, Assmus, Leistner et al. 2014) CCI [redacted]

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

CAP-1002 CDCs are grown from donated human myocardial tissue and CCI [redacted]

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Contrast dye is used for the angiography and MRI. There is a small risk of an allergic reaction causing rash, itching, hives or wheezing, but very rarely (0.07%) are reactions severe (Dillman, Ellis et al. 2007). Subjects will be assessed for any previous allergic reaction to contrast prior to procedures utilizing dye. Antihistamine and steroid may be used to pre-medicate subjects who have a history of sensitivity or allergy, according to the hospital's usual practice. There is also a small (5%) possibility of developing abnormal function of the kidneys (Katzberg and Newhouse 2010). This abnormal kidney function is usually temporary and less likely if there is no underlying kidney function abnormality. Additionally, the kidney abnormality is generally resolved by the natural elimination of the contrast dye from the subject's system. Creatinine clearance or GFR will be assessed prior to tests requiring contrast. Contrast solution and timing of the test may be adjusted in subjects with impairment of kidney function. Subjects will be closely monitored for any signs of allergic reaction or decrease in renal function as well as any other side effects.

2 STUDY OBJECTIVES

2.1 Safety Objective

The safety objective of the HOPE-Duchenne trial will be to investigate the safety and tolerability of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to Duchenne muscular dystrophy (DMD).

2.2 Efficacy Objective

The efficacy objective of the HOPE-Duchenne trial will be to investigate the efficacy of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to DMD by stabilizing or improving cardiac structure, by evaluating functional status, and by assessment of quality of life.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Male subjects with cardiomyopathy secondary to DMD meeting all inclusion and no exclusion criteria will be randomized. All subjects will be at least 12 years of age. They will be randomized in a 1:1 manner to either intracoronary infusion of CAP-1002 in three coronary arteries supplying the three major cardiac territories of the left ventricle of the heart (anterior, lateral, inferior/posterior) or usual care. In the active treatment arm, all three major cardiac territories will be treated (infused) during a single procedure in an open-label fashion.

Approximately 24, and not more than 30, subjects will be randomized into the study, in two sequential enrollment groups. Safety data from Group 1 will undergo a Data Safety Monitoring Board (DSMB) review prior to initiation of enrollment for Group 2.

The first 6-8 randomized subjects will comprise Group 1, and will include a minimum of 3 subjects completing intracoronary infusion with CAP-1002. The DSMB will conduct a review of interim safety data through 72 hours post-Day 0 for at least 3 infused subjects and for at least 6 subjects overall.

Enrollment of Group 2 will begin per DSMB recommendations following their review of the 72 hour safety data from Group 1. Group 2 will include approximately 18 subjects. Screening and randomization will continue until at total of 12 subjects are infused with CAP-1002 or 30 subjects are randomized into the study, whichever comes first.

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Subjects randomized to receive usual care will continue to be cared for and treated in whatever manner the investigator deems most appropriate for the subject on an ongoing basis, and will receive no infusion.

Subject infusions will be staggered by at least three days to allow for detection of acute procedure-related complications should they occur. Additionally, subject infusions in Group 2 will not begin until at least two weeks after the final infusion occurs in Group 1, to allow for the completion of the Group 1 safety data review through 72 hours post Day 0.

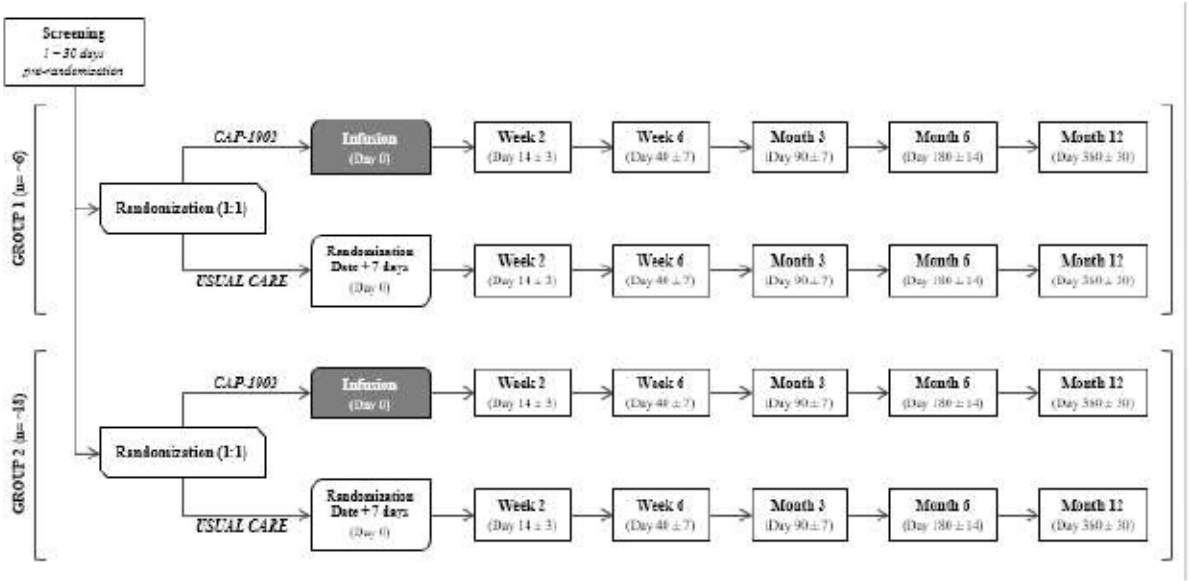
No screening procedures will take place until the subject is fully informed of the research and signs the informed consent or provides assent. Subjects 18 years of age or older must have the ability to provide informed consent and follow-up with protocol procedures. Subjects at least 12 years of age but younger than 18 years of age must have the ability to provide assent along with the subject's parent or guardian providing permission for study participation.

Randomization will take place within 30 days of the first screening procedure. After completion of the screening procedures, eligible subjects randomized to active treatment arm will receive CAP-1002 administered via intracoronary infusion on Day 0. Day 0 for eligible subjects randomized to the usual care arm will occur 7 days after the date of randomization, and a reference timepoint of 9:00 am on Day 0 will be used in place of infusion time. All randomized subjects will have a follow-up telephone call on Study Day 3, and study visits at Weeks 2 and 6, and at Months 3, 6 and 12 post Day 0. Key safety assessments such as sudden unexpected death, and other major adverse cardiac events (MACE), will be assessed for all subjects, with the exception of those only relevant to subjects assigned to the active treatment arm, such as new TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2 (persisting > 3 minutes after termination of cell infusion). Since CAP-1002 is allogeneic, humoral and cellular immune responses will also be evaluated.

The Data and Safety Monitoring Board (DSMB) will meet per charter, at least semiannually to review available data, and will conduct an interim review of safety data for Group 1 subjects through 72 hours post-day 0. They will review both safety and efficacy data after all subjects have completed 6 months of follow-up.

Figure 10 provides a schematic representation of the study design. Further details regarding specific study visits can be found in Appendix 1, Schedule of Events.

Figure 10. Schematic of the study design



3.2 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be evaluated at the six- and twelve-month follow-up visits. The exploratory efficacy endpoints include:

1. Cardiac Structural: Absolute and relative change in parameters measured by cardiac MRI, including:
    a. Left ventricular EF (%);
    b. Left ventricular end-diastolic volume and end-systolic volume;
    c. Left ventricular stroke volume;
    d. Regional left ventricular function assessment;
    e. Left ventricular LGE expressed as a percent of left ventricular mass;
    f. Left ventricular LGE expressed in grams;
    g. Left ventricular viable mass expressed in grams;
    h. Left ventricular circumferential strain;
    i. Number of left ventricular segments with LGE.
2. Functional: Serial changes in Performance of Upper Limb (PUL) scale, spirometry, and 6-minute walk test (6MWT) when deemed appropriate by the Investigator.

3. Quality of Life: Change in PedsQL (Pediatric Quality of Life Inventory), including the cardiac module, and PODCI Adolescent Questionnaire.

4. Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3; for subjects providing consent/assent, additional samples for exploratory analyses will be collected, archived, and available for future testing.

3.3 Safety Monitoring

The study will monitor the proportion of subjects experiencing any of the following events during or post intracoronary infusion delivery. For comparison, these same events will be monitored in usual care subjects using 9:00 am on Day 0 as the reference time point:

1. New TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2, noted immediately following intracoronary infusion of CAP-1002 and persisting >3 min after cell infusion, despite intracoronary vasodilator administration.

2. Sudden unexpected death within 72 hours of intracoronary infusion 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.

3. Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002. Troponin and CK-MB will be obtained every 8 hours (±30 minutes) at minimum for 20-24 hours after CAP-1002 infusion.

The study will evaluate the following during the six and twelve month follow-up period:

1. 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.

2. Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations), emergency room treatment for heart failure (including outpatient infusion), left ventricular assist device or heart transplant.

3. Any hospitalization due to a cardiovascular cause.

4. Any inter-current cardiovascular illness which prolongs hospitalization.

5. Development of, or an increase in the frequency of VT with duration of 30 seconds or longer ascertained by continuous cardiac rhythm monitoring.

6. Development of increased anti-Human Leukocyte Antigen (HLA) antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor at immunologically significant titers.

7. Peak change from baseline in troponin and CK-MB levels following CAP-1002 infusion.

3.4 Rationale for Study Design and Control Group

Male subjects with cardiomyopathy secondary to DMD are being recruited for this trial. DMD is an x-linked disease. Females only develop DMD when they are homozygous for the condition. This is so extremely rare that the chance of recruiting enough female subjects to this trial to make any safety conclusions makes the exclusion of females appropriate in this situation.

An open control group receiving usual care has been chosen for this study in order to have a clear comparator for safety efficacy. It was not felt reasonable to have control subjects undergo either multi-vessel placebo infusion or a sham procedure.

Cardiac involvement can start in childhood or adolescence and progress at a variable rate. While most adults with DMD have significant evidence of cardiac involvement, a significant proportion of adolescents have progressive significant cardiac involvement supporting the need to investigate the safety and effectiveness of this treatment in subjects at least 12 years of age.

3.5 Study Duration and Dates

No study-related procedures will be performed until a subject provides consent or assent along with parental or guardian permission. Afterwards, a single subject's participation is expected to last approximately thirteen months from the time of the first screening procedure. The study will require up to seven scheduled visits to the study site: Screening, Infusion, Weeks 2 and 6, and Months 3, 6, and 12. Annual follow-up phone calls will be conducted for an additional four years only if the subject provides separate consent or assent.

It is estimated that 12 months of accrual will be required to enroll the target sample size for this Phase II study.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately twenty-four (24) male subjects with cardiomyopathy secondary to DMD and left ventricular scar by late gadolinium enhancement (LGE) cardiac MRI in at least 4 segments will be considered for enrollment in the study.

4.2 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be randomized in the study:

1. Male subjects 18 years of age or older must be able to provide informed consent and follow up with protocol procedures. Male subjects at least 12 years of age but younger than 18 years of age must be able to provide assent with parent or guardian providing permission for study participation. Only male subjects will be randomized into this study.

2. Documented diagnosis of Duchenne Muscular Dystrophy by genetic mutation analysis.

3. Cardiomyopathy with left ventricular scar by LGE in at least 4 segments as assessed by contrast-enhanced MRI, and EF >35% at the time of screening.

4. Use of evidence based medical-therapy in accordance with the "DMD Care Considerations Working Group" guidelines for the management of DMD, for at least three months prior to signing the consent form (or, providing assent) or documented contraindication or intolerance or patient preference.

5. Subjects must be taking systemic glucocorticoids for at least six months prior to screening.

6. Subjects must be 12 years of age or older at screening.

7. Subjects must be appropriate candidates for cardiac catheterization and intracoronary infusion of CAP-1002, in the judgement of the site's interventional cardiologist.

4.3 Exclusion Criteria

Subjects that meet any of the following exclusion criteria will not be permitted to enroll into the study:

1. Therapy with intravenous inotropic or vasoactive medications at the time of screening.

2. Inability to undergo cardiac catheterization and/or MRI without general anesthesia.

3. Immunologic incompatibility with all available Master Cell Banks (MCBs) by single-antigen bead (SAB) serum antibody profiling.

4. Planned or likely major surgery in the next 12 months after planned randomization.

5. Left Ventricular Assist Devices (LVAD) or those subjects actively in the process of acquiring a LVAD.

6. Contraindication to cardiac MRI.

7. Known hypersensitivity to contrast agents.

8. Estimated glomerular filtration rate (GFR) <60 mL/min, as calculated by the CKD-EPI cystatin C equation (Inker, Schmid et al. 2012).

9. Active infection not responsive to treatment.

10. Active systemic allergic reaction(s), connective tissue disease or autoimmune disorder(s).

11. History of cardiac tumor or cardiac tumor demonstrated on screening MRI.

12. History of previous stem cell therapy.

13. History of use of medications listed in Appendix 3 within 3 months prior to signing the ICF / Assent through completion of the study infusion.

14. Known moderate-to-severe aortic stenosis/insufficiency or severe mitral stenosis/regurgitation.

15. Current active alcohol or drug abuse.

16. Known history of Human Immunodeficiency Virus (HIV) infection.

17. Known history of chronic viral hepatitis.

18. Abnormal liver function (ALT/AST >10 times the upper reference range) and/or abnormal hematology (hematocrit <25%, WBC <3000 µl, platelets <100,000 µl) studies without a reversible, identifiable cause.

19. Known hypersensitivity to bovine products.

20. Known hypersensitivity to dimethyl sulfoxide (DMSO).

21. Uncontrolled diabetes (HbA1c >9.0).

22. Inability to comply with protocol-related procedures, including required study visits.

23. Any condition or other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for the study.

24. Currently receiving investigational treatment on another clinical trial or expanded access protocol, including any of the following:
    - Received investigational intervention within 30 days prior to randomization
    - Treatment and/or an incomplete follow-up to treatment with any investigational cell based therapy within 6 months prior to randomization
    - Active participation in other research therapy for cardiovascular repair/regeneration

5 STUDY TREATMENT(S)

5.1 Investigational Product

CAP-1002 is an investigational product (IP) consisting of allogeneic cardiosphere-derived cells (CDCs). CCI [redacted]

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5.1.2 DSA Screening

CAP-1002 CDCs will be grown from donors unrelated to the recipients. All randomized subjects will be monitored during the course of the study for development of increased anti-human leukocyte antigen (HLA) antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor at immunologically significant titers (by solid phase immunoassay). While the HLA type of the recipient subject, donor and the CAP-1002 CDCs will be tested and known, primarily for product identification purposes, HLA matching of the donor and the recipient subjects will not be performed. Instead, subjects with measurable donor specific antibodies against (as measured by the SAB assay during screening) donor specific HLA in all available CAP-1002 master cell banks are excluded from the study.

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5.2 Usual Care

Usual care will include any appropriate treatment(s) per the investigator's discretion, except that usual care cannot include treatment with CAP-1002, other stem cell treatments, or other investigational therapies during the subject's 12 month study period.

Subjects randomized to usual care will receive optimal medical therapy according to the treatment plan of their primary DMD doctor and site investigator, informed by the evidence based medical-therapy in accordance with the "DMD Care Considerations Working Group" guidelines for the management of DMD (Bushby, Finkel et al. 2010a, Bushby, Finkel et al. 2010b).

5.2.1 CAP-1002 Access Post-Study

If the available evidence suggests an appropriate risk/benefit profile for this product, Capricor may (with DSMB agreement) open an open-label extension protocol to make CAP-1002 available for Usual Care subjects after they complete the 12-month study assessment period.

5.3 Randomization

Consented, eligible subjects will be randomized 1:1 to receive either CAP-1002 or usual care.

5.4 Concomitant Therapy

All medication therapies received from the time of signing consent will be collected (beginning with the Screening visit). Medications in use from initiation of the infusion procedure for active therapy subjects, or 9am on Day 0 for usual care subjects, are considered concomitant therapies. Concomitant therapies will be recorded at each study visit.

5.5 Prior Therapy Exclusions/Prohibited Medications

Subjects who have had any of the following prior therapies will not be eligible to participate in the study:

- Therapy with intravenous inotropic or vasoactive medications at the time of screening *(Exclusion Criterion 1)*
- Left Ventricular Assist Devices or actively in the process of acquiring a LVAD *(Exclusion Criterion 5)*
- Previous stem cell therapy *(Exclusion Criterion 12)*

Medications listed in Appendix 3 are prohibited within 3 months prior to signing the ICF / Assent through completion of the study infusion/Study Day 0. *(Exclusion Criteria 13)*

The following medications are prohibited from 30 days prior to randomization, through the Month 12/Early Termination study visit:

- Any stem cell therapies other than CAP-1002
- Any investigational treatments other than CAP-1002

5.6 Treatment Compliance

Treatment in HOPE-Duchenne is a one-time procedure. Therefore, continued compliance with the investigational product is not applicable. Study site personnel will document compliance with any concomitant medications and study follow-up procedures at each study visit.

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5.9 Investigational Product Retention at Study Site

Since product will be delivered as-needed on a per subject basis, there will be no product to retain at the site.

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects that are at least of 18 years of age must provide written consent prior to performing any study-related procedure. All subjects that are at least 12 years of age, but less than 18, must provide written assent along with parental or guardian written permission prior to performing any study-related procedure. An Informed Consent Form (ICF) will be provided to an adult subject for their consideration. An Assent Form (AF) will be provided to an adolescent subject and the subject's parent(s) or guardian(s) for their consideration. Each form will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the subject and subject's parent(s) or guardian(s), if applicable. The process of obtaining informed consent or assent will be in compliance with all federal regulations, International Conference on Harmonisation (ICH) requirements, and local laws.

The Investigator and/or designee must discuss the study with each subject and the subject's parent(s) or guardian(s), if applicable. The discussion will include the nature, scope, procedures, and possible consequences of the subject's participation in the study. The ICF/AF and discussion will be in a form understandable to the subject and the subject's parent(s) or guardian(s). The subject and subject's parent(s) or guardian(s) must be given adequate time to review the ICF/AF and ask questions regarding the IP, procedures, risks and other treatment. For subjects at least 18 years of age, an ICF must be signed and dated by the subject and the Investigator or designee before participation in the study. For subjects that are at least 12 years of age, but less than 18, an AF must be signed and dated by the subject, the subject's parent(s) or guardian(s), and the Investigator or designee before the subject can participate in the study. The subject will receive a copy of the signed and dated ICF, and the original will be retained in the site study files. The subject and parent(s) or guardian(s) will receive a copy of the signed and dated AF, and the original will be retained in the study site files. The Investigator or designee will emphasize to the subject and subject's parent(s) or guardian(s) that study participation is entirely voluntary and that consent and/or assent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Modifications to the study design, adjustments to the method of study conduct, or release of new safety information may occur during the course of the study that may require an amended ICF and/or AF. The amended ICF and/or AF will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the subject and subject's parent(s) or guardian(s). The site must use the amended ICF and/or AF for all new subjects. All ongoing subjects must repeat the consent and/or assent process with the Investigator or designee using the amended ICF and/or AF.

Ongoing subjects that mature to at least 18 years of age during the course of the study may be required to provide written informed consent (i.e., ICF) depending on the requirements of the reviewing IRB, as well as local regulations.

6.2 Medical History & Concomitant Medications

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

6.3 Cardiac and Limited Physical Examinations

A qualified physician, either the Investigator or Sub-Investigator, will perform a cardiovascular physical examination at each study visit.

A limited physical examination will be conducted at the screening visit and the 12 Month follow-up visit.

Weight and height will be collected at Screening, 6-month, and 12-month visits. Height alone will also be assessed at the 6-week and 3-month visits. If standing height cannot be measured, height will be calculated using a measurement of ulna length (Gauld et al 2004).

6.4 Vital Signs

Temperature, heart rate (seated), blood pressure (seated) and respiration rate will be recorded at each visit.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

Clinical laboratory tests will include those listed in 6.10.1 CAP-1002 Infusion, Appendix 1 (Schedule of Events), and Appendix 2 (Clinical Laboratory Tests). Subjects will be in a seated or supine position during blood collection.

6.5.2 Sample Collection, Storage, and Shipping

All clinical laboratory testing in this trial will be performed by central laboratory facilities, except those performed on Days 0 and 1 for subjects randomized to CAP-1002 only. All samples will be collected, processed, stored and shipped (as applicable) according to instructions in the Clinical Laboratory Manual for this trial.

For subjects randomized to CAP-1002, the clinical site should collect and process samples for the following tests in accordance with their institutional policies to appropriately monitor subject safety pre and post infusion:

Table 2. Local Laboratory Testing, Day 0 and Day 1 (CAP-1002 Arm Only)

Pre-Infusion	Post-Infusion
Troponin I	Troponin I *(serial collection)*
CK-MB	CK-MB *(serial collection)*
Serum Chemistry*	Serum Chemistry*
Hematology*	Hematology*
Urinalysis*	Urinalysis*
PTT & INR (if taking warfarin)	

*See Appendix 2 for details

Serum for the donor specific antibody (DSA) monitoring, HLA typing and blood for the ELISpot assay will be collected and processed at each site and then shipped to a central core laboratory for analysis within 24 hours of obtaining the specimens (See Laboratory Manual for shipping instructions). Subjects will be monitored for the development of a cellular immune response using the ELISpot (enzyme-linked immunosorbent spot) assay. The ELISpot assay will be performed at screening and at the Week 6 study visit.

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

For subjects who provide consent and/or assent, serum for clinical research into biomarkers will be collected at every scheduled visit (excluding infusion) and sent to the Sponsor, or designee, for storage and/or analysis (including and future analysis). Per the Code of Federal Regulations (21 CFR 320.38), serum samples collected from study subjects will be maintained in storage for at least five (5) years following the date on which the IND application or supplemental application is approved. If such application or supplemental application is not approved, serum samples will be maintained in storage for at least 5 years following the date of completion of the clinical research study.

6.6 12-Lead ECG

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

6.7 Continuous Cardiac Rhythm Monitoring

The sponsor will provide a wearable, wireless device for continuous cardiac rhythm monitoring. Subjects will wear a monitoring device for defined short-term intervals, starting at screening, on Day 1, and at the Week 6, Month 6, and Month 12 study visits. Table 3 details the continuous monitoring duration required at each study visit. The monitoring is

used to detect and record arrhythmias. All changes and any associated clinical significance will be evaluated and documented on the case report form.

Table 3. Per-Visit Minimum Continuous Cardiac Monitoring Durations

Study Visit	Minimum Continuous Monitoring Duration
Screening	24 hours
Day 1	72 hours
Week 6	72 hours
Month 6	7 days
Month 12	72 hours

6.8 Magnetic Resonance Imaging

All subjects will undergo contrast-enhanced MRI at screening and the Month 6 and 12 study visits (or, Early Termination Visit). It is anticipated that the duration of each MRI session will be 45-60 minutes. Acquisition parameters and techniques are specified in the MRI Imaging Manual. The site-based MRI technologists will be trained and certified in the common acquisition protocol prior to initiation of enrollment at each site.

6.8.1 Cine Imaging Protocol

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

6.8.2 Delayed Contrast-Enhancement Protocol

Subjects will undergo a standardized acquisition protocol including an intravenous injection of gadolinium contrast as defined in the MRI Imaging Manual consistent with institutional guidelines.

6.8.3 Image Analysis

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

6.8.4 Historical Cardiac MRI

If a subject has a historical cardiac MRI scan available prior to Screening date, the site should request that this historical cardiac MRI be sent to the imaging core lab for this trial, to potentially determine the rate of cardiac disease progression at the time of screening. If

multiple historical cMRIs are available, the most recent scan that occurred at least 6 weeks prior to screening should be transferred.

6.9 Clinical Function and Quality of Life Measures

At the screening, 6 Weeks, 3 Months, 6 Months, and 12 Months (or Early Termination) study visits, the subject will be asked to complete the Performance of Upper Limb (PUL) assessment and spirometry. Both the subject and the parent/guardian will be asked to complete the Pediatric Quality of Life Inventory (PedsQL) and the PODCI Adolescent Questionnaire (PODCI).

In addition, subjects assessed by the Investigator as capable of performing the Six Minute Walk Test (6MWT) will do so at screening, 6 Weeks, 3 Months, 6 Months, and 12 Months (or, Early Termination) study visits. Subjects unable to perform the Six Minute Walk Test at screening will not be required to perform the test at any subsequent visit.

6.10 Infusion Procedure

6.10.1 CAP-1002 Infusion

Every attempt should be made to infuse the three major cardiac territories of the left ventricle (anterior territory, lateral territory, and inferior/posterior territory). Additionally, the infusing Investigator may alter the infusion plan during the infusion procedure when deemed clinically necessary. The procedure will be performed as follows:

CCI

CCI

Following intracoronary infusion, subjects will be observed in the hospital for 20-24 hours with continuous cardiac (telemetry) monitoring. Troponin and CK-MB laboratory studies and vital signs (temperature, HR, BP, and RR) will be monitored every 8 hours (±30 minutes) from the end of the infusion. A total of three sets of cardiac enzymes will be evaluated to rule out cardiac injury during the post-infusion hospital stay through discharge. If the subject is discharged prior to 24 hours, cardiac enzymes will be drawn just prior to discharge.

Prior to discharge from the hospital, a physical assessment will be performed which will include chest pain assessment, review of laboratory results, 12-lead ECG, and arterial puncture site as well as assessment of adverse events. In the absence of serious adverse events, subjects will be discharged per standard of care practice.

6.10.2 Infusion Procedure Stopping Criteria

The operator will continuously monitor for the following Stopping Criteria. If any Stopping Criteria are met, the infusing Investigator must stop the infusion and assess for clinical significance. The infusing Investigator may continue with the infusion if, based on the infusing Investigator's medical judgement and clinical context, no additional risk is presented to the subject.

1. Development of TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2 persisting for >3 minutes after a cycle of infusion, despite administration of intracoronary vasodilators;
2. Sustained hypotension unresponsive to fluids and/or atropine/vasopressor administration;
3. Evidence of cerebrovascular accident;
4. Evidence of cardiac tamponade;
5. Hemopericardium requiring pericardiocentesis;

6. Sustained VT/VF that requires cardioversion/defibrillation or administration of an antiarrhythmic;
7. Evidence of thrombus in the aorta that was not previously seen;
8. Suspected or confirmed aortic dissection;
9. Suspected or confirmed coronary dissection;
10. Other evidence of acute myocardial infarction;
11. Acute onset of rigors (symptoms indicative of acute sensitivity or infection).

7 STUDY ACTIVITIES

Refer to Appendix 1 for the Schedule of Events for the conduct of this study.

7.1 Screening Visit

Written informed consent or assent must be obtained from the subject prior to performing any study-related tasks. Afterwards screening period for that subject will begin and the following screening procedures will be performed (not more than 30 days prior to randomization):

- Review of Inclusion / Exclusion Criteria (Section 4.2 and Section 4.3)
- Collection of demographic information
- Review of medical and cardiac history, and concomitant medications
- Measurement of vital signs (body temperature, HR, BP, and RR), weight and height
- 12-lead ECG
- 24-hour ECG via sponsor-provided continuous cardiac rhythm monitoring system
- Cardiac and limited physical examination
- Cardiac MRI
- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology, and serology (HbsAg, anti-HCV, anti-HIV 1/2), Cystatin C, Troponin and CK-MB
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: HLA, DSA, and ELISPOT
  - See 6.5 for additional information on clinical laboratory testing.
- A urine sample will be collected for urinalysis
- PUL Scale
- 6MWT (if capable)
- Pediatric QoL Inventory (PedsQL)
- PODCI
- Spirometry
- Adverse Event Assessment
- Submission of historical cardiac MRI

Subjects must continue to meet all of the inclusion and none of the exclusion criteria before proceeding to randomization. Subjects who do not proceed to randomization for any reason during screening will be withdrawn from the study as screen failures and will have no further follow up.

7.2 Randomization, Day 0, and Day 1

Subjects that continue to meet eligibility will be randomized (1:1) to either the active treatment arm (CAP-1002) or usual care arm.

For subjects that are randomized to the usual care arm, Day 0 will be defined as seven (7) days after the date of randomization. For subjects that are randomized to the active treatment arm, Day 0 will be defined as the date of the intracoronary infusion of CAP-1002.

For subjects randomized to CAP-1002 only, the infusion visit will include tests and assessments as described below and in accordance with the site's standard operating procedures.

Pre-Infusion:

- Eligibility Review
- Review of medical and cardiac history, and concomitant medications
- Cardiac physical examination
- Measurement of vital signs (temperature, HR, BP, and RR)
- 12-Lead ECG
- Venous blood will be collected for the following:
  - Clinical laboratory tests: chemistry, hematology
  - Coagulation if subject is taking warfarin
- Serial venous collection for cardiac enzymes (Troponin and CK-MB)
- A urine sample will be collected for urinalysis
- Adverse event assessment

Infusion

Reference Section 6.10 for complete infusion details

Post-infusion (D0-D1):

- Serial collection of vital signs (temperature, HR, BP, and RR) every 8 hours (± 30 minutes) from the end of the infusion.
- Cardiac Physical Examination
- 12-lead ECG
- Serial venous collection for cardiac enzymes (Troponin and CK-MB)
- Venous blood will be collected for clinical laboratory tests: chemistry, hematology, and urinalysis

Following intracoronary infusion, subjects will be observed in the hospital for 20-24 hours with continuous cardiac (telemetry) monitoring. Troponin and CK-MB laboratory studies will be monitored every 8 hours (±30 minutes) from the end of the infusion. A total of three

sets of cardiac enzymes will be evaluated to rule out cardiac injury during the post-infusion hospital stay through discharge. If the subject is discharged prior to 24 hours, cardiac enzymes will be drawn just prior to discharge.

Day 1 Prior to Hospital Discharge:

- Review of concomitant medications
- Adverse event assessment
- Physical assessment (chest pain, infusion/arterial puncture site(s))
- Review of lab results and 12-lead ECG

Prior to discharge from the hospital, a physical assessment will be performed which will include chest pain assessment, review of laboratory results, 12-lead ECG, and arterial puncture site as well as assessment of adverse events. In the absence of serious adverse events, subjects will be discharged per standard of care practice.

Day 1 for ALL SUBJECTS:

- Initiate 72-hour continuous cardiac rhythm monitoring using sponsor-supplied monitor system (indicated for home use)
- No study visit is required for Day 1, as subjects will receive prior instruction on use of the monitoring system

7.3 Day 3 Phone Visit

The investigator's site staff will contact the subject (or parent/guardian) by telephone on Study Day 3 (3 days post Day 0) for safety follow-up. Study Day 3 is 3 days post-infusion for subjects randomized to CAP-1002. For subjects randomized to usual care, Study Day 3 is ten days after randomization.

The site will inquire as to the subject's overall health and whether the subject has had any adverse events, especially any requiring hospitalization or other medical intervention, in the preceding 2 days (i.e., Day 1 – Day 3).

If necessary, the phone call may be conducted on Study Days 4, 5, or 6.

If the site is unable to reach the subject by telephone, the site should make two more attempts to contact the subject, one each on the next two days.

7.4 Week 2 Visit (Day 14 ± 3 days)

Subjects will return to the clinical site and complete the following procedures:

- Adverse event assessment
- Review of concomitant medications
- Measurement of vital signs (temperature, HR, BP, and RR)

- 12-Lead ECG
- Cardiac Physical Examination
- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology
  - Cardiac enzymes: Troponin and CK-MB
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: DSA
- A urine sample will be collected for urinalysis

7.5 Week 6 Visit (Day 40 ± 7 days)

Subjects will return to the clinical site and complete the following procedures:

- Adverse event assessment
- Review of concomitant medications
- Measurement of vital signs (temperature, HR, BP, and RR) and height
- 12-Lead ECG
- Cardiac Physical Examination
- 72-hour continuous cardiac rhythm monitoring using sponsor-supplied device
- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: DSA and ELISpot
- A urine sample will be collected for urinalysis
- PUL Scale
- 6MWT (if capable)
- Pediatric QL Inventory
- PODCI
- Spirometry

7.6 Month 3 Visit (Day 90 ± 7 days)

- Subjects will return to the clinical site and complete the following procedures:
- Adverse event assessment
- Review of concomitant medications
- Measurement of vital signs (temperature, HR, BP, and RR) and height
- 12-Lead ECG
- Cardiac Physical Examination

- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: DSA
- A urine sample will be collected for urinalysis
- PUL Scale
- 6MWT (if capable)
- Pediatric QL Inventory
- PODCI
- Spirometry

7.7 Month 6 Visit (Day 180 ± 14 days)

Subjects will return to the clinical site and complete the following procedures:

- Adverse event assessment
- Review of concomitant medications
- Measurement of vital signs (temperature, HR, BP, and RR), weight and height
- 12-Lead ECG
- Cardiac Physical Examination
- Cardiac MRI
  - Seven day continuous cardiac rhythm monitoring using sponsor-supplied device
- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology, and cystatin C
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: DSA
  - Cardiac enzymes: Troponin and CK-MB
- A urine sample will be collected for urinalysis
- PUL Scale
- 6MWT (if capable)
- Pediatric QL Inventory
- PODCI
- Spirometry

7.8 Month 12 Visit (Day 360 ± 30 days)

Subjects will return to the clinical site and complete the following procedures:

- Adverse event assessment
- Review of concomitant medications
- Measurement of vital signs (temperature, HR, BP, and RR),weight and height
- 12-Lead ECG
- Cardiac and limited physical examinations
- Cardiac MRI
- 72 hour continuous cardiac rhythm monitoring using sponsor-supplied device
- Venous blood will be collected for the following:
  - Clinical laboratory tests: serum chemistry, hematology, and cystatin C
  - Biomarkers: Osteopontin, ST2, IL-10, and Galectin-3
  - Exploratory biomarkers (if consent/assent provided)
  - Immunoassay: DSA
  - Cardiac enzymes: Troponin and CK-MB
- A urine sample will be collected for urinalysis
- PUL Scale
- 6MWT (if capable)
- Pediatric QL Inventory
- PODCI
- Spirometry

7.9 Annual Follow-up Phone Call

Following a subject's last site visit, annual follow-up phone calls will be conducted for an additional four years for subjects that provide consent and/or assent. Subjects will be contacted by phone annually (± 2 weeks) on the anniversary of their Day 0 through year 5 to assess for acute or planned procedure and/or admission for cardiac cause as well as survival. These annual follow-up phone calls will continue in concert with a subject's normal, annual clinical follow-up which may include annual cardiac MRI where clinically indicated.

7.10 Removal of Patients from the Trial or Study Drug

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

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

If a subject wishes to discontinue study participation solely for the purpose of enrolling in another clinical trial or expanded access protocol, the investigator should make every attempt to continue to collect follow-up medical information for the subject per this trial's schedule. This specific category of protocol violation (receipt of prohibited medications) will be managed as defined in the SAP.

7.11 Early Termination Procedures

Every reasonable effort will be made to retain subjects in the study. In the event that a subject must be withdrawn from the study early, study personnel should attempt to obtain testing and data required for the 12 Month Visit (see Section 7.8) as well as the reason for withdrawal, if known. A Cardiac MRI will be conducted provided the subject's most recent study-related Cardiac MRI was conducted at least three months (i.e., 12 weeks) prior to the Early Termination Visit.

If the subject permits, he or she should be contacted by study personnel at the time of their usual study visits (and annually through 5 years post-infusion), as described in the protocol.

7.12 Lost to Follow-Up

A subject can be considered "lost to follow-up" if he misses a visit and study personnel are unable to contact him, or parent(s)/guardian(s) as applicable, in a timely manner with a minimum of three documented phone calls. If contact with the subject, or parent(s)/guardian(s) as applicable, is not accomplished, study personnel should follow-up with certified mail in the following manner:

1. Mail a certified letter with return receipt requesting contact and expressing concern for the subject's well-being.

2. If the subject, or parent(s)/guardian(s) as applicable, does not respond within seven days, mail another certified letter with return receipt stating that the subject's participation in the study has been terminated.

3. If a signed mailing receipt for the second letter is returned, record the termination date as the date the subject, or parent(s)/guardian(s) as applicable, signed it. Otherwise, record the termination date as the date the second letter was mailed.

If, despite the efforts noted above, it is necessary to classify a subject as lost to follow-up, that subject's End of Study (EOS) is the date/time of last contact or known event (inclusive of study visits, telephone contacts, or other verification of subject survival or mortality).

7.13 Adverse Events Assessments

7.13.1 Performing Adverse Events Assessments

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

Examples of an AE include:

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

An AE does not include:

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

The Investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The Investigator will then record all relevant information regarding an AE/SAE into the data system. It is not acceptable for the Investigator to send photocopies of the subjects' medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when the Medical Monitor (an independent physician who is not participating in the clinical study), requests copies of medical records for certain cases. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the Medical Monitor.

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

7.13.2 Timing

Adverse event assessment and documentation will occur at every study visit from screening throughout the study. On the day of treatment administration, a subject's medical complaint will be considered to be a treatment-emergent adverse event if the event occurs any time after the first exposure of investigational product at the beginning of the catheterization for the infusion of CAP-1002. For subjects receiving usual care, an event is considered treatment-emergent if it occurs on or after 9:00 am (in the subject's time zone) on Day 0.

7.13.3 Severity

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

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

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

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in the Section 7.13.8 Serious Adverse Events.

7.13.4 Relationship

The Investigator is obligated to assess the relationship between study therapy and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the study agent, or the infusion procedure itself, was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study agent will be considered and investigated. The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

All AE/SAE that occur during the course of the clinical study will be evaluated. For each AE/SAE, the investigator will make a determination of relatedness to the investigational product and, separately, assess relatedness to the procedure. Each will be defined according to one of the following categories:

Definite: The AE/SAE is clearly related to the investigational product or procedure.

Probable: The AE/SAE is likely related to the investigational product or procedure.

Possible: The AE/SAE may be related to the investigational product or procedure. All AEs and SAEs that occur within 24 hours of intervention will, because of the temporal relationship, be considered as at least possibly related to the procedure and will be reported to the DSMB.

Unlikely: The AE/SAE is doubtfully related to the investigational product or procedure.

Unrelated: The AE/SAE is clearly NOT related to the investigational product or procedure.

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

7.13.5 Expectedness

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

- Some premature ventricular contractions, non-sustained ventricular tachycardia (<30 sec duration)
- Hypotension (Systolic Blood Pressure <80mmHg) and/or bradycardia (Heart Rate <50 beats/min) that responds rapidly to fluid, atropine and possibly vasopressor administration, if required
- Reduction of coronary blood flow, TIMI flow grade I or II, persisting <3 min after balloon deflation, during cell infusion
- Angina, duration <10 min during cell infusion
- ST elevations, duration <3min during cell infusion, troponin elevations above the 99th percentile but not more than 3x, at any time during the first 24 hours after cell infusion
- Dissection of one or more of the infused arteries
- Bleeding, bruising and/or hematoma formation at the site of vascular access for the cell infusion procedure, at any time within the first 24 hours after cell infusion

All adverse events expected or otherwise, should be reported in the subject data. Serious Adverse Events (SAEs) should be reported to the Sponsor within 24 hours of the site learning of the event.

7.13.6 Clinical Significance

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

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

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

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

7.13.7 Clinical Laboratory Adverse Events

Abnormal laboratory findings (e.g. clinical chemistry, hematology, and urinalysis) that are judged by the Investigator as clinically significant (CS) will be documented as described in Section 7.13.1 and will be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 7.13.1 or SAE, as defined in Section 7.13.8.

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

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

7.13.8 Serious Adverse Events

7.13.8.1 Definition

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

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

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.

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

7.13.8.2 Reporting Serious Adverse Events

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

To report the event, an SAE from must be completed and submitted to the data management group within the appropriate reporting timelines as further described in the study manual. Additionally, the Medical Monitor should be contacted and informed of the event, preferably by fax, as follows:

United BioSource Corporation
Phone: 1-800-829-6170
Fax: 1-877-200-2945
Email: CapricorSafety@unitedbiosource.com

The Medical Monitor will review all information provided and contact the Investigator for additional information, as necessary.

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

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

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

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

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

This protocol is being filed under an Investigational New Drug (IND) application with the FDA in the US as well as with other international regulatory agencies. A given SAE may qualify for an Expedited Safety Report (ESR) if the SAE is both attributable to study therapy and unexpected. In this case, all Investigators participating in the study will receive the ESR. The purpose of the ESR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

7.13.9 Sponsor Monitoring of Adverse Events

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

- All SAEs will be reviewed by the Sponsor's Medical Monitor or designee within 1 business day of receiving the serious adverse event form from the clinical center.
- If the Medical Monitor requires additional information to make his/her assessment, the clinical centers will have 2 business days to respond to the request for additional information.

7.13.10 Post-Study Adverse Events and Serious Adverse Events

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

8 QUALITY CONTROL AND ASSURANCE

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

A site initiation visit will be conducted at each site participating in the study. During this visit, there will be a review of the study protocol, study procedures, the case report forms, the data collection and submission process, and the site's regulatory obligations as well as any special procedures with the center personnel. A representative from the Sponsor, or designee, will lead the site initiation visits. All training will be documented. A formal, centralized investigator meeting may be held prior to initiation of the study, but will not remove the requirement for conducting a site initiation visit at each participating site.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Any changes made to the analysis of the data not stated in the protocol will be described in the Statistical Analysis Plan.

9.2 Determination of Sample Size

This sample size is adequate to support an assessment of safety and tolerability of intracoronary infusion of CAP-1002 in this disease population, as well as an exploratory assessment of efficacy.

9.3 Analysis Populations

- Intent to Treat (ITT) Population: All subjects randomized. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment (CAP-1002 or usual care) actually received.
- Modified ITT (mITT) Population: Subjects in the CAP-1002 treatment group who received the IP, and all subjects in the usual care treatment group who remain on study as of 9:00 am (subject's time zone) on Day 0. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment (CAP-1002 or usual care) actually received.
- Per Protocol Population: Subjects with no major protocol violations. The list of subjects with major protocol violations will be compiled prior to database lock.
- Safety Population: Subjects randomized to CAP-1002 treatment who received the IP, and all subjects in the usual care treatment group who remain on study as of 9:00 am (subject's time zone) on Day 0. Subjects will be summarized and analyzed per treatment actually received, regardless of their randomization assignment.

9.4 Efficacy Analysis

The primary analysis of efficacy will be performed for the mITT Population as defined above. Additional analyses will be defined in the SAP.

9.4.1 Cardiac MRI, Mobility, and Quality of Life Parameters

Cardiac structural results will be summarized for the intervention and control groups for each visit at which they are performed. Absolute and relative changes compared to baseline will be summarized using descriptive statistics.

Functional and mobility values will be summarized using descriptive statistics and changes from baseline will be compared between groups.

Improvements in quality of life parameters will be listed and summarized using descriptive statistics and compared between groups.

9.4.2 Biomarkers

Biomarker results for Osteopontin, ST2, IL-10, and Galectin-3 will be listed and summarized using descriptive statistics.

9.5 Safety Analysis

The primary analysis of safety will be performed on the Safety Population as defined above. Additional analyses will be defined in the SAP.

9.5.1 Safety Endpoints

Safety and tolerability of intracoronary infusion of CAP-1002 will be evaluated by the occurrence of reduction in TIMI flow and major cardiac events, frequency and severity of adverse events, and by changes from baseline in laboratory assessments, vital signs, physical examination, and ECG.

9.5.2 Adverse Events

Adverse events will be coded using the MedDRA dictionary and tabulated.

Treatment-emergent adverse events (TEAEs) are defined as any AE that started after the first exposure of investigational product or started prior to the first exposure but increased in severity or frequency after infusion. For those subjects randomized to usual care, TEAEs are defined as any adverse event beginning on or after 9:00 am (subject's time zone) on Day 0 or that increased in severity or frequency after that time. The incidence of TEAEs will be presented by system organ class and preferred term. Adverse events will also be summarized by severity and relationship to the investigational product and procedure.

The incidence of TEAEs leading to withdrawal from the study will be presented.

Listings of any serious adverse events (SAEs), deaths, and AEs or abnormal laboratory values leading to discontinuation of a subject from the study will be presented.

9.5.3 Laboratory Evaluations

Laboratory values at each collection time will be listed and summarized using descriptive statistics. Each post-treatment laboratory value will be compared to baseline (last value prior to starting treatment).

9.6 Missing Data

Handling of missing data will be detailed in the SAP.

9.7 Study Stopping Rules

The study will be halted if continuation represents an unacceptable risk/benefit profile for study subjects, as determined by the sponsor, the DSMB, or applicable regulatory authorities. Study stopping rules, finalized by consensus of the DSMB, are detailed in the DSMB Charter.

10 INDEPENDENT OVERSIGHT COMMITTEES

10.1 Clinical Events Committee (CEC)

The charge of the Clinical Events Committee (CEC) is to review source documents and to adjudicate (a) all primary and secondary safety endpoint events, (b) all serious, all protocol-defined, and intervention-related adverse events, the severity and relatedness of the adverse events, and (c) the causes of mortality events. The individuals who will serve on the committee are unaffiliated with the clinical site and the study drug manufacturer (Capricor, Inc.), and will be appointed by the Sponsor. The committee will consist of, at least, a heart failure cardiologist and interventional cardiologists. Additional experts in immunology will be consultants to the committee as necessary. The CEC will meet every 6 months or as needed to adjudicate adverse events and outcomes data for each subject randomized.

10.2 Data Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent DSMB will monitor results during the study. The board consists of physicians and biostatistician(s), who have no formal involvement or conflict of interest with the subjects, manufacturer (Capricor, Inc.), the investigators, or the clinical sites, and will be appointed by the sponsor. The DSMB will act in a senior advisory capacity to the sponsor regarding data and safety matters throughout the duration of the study. The board will meet on a periodic basis according to the DSMB charter to monitor the available information regarding safety, efficacy, and quality of trial conduct. As noted in Section 3.1, the DSMB will review the 72 hour safety data for Group 1, to determine whether enrollment for Group 2 may initiate. In addition, the DSMB will review interim summary results of the accumulating data from the Clinical Events Committee every 6 months. They will communicate their findings directly with the sponsor. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

A complete list of participating Investigators and institutions will be maintained by the Sponsor and will be posted at http:/www.clinicaltrials.gov in the listing for this study.

Should a question arise during the study from the Investigator or study staff, the staff may contact the Sponsor staff using the current study contact information as provided on http:/www.clinicaltrials.gov in the listing for this study.

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

Sponsor Medical Monitor:

PPD , MD
PPD , Capricor Inc.
PPD

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

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

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

11.2 Institutional Review Board (IRB) Approval

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

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

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

11.3 Ethical Conduct of the Study

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

11.4 Subject Information, Consent, and Assent

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

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

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

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

11.5 Subject Confidentiality

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

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

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

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

11.6 Study Monitoring

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

11.7 Case Report Forms and Study Records

All case report forms (CRF) will be completed in accordance with GCP guidelines and as soon as possible after each clinical trial visit. A data capture system will be utilized to record all of the protocol required information to be reported to the Sponsor on each trial subject. Study personnel from each site will be trained in how to access and use the data system to enter and transmit data for the study. Study personnel will be given a "sign in" and password unique to them which will not be used by any other personnel. Study personnel will be trained regarding proper correction of data entries in the data system.

Study personnel are responsible to ensure that all entries are accurate, legible and verifiable with the source data in the medical record. A source document is defined as the place in the medical record where a given data point first appears.

11.8 Protocol Violations/Deviations

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

11.9 Access to Source Documentation

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

11.10 Data Generation and Analysis

Contract research organizations (CROs) will provide data management and analysis and reporting services to the Sponsor. A validated data system proprietary to the CRO will be utilized to collect data and generate a database. Study sites will be responsible for entering data collected at the site. External data sources (i.e., central labs and core imaging center) are expected either to provide data sets for electronic upload into the database or enter the appropriate data directly into the system. Data queries will be generated by the data system, CRO data managers, and study monitors, then forwarded to the sites for resolution.
Retention of Data

11.11 Data Retention

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

11.12 Financial Disclosure

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

11.13 Publication, Use and Disclosure Policy

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

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Appendix 1 Schedule of Events

Procedure / Event	**Screening**	**Infusion (CAP-1002 only)[1]**		**Day 1 (Home)**	**Day 3 (Phone)**	**Week 2**	**Week 6**	**Month 3**	**Month 6**	**Month 12**	**Early Termination[2]**
Study Day	≤30 days prior to randomization	Day 0		Day 1[3]	Day 3 (+3)	Day 14 (±3)	Day 40 (±7)	Day 90 (±7)	Day 180 (±14)	Day 360 (±30)	As Needed
		PRE	*POST*								
Informed Consent	X										
Eligibility Assessment	X	X									
Demographics	X										
Medical History	X	X									
Cardiac History	X	X									
Concomitant Medications	X	X	X			X	X	X	X	X	X
Vital Signs	X	X	X			X	X	X	X	X	X
Weight	X								X	X	X
Height[4]	X						X	X	X	X	X
12-Lead ECG	X	X	X			X	X	X	X	X	X
Limited Physical Examination	X									X	X
Cardiac Physical Examination	X	X	X			X	X	X	X	X	X
Cardiac MRI	X								X	X	X
Continuous cardiac rhythm monitoring	X			X			X		X	X	X
Clinical Laboratory Tests (includes Chemistry, Hematology, Urinalysis)	X	X	X			X	X	X	X	X	X
Serology[5]	X										
Osteopontin	X					X	X	X	X	X	X
ST2	X					X	X	X	X	X	X
IL-10	X					X	X	X	X	X	X
Galectin-3	X					X	X	X	X	X	X
Exploratory Biomarkers	X					X	X	X	X	X	X

Procedure / Event	**Screening**	**Infusion (CAP-1002 only)[1]**		**Day 1 (Home)**	**Day 3 (Phone)**	**Week 2**	**Week 6**	**Month 3**	**Month 6**	**Month 12**	**Early Termination[2]**
Study Day	≤30 days prior to randomization	Day 0		Day 1[3]	Day 3 (+3)	Day 14 (±3)	Day 40 (±7)	Day 90 (±7)	Day 180 (±14)	Day 360 (±30)	As Needed
		PRE	*POST*								
HLA	X										
DSA	X					X	X	X	X	X	X
ELISpot	X						X				
PUL scale	X						X	X	X	X	X
6MWT	X						X	X	X	X	X
Pediatric QL Inventory	X						X	X	X	X	X
PODCI	X						X	X	X	X	X
Spirometry	X						X	X	X	X	X
Coagulation		X									
Serum Troponin & CK-MB	X	X	X			X			X	X	X
Intracoronary Infusion		X									
Adverse Event Assessment	X	X	X		X	X	X	X	X	X	X

[1] Day 0 is the infusion date for subjects randomized to CAP-1002. All items listed for Infusion visit and assessments on Day 0 are only applicable for subjects randomized to CAP-1002. Subjects randomized to Usual Care do not have a Day 0 visit.

[2] Early Termination Visit procedures to be completed at time of withdrawal, should subject be withdrawn before Month 12 Visit. . A Cardiac MRI will be conducted provided the subject's most recent study-related Cardiac MRI was conducted at least three months (i.e., 12 weeks) prior to the Early Termination Visit.

[3] For eligible subjects randomized to the usual care arm, Day 1 is established as 8 days after the date of randomization, without an actual Day 1 visit. All study subjects initiate 72-hour continuous cardiac rhythm monitoring on Day 1.

[4] If standing height cannot be measured, height will be calculated using a measurement of ulna length (Gauld et al 2004).

[5] Serology includes HIV and hepatitis testing

Appendix 2 Clinical Laboratory Tests

Clinical laboratory tests are to include the following. All subjects will have the same samples drawn and the same assessments performed at each study visit, except at D0 and D1 which are not study visits for subjects randomized to usual care.

Serum Chemistry

- ALT (SGPT)
- AST (SGOT)
- BUN
- Creatinine
- eGFR (CKD-EPI Cystatin C [2012])
- Glucose
- Lactate dehydrogenase (LDH)
- Sodium
- Potassium
- Chloride
- Bilirubin
- Albumin

Hematology

- WBC
- RBC
- Hemoglobin
- Hematocrit
- Platelet count
- WBC (total and differential counts)

Serology

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C Virus antibody (anti-HCV)
- Human Immunodeficiency Virus antibody (HIV)

Additional

- HbA1c
- Troponin I
- CK-MB
- Cystatin C

Urinalysis

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

Coagulation
Infusion Visit only for subjects taking warfarin

- PTT
- INR

Immunoassay Laboratories

- DSA
- HLA
- ELISpot

Biomarkers

- Galectin-3
- IL-10
- Osteopontin
- ST2
- Exploratory Biomarkers (*if consent/assent provided*)

All study specimens for this trial will be examined by central laboratory facilities, except as necessary on Day 0 and Day 1 for subjects undergoing infusion with CAP-1002.

Appendix 3 Prohibited Prior Medications

As they may interfere with the function of CDCs, the following medications are prohibited from three months prior to the screening visit, through Study Day 0

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

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

GENERIC NAME	TRADE NAME
Imatinib mesylate	Gleevac
Indinavir	Crixivan®
Infliximab	Remicade®
Interferon alfa-2a	Roferon-A®
Interferon alfa-2b	Intron-A®
Interferon alfacon-1)	Inferge ®
Interferon beta-1a	Avonex®
Interferon beta-1b	Betaseron®
Interferon beta-1b	Extavia®
Interferon beta-lb	Betaseron®
Interferon gamma-1b	Actimmune®
Interleukin-2	Proleukin
Irinotecan	Camptosar
Lamivudine	Epivir®
Lamivudine & Zidovudine	Combivir®
Lanreotide	Somatuline® Depot
Lapatinib	Tykerb®
Leflunomide	Arava®
Lenalidomide	Revlimid
Letrozole	Femara®
Leuprolide	Lupron®
Leuprolide	Eligard®
Lomustine	CeeNu® (CCNU)
Maraviroc	Selzentry
Mechlorethamine HCI	Mustargen®
Megestrol	Megace®
Melphalan	Alkeran®
Mercaptopurine	Purinethol®
Methotrexate	Rheumatrex®
Methotrexate	Trexall™
Mitomycin	Mutamycin®
Mitotane	Lysodren®
Mitoxantrone	Novantrone®
Muromonab-CD3	Orthoclone-OKT3
Mycophenolate	CellCept®
Nelfinavir	Viracept®
Nevirapine	Viramune®
Nilotinib	Tasigna®

GENERIC NAME	TRADE NAME
Octreotide acetate	Sandostatin®
Paclitaxel	Taxol®
Paclitaxel	Abraxane®
Pazopanib	Votrient®
Pegaspargase	Oncaspar®
Peginterferon alfa-2a	Pegasys®
Peginterferon alfa-2b	Peg-Intron®
Penicillamine	Cuprimine®
Procarbazine	Matulane®
Raltegravir	Isentress®
Ribavirin	Copegus®
Rilonacep	Arcalyst™
Ritonavir	Norvir®
Ritonavir/Lopinovir	Kaletra®
Rituximab	Rituxan®
Saquinavir	Invirase®
Sargramostim	Leukine®
Sirolimus	Rapamune®
Sorafenib	Nexavar®
Stavudine	Zerit®
Streptozocin	Zanosar®
Sulfasalazine	Azulfidine EN-tabs®
Sunitinib malate	Sutent®
Tacrolimus	Prograf®
Tamoxifen citrate	Nolvadex
Temozolomide	Temodar®
Temsirolimus injection	Torisel®
Teniposide	Vumon®
Tenofovir disoproxil fumarate	Viread®
Thalidomide	Thalomid®
Thioguanine	Tabloid®
Thiotepa	Thiotepa
Tipranavir	Aptivus®
Tocilizumab	Actemra®
Topotecan	Hycamtin®
Toremifene citrate	Fareston®
Trastuzumab	Herceptin®
Tretinoin	Vesanoid®

GENERIC NAME	TRADE NAME
Valrubicin	Valstar®
Vinblastine	Vinblastine
Vincristine	Vincristine
Vinorelbine	Navelbine®
Vorinostat	Zolinza®
Zalcitabine	Hivid®
Zidovudine	Retrovir®

Appendix 4 Amendment 3 Changes (Protocol Version 18 July 2016)

The following table presents a complete list of content changes in this protocol amendment. To avoid redundancy, the "sections affected" column does not list the protocol synopsis as an affected section.

Description of Change	Rationale/Justification	Sections Affected
Study Assessments		
"24-hour ambulatory ECG monitoring" is replaced by "continuous cardiac rhythm monitoring" for 7 days at Month 6, and for 72 hours at Day 1, Week 6, and Month 12.	The protocol already provided for non-invasive cardiac event monitoring at these time points as a key safety assessment. The duration for each of these monitoring assessments is being extended to provide additional information on the frequency and intensity of arrhythmias in DMD patients with cardiomyopathy.	Synopsis 3.3 Safety Monitoring 6.7 Portable ECG Monitor 7.1 Screening Visit 7.2 Randomization and Day 0 7.5 Week 6 Visit 7.7 Month 6 Visit 7.8 Month 12 Visit Appendix 1 Schedule of Events
"ambulatory ECG monitoring via Holter Monitor or ZIO® Patch" is replaced by "sponsor-supplied continuous cardiac rhythm monitoring".	Previously, the ambulatory ECG monitoring system was determined by the standard of care at the study site. With the decision to extend the duration of the cardiac monitoring assessments, the sponsor will provide monitoring devices to ensure consistency of assessments at all study sites.	
Clarifications/Corrections		
Events "Post-Infusion" are now divided to "Post-Infusion (D0-D1)" versus "Pre-Hospital Discharge (D1)"	This editorial change is made to clarify the separation of in-hospital ECG monitoring on Day 0 (for CAP-1002 patients only) versus 72-hour continuous cardiac rhythm monitoring on Day 1 (for all patients).	7.2 Randomization and Day 0
Total dose received is 62.5M cells, not 67.5M cells as stated previously, for special cases where infusion of 12.5M cells for that cardiac territory is warranted rather than the usual dose of 25M cells.	Correction to arithmetic error in prior versions of the protocol. In cases where the infusing Investigator deems that one of the three coronary arteries supplies less than 30% of the left ventricular myocardium, the infusing Investigator may choose to infuse only 12.5M cells into that coronary artery or arteries.	Synopsis 3.1 Overall Study Design and Plan 5.1.1 CAP-1002 Dosing Considerations

Description of Change	Rationale/Justification	Sections Affected
Text added to clarify the timing of serial collection of vital signs post-infusion.	Previously, Section 7.2 specified "Post-infusion: serial collection of vital signs (temp, HR, BP, RR)" but did not specify timing. Text now added to clarify as "every 8 hours +/- 30 minutes from the end of infusion", consistent with existing CRF completion guidelines and site training documents.	sections 6.10.1 CAP-1002 Infusion 7.2 Randomization and Day 0 Appendix 1 Schedule of Events

Appendix 5 Amendment 2 Changes (Protocol Version 29 February 2016)

The following table presents a complete list of content changes in this protocol amendment. To avoid redundancy, the "sections affected" column does not list the protocol synopsis as an affected section. For changes shown verbatim, **deleted text** is shown in ~~**strikethrough font**~~, and *new text* is shown in *red italicized font*.

Description of Change	Rationale/Justification	Sections Affected
Modifications to Eligibility and Early Termination Criteria		
Removal of inclusion criterion requiring subject body weight > 50 kg.	The original body weight criterion was an arbitrary threshold intended to exclude subjects too small to safely undergo cardiac catheterization. However, more appropriate criteria exist to provide meaningful predictors of safety, without excluding subjects who would be otherwise eligible for the trial.	Inclusion Criterion 6: 3.1 Overall Study Design and Plan 4.2 Inclusion Criteria
New inclusion criterion: *Subjects must be appropriate candidates for cardiac catheterization and intracoronary infusion of CAP-1002, in the judgement of the site's interventional cardiologist.*	This criterion is added as a more meaningful safeguard than the prior inclusion criterion of 50kg minimum body weight.	Inclusion Criterion 7: 3.1 Overall Study Design and Plan 4.2 Inclusion Criteria
Editorial clarification: A single, compound inclusion criterion (#4) is separated to two distinct items (#4 and #5), as shown at right:	4. Use of evidence based medical-therapy in accordance with the "DMD Care Considerations Working Group" guidelines for the management of DMD, for at least three months prior to signing the consent form (or, providing assent) or documented contraindication or intolerance or patient preference. ~~**Additionally,**~~ *5.* Subjects must be taking systemic glucocorticoids for at least six months prior to screening	Inclusion Criteria 4,5: 4.2 Inclusion Criteria
New Exclusion Criterion: *Currently receiving investigational treatment on another clinical trial or expanded access protocol.*	Treatment with other investigational agents would confound data from both trials.	Exclusion Criterion 24: 4.3 Exclusion Criteria

Description of Change	Rationale/Justification	Sections Affected
Modifications to Eligibility and Early Termination Criteria (continued)		
Clarification of Exclusion Criterion 8 as follows: Estimated glomerular filtration rate (GFR) <60 mL/min , *as calculated by the CKD-EPI cystatin C equation (Inker et al NEJM 2012)*.	Clarification to ensure consistent assessment for all subjects	Exclusion Criterion 8: 4.3 Exclusion Criteria Appendix 2 Clinical Laboratory Tests
Deleted statement: ~~Subjects randomized to CAP-1002 but not infused for any reason will be asked to complete the Early Termination Visit.~~	Randomized subjects will not be replaced. This is consistent with the analysis populations defined in this amendment and further detailed in the SAP.	3.1 Overall Study Design and Plan
Usual Care		
New section defining "usual care".	Protocol did not previously define treatment available to subjects randomized to receive usual care.	5.2 Usual Care
Stipulation that, if recommended by the DSMB, control subjects completing 12 months follow-up with usual care may be eligible to receive CAP-1002 in an open-label extension study.	Open-label access to CAP-1002 after individual subjects complete the 12-month assessment may encourage subject compliance, for the subjects randomized to usual care. This access would not impact the integrity of assessments for the primary and secondary study objectives, as all of these are based on observations collected within 12 months on study.	5.2 Usual Care
Concomitant/Prohibited Medications		
Other investigational therapies are now prohibited from 30 days pre-randomization through the Month 12 study visit.	This change is necessary to prevent confounding of trial data.	3.4 Rationale for Study Design and Control Group 5.2 Usual Care 5.5 Prior Therapy Exclusions/Prohibited Medications
Investigational treatments and stem cell therapies are newly listed as prohibited medications.	These medications are prohibited on study to avoid confounding study data.	5.2 Usual Care 5.5 Prior Therapy Exclusions/Prohibited Medications

Description of Change	Rationale/Justification	Sections Affected
Concomitant/Prohibited Medications (continued)		
Concomitant therapies redefined as those received on or after Day 0 (previously were tied to screening and/or informed consent).	Day 0 is first day of product exposure.	5.4 Concomitant Therapy
Note that subjects should not be removed from the trial solely for use of prohibited medications (including other investigational therapies). Analysis of data from subjects with this class of significant protocol violation will be managed as detailed in the SAP.	Study treatment in this trial consists of only a single infusion for subjects randomized to CAP-1002, and only usual care for other subjects. Treatment with prohibited medications (such as other investigational therapies) therefore is highly unlikely to present any special safety risk for the subjects, although it impacts the integrity of the study data. Given the seriousness of the disease state, however, some subjects may feel compelled to seek other investigational treatments. In such cases, it would be more useful to continue to follow these subjects than to receive no further data from them. Such continued follow-up should not entail any significant risk to study subjects.	7.10 Removal of Patients from the Trial or Study Drug
Statistical Analyses		
Efficacy analysis populations redefined as ITT, mITT, and Per-Protocol.	The new definitions are a better fit with ICH E9. New text also specifies that subjects will be analyzed for efficacy as randomized, regardless of actual treatment received.	9.3 Analysis Populations
Safety analysis population clarified (starting points for both study arms).	New text is better balanced between study groups (initiation of vascular access for subjects randomized to CAP-1002 infusion, versus 9:00 am on Day 7 for usual care subjects). New text also specifies that subjects will be analyzed for safety as actually treated, regardless of randomization.	9.3 Analysis Populations
Efficacy analysis plan outlined. Primary analysis of efficacy will utilize the mITT population.	This clarification is consistent with the intention as suggested in the prior versions of the protocol.	9.4 Efficacy Analysis

Description of Change	Rationale/Justification	Sections Affected
Statistical Analyses (continued)		
Safety analysis plan outlined. Primary analysis of efficacy will utilize the Product Safety population.	Safety analysis plan was not previously outlined in the protocol.	9.5 Safety Analysis
Handling of missing data will be detailed in the Statistical Analysis Plan (SAP). ~~**No imputations will be made for missing data.**~~	Imputations for missing data may be necessary.	9.6 Missing Data
This sample size is adequate to support an assessment of safety and tolerability of intracoronary infusion of CAP-1002 in this disease population, as well as an exploratory assessment of efficacy. ~~**Twenty four patients (randomized 1:1) will be evaluated as exploratory efficacy endpoints at six- and twelve-month follow-up visits.**~~	The former text did not discuss the sample size rationale in terms of the primary study objective (safety).	9.2 Determination of Sample Size
Redundant text removed from definitions of safety populations.	Previously, identical text was supplied in both sections 9.3.2 and 9.4.1.	9.3.2 Safety Population
TEAE definition initiates with product exposure (previously initiated with vascular access)	Clarification to match TEAE definition as present in section 9.5.2 (Adverse Events)	7.13.2 Timing
Study assessments		
Historical MRI data (6 to 15 months prior to screening), if available, will be collected and sent to the MRI core lab for assessment.	If available, this data will be used to potentially determine the rate of cardiac disease progression at the time of screening.	6.8.4 Historical Cardiac MRI 7.1 Screening Visit
Addition of Day 3 phone assessment	To assess AEs for both study arms between D0 and the Week 2 visit.	3.1 Overall Study Design and Plan 7.3 Day 3 Phone Visit Appendix 1 Schedule of Events

Description of Change	Rationale/Justification	Sections Affected
Study assessments (continued)		
All study assessments will be performed by central laboratories, except for local lab assessments as needed for subject safety on the day of and day after infusion with CAP-1002.	Central laboratory services are added to improve consistency of assessments between study sites. Local laboratory assessments on Day 0 and Day 1 for subjects receiving CAP-1002 are indicated to manage subject safety.	6.5.2 Sample Collection, Storage, and Shipping Appendix 2 Clinical Laboratory Tests
Assessment of height added (screening, 6 weeks, 3 months, 6 months, and 12 months). If standing height cannot be measured, height will be calculated using a measurement of ulna length (Gauld et al 2004)	Subjects as young as 12 years old may be eligible for this study. At this age, tracking of height is a standard component of routing physical examinations and may be informative regarding subject health. Height is added at every study visit where spirometry is measured.	6.3 Cardiac and Limited Physical Examinations 7.1 Screening Visit 7.5 Week 6 Visit (Day 40 ± 7 days) 7.6 Month 3 Visit (Day 90 ± 7 days) 7.7 Month 6 Visit (Day 180 ± 14 days) 7.8 Month 12 Visit (Day 360 ± 30 days) Appendix 1 Schedule of Events
Troponin and CK-MB will be obtained every 8 hours *(±30 minutes)* at minimum for 20-24 hours after CAP-1002 infusion.	This 30-minute window for each assessment is now specified in the protocol to allow some flexibility in the timing of specimen collections, while still providing appropriate follow-up for evidence of myocardial infarction injury post-infusion.	3.3 Safety Monitoring 6.10.1 CAP-1002 Infusion 7.2 Randomization, Day 0
Annual follow-up phone call tied to anniversary of Day 0 for both study arms.	Change implemented for parity between arms. Previously, follow-up call was tied to infusion date for CAP-1002 subjects, but to randomization for usual care subjects.	7.9 Annual Follow-up Phone Call
Urobilinogen removed from urinalysis assessments	This parameter not a component of the central laboratory's urinalysis assessment. Urobilinogen is unlikely to be affected by treatment with CAP-1002.	Appendix 2 Clinical Laboratory Tests

Description of Change	Rationale/Justification	Sections Affected
Study assessments (continued)		
Addition of clarifying text regarding which assessments are for both study arms versus assessments for CAP-1002 only, and which assessments are performed by central vs. local lab	Clarification to ensure that appropriate laboratory assessments are performed for usual care subjects, and that assessments are performed by the central laboratory for consistency.	Appendix 2 Clinical Laboratory Tests
Modified text regarding key safety assessments to be performed through the study for all subjects.	Clarification that key safety assessments will be performed for all subjects, with the exception of those post-infusion assessments relevant only to subjects receiving CAP-1002.	3.1 Overall Study Design and Plan
~~*Subjects will be evaluated overall, once all subjects enrolled in the study have reached the Week 6 visit.*~~ is replaced with text defining DSMB reviews for Group 1 (72-hour data) and for all subjects (6-month data).	This text is changed to be consistent with the safety review plan established by the DSMB, as defined in the current DSMB charter v1.0.	3.1 Overall Study Design and Plan
Clarification: A 24 hour ambulatory ECG monitor… will be performed at the screening visit *(all subjects)*, during the 24- hours following release (discharge) from the hospital *(for subjects receiving CAP-1002 infusion only)* and also *for all subjects* at the Week 6, Month 6, and Month 12 study visits.	Clarification that all subjects will receive this ECG monitoring at timepoints as previously indicated in Appendix 1 Schedule of Events – with the exception of post-infusion monitoring which is only for subjects receiving CAP-1002.	6.7 Continuous Cardiac Rhythm Monitor
Clarification that both the parent/guardian and the subject (not the subject alone) complete the QoL assessments	The PedsQL and the PODCI assessments are designed to be used for both the subject and the parent/guardian	6.9 Clinical Function and Quality of Life Measures
Clarification that the PI will separately assess relationship of the AE to the CAP-1002 product, and relationship to the infusion procedure.	Previously, AE reporting forms required assessment of AE relationship to the infusion procedure; however, this was not specified in the protocol.	7.13.4 Relationship
Clarifying information added regarding product description, reconstitution, and storage.	Text added to clarify handling of the product.	5.1 Investigational Product
Subheadings added to this section	Subheadings added to existing text in this section to separate distinct topics	5.1 Investigational Product

Description of Change	Rationale/Justification	Sections Affected
Other Clarifications and Minor Changes		
Clarification in cited sections that 9 am on Day 0 is defined, for usual care subjects, as the equivalent timepoint to the start of infusion for subjects receiving CAP-1002	A usual-care equivalent to the start of infusion time was established in Amendment 1 for parity between study arms, to the extent possible. These changes are corrections to clarify the implementation of the prior change.	3.1 Overall Study Design and Plan 7.13.2 Timing 7.2 Randomization, Day 0 9.5.2 Adverse Events
Clarification that for LTF subjects, End of Study date is date/time of last contact or known event. New subheading "Lost to Follow-Up" highlights this section.	Clarification as prior text did not specify assessment of "end of study" date for LTF subjects. New subheading is added to highlight prior text regarding management of subjects who may be lost to follow-up.	7.12 Lost to Follow-Up
CCI [redacted]	[redacted]	[redacted]
No subject has experienced a TEAE *classified as* ~~considered~~ related to CAP-1002 ~~but~~ *that was* not also *classified as related* to the catheterization *and infusion* procedure.	CCI [redacted]	1.2.3.2 Treatment Emergent Adverse Events (TEAEs)
CCI [redacted]	Editorial clarification	1.2.5.1 Efficacy Conclusions
p-value added to legend of Figure 7	The p-value was not previously listed	Figure 7
DSA = donor specific *antibody*, not donor-specific ~~antigen~~	Correction in this section only (this abbreviation and term previously were correct in other protocol sections, including the list of abbreviations)	CCI [redacted]
…techniques ~~will be protocolled~~ *are specified in the MRI Imaging Manual*.	Editorial clarification	6.8 Magnetic Resonance Imaging
"~~enrolled~~" changed to "*randomized*" in most instances pertaining to the HOPE trial	"randomized" is a more accurate and precise term than "enrolled" in the instances replaced	Multiple sections
Reference additions: Gauld et al 2004, Inker et al 2012	Gauld reference: height estimation per ulna; Inker reference: eGFR estimation	12 Reference List

Appendix 6 Amendment 1 Changes (Protocol Version 27 January 2016)

The following table presents a complete list of content changes in this protocol amendment. To avoid redundancy, the "sections affected" column does not list the protocol synopsis as an affected section. For changes shown verbatim, **deleted text** is shown in ~~strikethrough font~~, and *new text* is shown in *red italicized font*.

Description of Change	Rationale/Justification	Sections Affected
Clinical Data Updates: Other Trials with CAP-1002		
CCI [redacted]	Since the original protocol was issued, clinical experience with the product for treatment use has expanded. Additional safety and efficacy data from the ongoing trials support an improved risk/benefit profile for the product.	1.2 Summary of Clinical Data Figure 7
Modifications to Eligibility Criteria		
Age range eligible for randomization into Group 1 is expanded to include males 12+ years old.	CCI [redacted]	Inclusion Criterion 5: 3.1 Overall Study Design and Plan 4.2 Inclusion Criteria
MRI assessment at 6-15 months prior to screening no longer required; instead, eligibility assessment will utilize contrast-enhanced MRI at Screening	Historical MRI scan was previously required solely to assist in study stratification, but has been a barrier to study entry for subjects otherwise eligible. Given the small number of available subjects and the small study size, the utility of stratifying the population did not justify excluding subjects solely for absence of MRI history.	Inclusion Criterion 3: 4.2 Inclusion Criteria
Therapy with ~~chronic inotropes, or currently receiving~~ intravenous *inotropic or* vasoactive medications at the time of screening.	Editorial clarification	Exclusion criterion 1: 4.3 Exclusion Criteria 5.4 Prior Therapy Exclusions
… subjects must be taking systemic glucocorticoids for at least six months prior to ~~signing the consent and/or assent~~ *screening*.	Revising the definition to 6 months of glucocorticoid therapy prior to screening is medically relevant; the prior requirement was not.	Inclusion criterion 4: 4.2 Inclusion Criteria

Description of Change	Rationale/Justification	Sections Affected
Screening and Randomization		
Enrollment will continue until 12 subjects are infused or 30 subjects are enrolled. No subjects will be replaced. Previously, enrollment target was 12 infused and 12 control subjects, with replacement of subjects randomized to CAP-1002 but who did not complete infusion.	Prior enrollment plan allowed for replacement of subjects on only one study arm. New plan is more balanced, as no randomized subjects will be replaced.	3.1 Overall Study Design and Plan 9.2 Determination of Sample Size
Randomization will be simplified and will no longer attempt to stratify assignments based on historical MRI readings or chronic use of steroids.	The study size (24 subjects) is too small to support stratification, and the requirement for historical MRI is being removed (as explained above).	3.1 Overall Study Design and Plan 5.2 Randomization
Additional laboratory tests at screening: venous blood assessments for Troponin, CK-MB (previously these parameters were assessed post-screening only)	Screening values for these parameters will provide a baseline for the assessments collected later in the study.	7.1 Screening Visit Appendix 1 Schedule of Events Appendix 2 Clinical Laboratory Tests
New testing for Cystatin C at screening, M6, and M12.	Cystatin C is added as a tool for monitoring cardiovascular disease.	
Venous blood specimen for ELISPOT immunoassay collected at Screening instead of pre-infusion	Timing for collection of this sample is adjusted to improve balance between study arms	7.1 Screening Visit 7.2 Randomization and Day 0 Appendix 1 Schedule of Events
Safety and Efficacy Analyses		
New text discussing Independent Oversight Committees (DSMB and CEC)	Original protocol did not explicitly state that study would be overseen by a DSMB, and did not discuss the CEC.	3.1 Overall Study Design and Plan 10 Independent Oversight Committees
Study stopping rules are now defined by reference to the DSMB Charter.	Original Protocol did not define study stopping rules. The study stopping rules have now been established by unanimous vote of the DSMB, and are detailed in the DSMB Charter.	9.8 Study Stopping Rules
Biomarkers for the study are now defined (Galectin-3, IL-10, Osteopontin, ST2)	Biomarkers to be assessed in the protocol were not listed previously.	Appendix 2 Clinical Laboratory Tests

Description of Change	Rationale/Justification	Sections Affected
The study will monitor the proportion of subjects experiencing any of the following events during or post intracoronary infusion delivery. *For comparison, these same events will be monitored in usual care subjects using 9:00 am on Day 0 as the reference time point:*	Original protocol did not explicitly state a method for comparison of safety between infused subjects and control subjects, for the period during and immediately following intracoronary infusion of the subjects receiving CAP-1002.	3.3 Safety Monitoring
Clarifications, Administrative Changes and Updates		
Change of Sponsor Contact and Medical Monitor	Personnel change	7.11.8.2 Reporting Serious Adverse Events 11.1 Investigators and Study Administrative Structure
Study Day 0 redefined as date of product infusion for CAP-1002 subjects, and as 7 days after randomization for control subjects. Previously, day 0 was the date of randomization.	Redefining Day 0 as the date of initial product exposure is more meaningful than randomization date for statistical assessments of safety and product efficacy. "Day 0" for control subjects is defined as "randomization + 7 days" to be as consistent as possible with the other study arm (infusion date is anticipated to occur 7 days after randomization, but some schedule variations may occur).	3.1 Overall Study Design and Plan Figure 10 7.2 Randomization and Day 0 7.11.2 Timing 9.6.1 Safety Endpoints 9.6.2 Adverse Events
Target infusion times for wash solution, IP (CAP-1002) and 2nd wash solution now define windows (±5-30 seconds) permitted for each step.	Original protocol did not define permitted range of deviation from target infusion times.	6.10.1 CAP-1002 Infusion
Efficacy Assessment 2 (Functional): Serial change*s* in ~~**mobility measurements and**~~ Performance of Upper Limb (PUL) scale, spirometry, and 6-minute walk test (6MWT) when deemed appropriate by the Investigator.	Clarification of functional assessments to be performed	3.2 Exploratory Efficacy Endpoints
Addition of terms to the "List of Abbreviations and Definitions" (CEC, DSMB, LGE, TEAE, TMPG)	These abbreviations in the protocol were not previously defined in this section	List of Abbreviations and Definitions

Description of Change	Rationale/Justification	Sections Affected
Visit windows previously defined in Appendix 1 and Section 7 are now referenced in Section 3.1 also	Visit windows previously were defined in the protocol but were omitted in section 3.1	3.1 Overall Study Design and Plan
Figure 4 – definition of X-axis	X-axis parameters for this figure were not labeled previously.	Figure 4
~~AEs will be regarded as 'pretreatment' if they occur prior to the first exposure to treatment.~~	Text removed was redundant with the paragraph immediately following, which defined TEAEs.	9.6.2 Adverse Events
Reference addition: CCI [redacted]	CCI [redacted]	12 Reference List

Appendix 7 Sponsor Signature

Study Title: A Randomized, Open-label Study of the Safety and Efficacy of Multi-Vessel Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with Cardiomyopathy Secondary to Duchenne Muscular Dystrophy [**HOPE**-Duchenne (**H**alt cardiomy**OP**athy progr**E**ssion in Duchenne)]

Study Number: CAP-1002-DMD-01

Original Protocol: 01 May 2015

Amendment 3.0: 18 July 2016

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

Signed: _____ Date: 18 July 2016

PPD , MD
PPD & Medical Monitor
Capricor, Inc.

Appendix 8 Investigator's Signature

Study Title:	A Randomized, Open-label Study of the Safety and Efficacy of Multi-Vessel Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with Cardiomyopathy Secondary to Duchenne Muscular Dystrophy [**HOPE**-Duchenne (**H**alt cardiomy**OP**athy progr**E**ssion in Duchenne)]
Study Number:	CAP-1002-DMD-01
Original Protocol:	01 May 2015
Amendment 3.0:	18 July 2016

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

Signed:_____ Date:_____

_____
Name, Credentials