CLINICAL TRIAL PROTOCOL

OPEN-LABEL EXTENSION OF THE HOPE-2 DUCHENNE MUSCULAR DYSTROPHY TRIAL (HOPE-2-OLE)

Protocol Number:	CAP-1002-DMD-02-OLE
NCT Number:	NCT04428476
Trial Phase:	Phase 2
Product Name:	Deramiocel (CAP-1002) Allogeneic Cardiosphere-Derived Cells
IND Number:	[redacted]
Indication:	Duchenne Muscular Dystrophy
Sponsor:	Capricor, Inc. 10865 Road to the Cure, Suite 150 San Diego, CA 92121
Sponsor Contact:	[redacted]
Original Protocol:	27-Apr-2020
Amendment 1:	12-Aug-2020
Amendment 2:	16-Aug-2021
Amendment 3:	11-Jul-2022
Amendment 4:	19-Jul-2023
Amendment 5:	12-Jul-2024

INVESTIGATOR'S AGREEMENT

Trial Title:	Open Label Extension of the HOPE-2 Duchenne Muscular Dystrophy Trial (HOPE-2-OLE)
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Amendment 5:	12-Jul-2024

I have read this clinical trial protocol and agree to conduct the trial according to the investigational plan. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR APPROVAL

Trial Title:	Open Label Extension of the HOPE-2 Duchenne Muscular Dystrophy Trial (HOPE-2-OLE)
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Amendment 4:	19-Jul-2023
Amendment 5:	12-Jul-2024

The clinical trial protocol was subject to critical review and quality assurance and has been approved by Capricor.

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Name:	[redacted]
Company:	Syneos Health
Title:	[redacted]
Address:	[redacted]
Phone:	[redacted]
E-mail:	[redacted]

STATEMENT OF COMPLIANCE

The protocol will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council on Harmonization and Good Clinical Practice (ICH-GCP), and applicable regulatory requirements.

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

The clinical site is required to follow their institutional guidelines for obtaining initial approval by the Institutional Review Board (IRB) and for submitting continuing reviews to the IRB. Subject enrollment at a clinical site will not commence until initial IRB approval documentation has been received and reviewed by the Sponsor. The composition and conduct of this committee must conform to the United States Code of Federal Regulations (CFR) and ICH E6.

The informed consent must be reapproved in accordance with the clinical site's IRB policies or at least annually.

The Sponsor will provide the clinical site with serious adverse drug reactions and any other applicable correspondence during the trial. The clinical site is to follow their institutional policies for reporting these correspondences and documents to their IRB.

All IRB approvals and all materials approved/acknowledged by the IRB for this protocol, including the subject consent form or safety event notifications, must be maintained by the Investigator, and made available for inspection.

1. SYNOPSIS

Name of Sponsor: Capricor, Inc.	
Name of Investigational Product: Deramiocel (CAP-1002) Allogeneic Cardiosphere-Derived Cells	
Name of Active Ingredient: Cardiosphere-Derived Cells	
Title of Trial: Open Label Extension of the HOPE-2 Duchenne Muscular Dystrophy Trial (HOPE-2-OLE)	
Protocol No. CAP-1002-DMD-02-OLE	
Trial Centers: Up to 5 (USA)	
Principal Investigators: This is a multi-center trial with multiple Principal Investigators.	
Studied Period: Approximately 60 months	**Phase of Development:** 2

Objectives:

Primary: To provide deramiocel, previously referred to as CAP-1002, to subjects who were enrolled in the HOPE-2 trial and completed 12 months of follow-up.

Secondary: To assess the safety and efficacy of intravenous administration of deramiocel every three months for a total of up to 20 doses administered over a period of approximately 60 months.

Methodology: This Phase 2, multi-center, open label extension trial will provide deramiocel to subjects that were enrolled in the HOPE-2 trial (CAP-1002-DMD-02) and completed 12 months of follow-up. The trial will assess the safety and efficacy of up to 20 intravenous administrations of deramiocel, each separated by three months. Subjects will undergo a targeted screening during a 30-day screening period to determine eligibility based on protocol inclusion and exclusion criteria.

Eligible subjects will undergo baseline safety and efficacy assessments on Day 1 prior to their first infusion of deramiocel. Administration of deramiocel (Day 1) should occur within a maximum of 30 days following confirmation of eligibility; if a delay of more than 30 days between enrollment and IP administration is unavoidable, a conversation between the Investigator and Medical Monitor should occur to determine the need for repeat assessments prior to infusion.

Subjects will complete trial assessments at Screening; Day 1; Months 3, 6, 9, 12 (±14 days, each), 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 (±21 days, each). Safety and efficacy assessments will be conducted prior to deramiocel administration at the Day 1, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42,45, 48, 51, 54, and 57 trial visits, unless otherwise indicated.

All deramiocel infusions will be conducted in an outpatient setting at the investigative site on Day 1 and Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57 trial visits. Prior to each deramiocel administration, medications will be administered to the subject as determined by the Investigator based on the pre-treatment guidelines provided by Capricor and/or institutional protocols to minimize the risk of potential severe allergic reactions such as anaphylaxis. Subjects will be

observed in the outpatient setting for at least two hours post infusion and then discharged the same day if medically cleared by the site Investigator.

If clinically indicated, an unscheduled in-person visit will be performed at the investigative site with targeted assessments based on presentation of signs and symptoms following any infusion.

The ***primary safety endpoint*** is the incidence and severity of all treatment-emergent adverse events from baseline through Month 12.

The ***secondary safety endpoint*** is the incidence and severity of all treatment-emergent adverse events from baseline through Month 60.

The ***primary efficacy endpoint*** is change from baseline at the Month 12 timepoint in functional capacity as assessed by the full PUL 2.0 (high-level + mid-level + distal level dimensions).

The ***secondary efficacy endpoints*** include the changes from baseline through the Month 60 timepoint for the following:

- Upper body functionality using PUL 2.0 assessment at Months 12, 24, 36, 48, and 60
- Distal-level PUL 2.0 for subgroup of subjects with entry level scores of 2 and 3 at Months 12, 24, 36, 48, and 60
- Mid-level PUL 2.0 for subgroup of subjects with entry level scores of 4 and 5 at Months 12, 24, 36, 48, and 60
- Left Ventricular Ejection Fraction (LVEF) (i.e., Cardiac MRI) measurement at Month 24, Month 36, 48, and 60
- Left Ventricular End Systolic Volumes-Indexed (ESVI) measurement at Month 24, 36, 48, and 60
- Left Ventricular End Diastolic Volumes-Indexed (EDVI) measurement at Month 24, 36, 48, and 60
- Other cardiac parameters, including but not limited to mass, unindexed volumes, cardiac output, wall thickening percentage, and end diastolic and end systolic wall thickness at Month 24, 36, 48, and 60

Oversight of the trial will be provided by an independent Data Safety Monitoring Board (DSMB).

The ***exploratory efficacy endpoints*** include retrospective standard-of-care patient data from HOPE-2 to the beginning of HOPE-2-OLE and/or an external comparator pertaining to the following at appropriate timepoints:

- Upper body functionality (i.e., PUL 2.0)
- Left ventricular ejection fraction (LVEF) (i.e., cardiac MRI)

Exploratory safety endpoints include the analysis of the elevation of HLA antibodies against the donor cells (i.e., DSAs) to determine a level considered clinically significant using mean florescence intensity [MFI].

Number of Subjects: Up to 16 subjects will be enrolled

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in the HOPE-2 trial and who completed the 12-month follow-up period will be evaluated for eligibility to participate in this Open Label Extension trial. Eligibility criteria will be assessed within 30 days prior to first infusion on Day 1, unless otherwise noted.

Inclusion Criteria:

1. Documented enrollment in the HOPE-2 trial and completion of trial follow-up through Month 12
2. Willing and able to provide informed consent to participate in the trial if ≥ 18 years of age, and assent with parental or guardian informed consent if < 18 years of age
3. Adequate venous access for intravenous deramiocel infusions in the judgement of the Investigator
4. Assessed by the Investigator as willing and able to comply with the requirements of the trial

Exclusion Criteria:

1. Planned or likely major surgery in the next 12 months after planned first infusion
2. Risk of near-term respiratory decompensation in the judgment of the investigator, or the need for initiation of non-invasive ventilator support as defined by serum bicarbonate ≥ 29 mmol/L
3. History of non DMD-related chronic respiratory disease including, but not limited to, asthma, bronchitis, and tuberculosis
4. Acute respiratory illness within 60 days prior to first infusion
5. Known allergy or hypersensitivity to any of the IP constituents such as dimethyl sulfoxide (DMSO) or bovine proteins
6. Treatment with an investigational product ≤ 6 months prior to first infusion
7. History, or current use, of drugs or alcohol that could impair ability to comply with participation in the trial
8. Inability to comply with the investigational plan and follow-up visit schedule for any reason, in the judgment of the investigator

[redacted]

50M CDCs.

[redacted]

Duration of Treatment: Deramiocel (150 million CDCs) is administered once every 3 months for a total of up to 20 infusions.

Duration of Trial: All subjects will be followed for approximately 60 months post Day 1 infusion.

Criteria for evaluation:

Safety

Safety assessments at Screening, Day 1, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 unless otherwise indicated, will include the following: vital signs, height, weight, physical examination, and adverse events. Standard safety blood work will be collected at Month 24, Month 36, Month 48, and Month 60. Blood for a coagulation panel consisting of D-dimer, fibrinogen, PT/aPTT, INR, CRP, and ESR will be collected and analyzed locally at Months 48, 51, 54, and 57. During each visit, the coagulation panel will be drawn pre-dose, 2-hours post dose, and 24-hours post dose. An unscheduled in-person visit will be performed at the investigative site with targeted assessments based on presentation of signs and symptoms of subject.

Efficacy

Functional capacity assessed by PUL 2.0 will be performed at Day 1, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60.

Assessment of the Left Ventricular Ejection Fraction (i.e., cardiac MRI) will be assessed at the Month 24, Month 36, Month 48, and Month 60 visits.

Exploratory

Retrospective standard-of-care assessments of upper limb function via PUL 2.0 and Left Ventricular Ejection Fraction (LVEF) will be collected if available.

Analysis of the elevation of HLA antibodies against the donor cells (i.e., DSAs) to determine a level considered clinically significant using mean florescence intensity [MFI].

Statistical Methods:

Sample Size

Up to 13 subjects that were enrolled in the HOPE-2 trial and completed the 12-month follow-up period will be enrolled in this trial.

Analysis Population

Safety Population: Subjects who begin an infusion of deramiocel.

Safety Analysis

The primary safety endpoint and other observed adverse events will be documented and reported. Adverse events will be summarized by the incidence of events by type and by percentage of subjects with those events, by the relatedness to the trial treatment and severity level.

Efficacy Analysis

Descriptive statistics will be used to summarize changes from baseline in the PUL 2.0 scores and in Left Ventricular Ejection Fraction (LVEF) assessed by Cardiac MRI.

Exploratory Analysis

Descriptive statistics will be used to summarize changes in collected retrospective standard-of-care data pertaining to upper body functionality and Left Ventricular Ejection Fraction (LVEF).

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this trial protocol.

Table 1: Abbreviations and Specialist Terms

Term	Explanation
6MWT	Six-Minute Walk Test
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
C	Celsius
CBC	Complete Blood Count
CDC	Cardiosphere-Derived Cells
CFR	Code of Federal Regulations
CK-MB	Creatine kinase MB Isoenzyme
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C- Reactive Protein
DCM	Dilated Cardiomyopathy
DMD	Duchenne Muscular Dystrophy
DMSO	Dimethyl Sulfoxide
DSA	Donor-Specific Antibody
DSMB	Data Safety Monitoring Board
DVA	Duchenne Video Assessment
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDC	Electronic Data Capture
EDVI	End Diastolic Volume-Indexed
ESR	Erythrocyte sedimentation rate
EDSI	End Systolic Volume-Indexed
ET	Early Termination
FDA	U.S. Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FVC	Force Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
HEENT	Head, Eyes, Ears, Nose, and Throat
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IFR	Inspiratory Flow Reserve

Term	Explanation
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
LV	Left Ventricle / Left Ventricular
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
M	Million
MACE	Major Adverse Cardiac Event
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Mean Expiratory Pressure
MFI	Mean Fluorescence Intensity
MHC	Major Histocompatibility Complex
MI	Myocardial Infarction
MIP	Mean Inspiratory Pressure
mL	Milliliter
MRI	Magnetic Resonance Image
MSC	Mesenchymal Stem Cells
OAE	Other Adverse Events
OLE	Open Label Extension
PCF	Peak Cough Flow
PE	Physical Exam
PEF	Peak Expiratory Flow
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
PT/aPTT	Prothrombin Time/activated Partial Thromboplastin
PUL	Performance of the Upper Limb
RV	Residual Volume
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SpO2	Peripheral Capillary Hemoglobin Oxygen Saturation
SVC	Slow Vital Capacity
TEAE	Treatment-Emergent Adverse Events
Term	Explanation
TIMI	Thrombolysis in Myocardial Infarction
v/v	Volume to Volume
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

4. INTRODUCTION

4.1. Background

Duchenne muscular dystrophy (DMD) is a severe, X-linked, progressive disease affecting approximately one in 3,600 to 9,200 male births (Mah et al., 2014). It is caused by mutations in the dystrophin gene resulting in the absence of or non-functional dystrophin protein (Hoffman et al., 1988).

Dystrophin is a cytoplasmic protein encoded by the *DMD* gene, which links cytoskeletal actin filaments to membrane proteins. The dystrophin protein acts as a shock absorber during muscle fiber contraction by linking the actin of the contractile apparatus to the layer of connective tissue that surrounds each muscle fiber (Koenig et al., 1988; Fairclough et al., 2013; Aartsma-Rus et al., 2016).

Due to the lack of dystrophin, the connection between the actin cytoskeleton and connective tissue is lost, inducing excessive membrane fragility and permeability, dysregulation of calcium homeostasis, and oxidative damage, which results in muscle cell necrosis and a chronic inflammatory state. Initially, muscle necrosis is followed by regeneration, but with age, the regenerative ability of myofibers is lost and muscle fibers are gradually replaced by connective and adipose tissue. It has been postulated that chronic injury and regeneration induce satellite cell exhaustion. Recent studies suggest that the absence of dystrophin in satellite cells impairs their ability to divide properly, thus reducing the generation of myogenic progenitors that are needed for proper muscle regeneration (Dumont et al., 2015). As a consequence, muscle function is lost (Muntoni et al., 2003; Deconinck and Dan, 2007; Falzarano et al., 2015).

DMD symptoms begin in early childhood, with degeneration occurring progressively in the skeletal musculature and ultimately in the heart and respiratory muscles, resulting in premature death (Hendriksen et al., 2015). Progressive weakness and muscle atrophy caused by degenerating muscle fibers begins in the lower extremities and pelvis before spreading into the upper extremities. Other symptoms include loss of some reflexes, a waddling gait, frequent falls, difficulty when rising from a sitting or lying position or when climbing stairs, changes to overall posture, and impaired breathing. Many children precipitously lose the ability to run or jump. The atrophied muscles, in particular the calf muscles, and less commonly, muscles in the buttocks, shoulders, and arms, may be enlarged by an accumulation of fat and connective tissue, causing them to look larger and healthier than they actually are ("pseudohypertrophy"). Bone thinning and scoliosis are common. Ultimately, a wheelchair becomes necessary, in most cases between 12 to15 years of age (Henricson et al., 2013).

As the disease progresses, the muscles in the diaphragm that assist in breathing and coughing become weaker. Affected individuals experience breathing difficulties, respiratory infections, and swallowing problems. Almost all DMD patients will develop cardiomyopathy (Aartsma-Rus et al., 2016). Pneumonia, compounded by cardiac involvement, is the most frequent cause of death, which typically occurs in the late teens or early 20s. However, improvements in multidisciplinary care, in particular respiratory care and various forms of assisted ventilation, have extended the life expectancy; numerous individuals with DMD now survive into their 30s, and some even into their 40s (Emery, 2002; Bushby et al., 2010; Bushby et al., 2010).

No pharmacologic or biological therapies proven to stop or reverse the progression of DMD have been approved in the US. Disease management consists primarily of preventive measures as well as active interventions to address the primary and secondary aspects of the disorder.

[redacted]

4.4. HOPE-2-OLE Safety and Efficacy Summary

Interim data of the HOPE-2-OLE study showed sustained safety and effectiveness of deramiocel for DMD patients who continued to receive infusions for additional dosing after the completion of HOPE-2. Deramiocel continued to slow disease progression in upper limb function.

[redacted]

[redacted]

Based on these data, the benefit-risk balance for deramiocel is considered favorable and warrants additional clinical investigation.

4.6. Trial Rationale

The proposed open-label extension (HOPE-2-OLE) trial will enroll HOPE-2 trial (CAP-1002-DMD-02) subjects who completed the 12-month follow-up period. All subjects enrolled in the HOPE-2-OLE trial will receive deramiocel.

Deramiocel is intended to be used as a therapy to improve the morbidities associated with DMD and thus improve or prevent decline in muscle function through its composite immune-modulatory, anti-fibrotic, and regenerative mechanisms of action. [redacted]

[redacted] This clinical evidence suggests that deramiocel has the potential to address unmet needs in patients with DMD.

4.7. Dose Justification

4.7.1. Dosing Interval

Data [redacted] showed a maintenance of benefit in PUL 1.2 with CAP-1002 treatment up to 3 months post dose that then wanes by 6 months. This observation that some benefits of a CAP-1002 dose may be transient inspired the plan for a repeat administration regimen [redacted] with doses re-administered every 3 months. [redacted] However, repeat dosing of CDCs at an interval of 3 weeks did not noticeably enhance exercise capacity or skeletal muscle force production beyond the effect achieved with one dose, which may be attributable in part to the abbreviated dosing interval.

Data [redacted] shows a maintenance of benefit in upper limb function with deramiocel treatment administered every 3 months.

4.7.2. Dose Selection

The 150M dose selected [redacted] hus, 150M was selected as a dose below the anticipated maximum tolerated dose and in the anticipated effective dose range. Notably, the dose of [redacted] already had demonstrated preliminary efficacy via intracoronary administration [redacted] would be expected to be similarly efficacious via intravenous administration, given what is known about cell biodistribution and engraftment post infusion by either route.

HOPE-2-OLE will provide HOPE-2 subjects who completed the 12-month follow-up period access to deramiocel. Thus, the treatment regimen in HOPE-2-OLE will be identical to the one in the HOPE-2 trial but with extended treatment to 60 months, i.e., 20 CAP-1002 administrations (150M CDCs) separated by three months.

4.7.3. Repeat Administrations

One element of safety relevant for the proposed clinical trial and related to the planned dosing regimen, is the potential for an immune response to the allogeneic product, planned for repeated administrations. Several lines of evidence suggest that repeat administration of deramiocel should have low immunotoxicity risk in humans. [redacted] In fact, equivalent primary (i.e., after a first dose) and secondary (i.e., after a second dose) efficacy benefits (i.e., improvements in LVEF) were observed using allogeneic and syngeneic CDCs in this study. Furthermore, there was no evidence of an increased cellular or humoral immune memory response using allogenic compared to syngeneic CDCs.

[redacted] Further information about the allergic reactions is found in the Investigator's Brochure.

These collective data suggest that repeat administration of deramiocel should be reasonably safe in humans. However, the risk of severe allergic reactions should be minimized by administration of medications that will be determined by the Investigator based on the pre-treatment guidelines provided by Capricor (Section 9.7) and/or institutional protocols.

4.8. Trial Population

The target population for this trial is pediatric and adult males with a diagnosis of DMD who participated in the HOPE-2 trial and completed the 12-month follow-up period and meet the OLE trial eligibility criteria (see Section 7) that focuses on minimizing the risks of participation in the extension trial.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this trial is to provide deramiocel to subjects who were enrolled in the HOPE-2 trial and completed the 12-month follow-up period.

5.2. Secondary Objectives

The secondary objectives of this trial are to assess the safety and efficacy of intravenous administration of deramiocel with repeat dosing at Day 1 and Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57.

6. INVESTIGATIONAL PLAN

6.1. Overall Trial Design

This Phase 2, multi-center, open-label extension trial will provide deramiocel to HOPE-2 trial subjects who completed 12 months of follow-up. The trial will assess the safety and efficacy of deramiocel administered as 20 IV infusions, each separated by 3 months. All subjects will undergo a targeted screening assessment within 30 days prior to first infusion, unless otherwise stated, to confirm eligibility based on protocol inclusion and exclusion criteria.

Administration of deramiocel (Day 1) should occur within a maximum of 30 days following confirmation of eligibility; if a delay of more than 30 days between enrollment and deramiocel administration is unavoidable, a conversation between the Investigator and Medical Monitor should occur to determine the need for repeat screening prior to infusion. For the purposes of this trial, subjects that initiate an infusion at Day 1 and receive any amount of deramiocel are considered enrolled.

A schematic of the trial design is provided in Appendix A and a summary of all assessments is provided in Appendix B.

Subjects will complete trial assessments at Screening; Day 1; Months 3, 6, 9, 12 (±14 days, each), 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 (±21 days, each). Baseline safety and efficacy assessments will be conducted prior to first infusion on Day 1. For subsequent infusions at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57 safety and efficacy assessments will be conducted prior to infusion, unless otherwise specified.

All intravenous infusions will be conducted in an outpatient setting at the investigative site on Day 1 and at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57. Prior to each IP infusion, medication(s) will be administered to the subject as determined by the Investigator based on the pre-treatment guidelines Section 9.7 and/or institutional protocols to minimize the risk of potential severe allergic reactions such as anaphylaxis. Subjects will be observed in the outpatient setting for at least two hours post infusion and then discharged the same day if medically cleared by the site Investigator.

If clinically indicated, an unscheduled in-person visit will be performed at the investigative site with targeted assessments based on presentation of signs and symptoms after any infusion.

6.2. Trial Endpoints

6.2.1. Primary Endpoints

The ***primary safety endpoint*** is the incidence and severity of all treatment-emergent adverse events from baseline through Month 12.

The ***primary efficacy endpoint*** is change from baseline at the Month 12 timepoint in functional capacity as assessed by the full PUL 2.0 (high-level + mid-level + distal level dimensions).

6.2.2. Secondary Endpoints

The ***secondary safety endpoint*** is the incidence and severity of all treatment-emergent adverse events from baseline through Month 60.

The ***secondary efficacy endpoints*** include the changes from baseline through the Month 60 timepoint for the following:

- Upper body functionality using PUL 2.0 assessment at Months 12, 24, 36, 48, and 60
- Distal-level PUL 2.0 for subgroup of subjects with entry level scores of 2 and 3 at Months 12, 24, 36, 48, and 60
- Mid-level PUL 2.0 for subgroup of subjects with entry level scores of 4 and 5 at Months 12, 24, 36, 48, and 60
- Left Ventricular Ejection Fraction (LVEF) (i.e., Cardiac MRI) measurement at Month 24, 36, 48, and 60
- Left Ventricular End Systolic Volumes-Indexed (ESVI) measurement at Month 24, 36, 48, and 60
- Left Ventricular End Diastolic Volumes-Indexed (EDVI) measurement at Month 24, Month 36, 48, and 60
- Other cardiac parameters, including but not limited to mass, unindexed volumes, cardiac output, wall thickening percentage, and end diastolic and end systolic wall thickness at 24, 36, 48, and 60

6.2.3. Exploratory Endpoints

The ***exploratory efficacy endpoints*** include the retrospective standard-of-care patient data from HOPE-2 to the beginning of HOPE-2-OLE and/or an external comparator pertaining to the following at appropriate timepoints:

- Upper body functionality (i.e., PUL 2.0)
- Left ventricular Ejection fraction (LVEF) (i.e., cardiac MRI)

Exploratory safety endpoints include the analysis of the elevation of HLA antibodies against the donor cells (i.e., DSAs) to determine a level considered clinically significant using mean florescence intensity [MFI].

6.3. Number of Subjects

Up to 16 subjects will be enrolled.

6.4. Deramiocel Treatment

All subjects will receive open-label deramiocel (150M CDCs) administered as an intravenous infusion on Day 1 and Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57.

6.5. Dose Adjustment Criteria

There are no planned dose adjustments. Should an acute toxicity arise during the infusion (e.g., hypersensitivity reaction, pulmonary decompensation, etc.), the infusion should be terminated immediately, and the actual total dose administered recorded. Any decision about re-challenging in a subsequent infusion should be made after discussions with the Investigator, Medical Monitor, Data Safety Monitoring Board (DSMB), and other medical experts that may be required to make an informed decision.

6.6. Criteria for Trial Termination

The trial may be terminated at any time and for any reason, including, but not limited to, a recommendation by the DSMB for safety reasons, an action by the FDA, or decision by Capricor.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who meet all inclusion criteria and no exclusion criteria will be eligible for the trial.

7.1. Subject Inclusion Criteria

Inclusion criteria will be assessed within 30 days prior to first infusion on Day 1 unless otherwise noted:

1. Documented enrollment in the HOPE-2 trial and completion of trial follow-up through Month 12
2. Willing and able to provide informed consent to participate in the trial if ≥ 18 years of age, and assent with parental or guardian informed consent if < 18 years of age
3. Adequate venous access for intravenous deramiocel infusions in the judgement of the Investigator
4. Assessed by the Investigator as willing and able to comply with the requirements of the trial

7.2. Subject Exclusion Criteria

Exclusion criteria will be assessed within 30 days prior to first infusion on Day 1 unless otherwise indicated:

1. Planned or likely major surgery in the next 12 months after planned first infusion
2. Risk of near-term respiratory decompensation in the judgment of the investigator, *or* the need for initiation of non-invasive ventilator support as defined by serum bicarbonate ≥ 29 mmol/L
3. History of non DMD-related chronic respiratory disease including, but not limited to, asthma, bronchitis, and tuberculosis
4. Acute respiratory illness within 60 days prior to first infusion
5. Known allergy or hypersensitivity to any of the IP constituents such as dimethyl sulfoxide (DMSO) or bovine proteins
6. Treatment with an investigational product ≤ 6 months prior to first infusion
7. History, or current use, of drugs or alcohol that could impair ability to comply with participation in the trial
8. Inability to comply with the investigational plan and follow-up visit schedule for any reason, in the judgment of the investigator

7.3. Screen Failures

Any subject who provides written informed consent/assent and is ultimately not infused for whatever reason will be classified as a screen failure. Screen failures will be recorded on a trial

log outside of the clinical database and submitted at the end of the trial to Capricor. Please reference the Manual of Operations for further information on capturing screen failure data.

7.4. Subject Withdrawal Criteria

Every effort will be made to have each subject complete all elements of the trial. If a subject has started at least one IP infusion and withdraws prior to trial completion, all attempts must be made to perform the trial assessments indicated for Month 60 visit.

Criteria for withdrawal from trial participation include the following reasons:

- A subject may withdraw his consent at any time without prejudice to his care.
- At the discretion of the Investigator, the subject may be withdrawn from the trial for lack of adherence to the investigational plan.
- A subject may be withdrawn from the trial for an acute reaction to deramiocel or other safety issue that prevents repeat infusions. In this instance, the subject should be followed on trial for at least 3 months after the last deramiocel infusion and then complete the Month 60 visit.

8. TREATMENT OF SUBJECTS

8.1. Description of Investigational Product

Deramiocel is provided in units per vial of 75 million CDCs in a cryogenic cell preservation solution. Two units of deramiocel comprise a single dose of 150 million CDCs for intravenous infusion.

Please see Section 9 for more information on investigational product.

8.2. Concomitant Medications

Refer to exclusion criteria for medications / therapies that exclude a subject from trial participation.

All efforts should be made to maintain the same DMD medication regimen throughout the course of the trial. This should be discussed with the subject's primary medical doctor and caregivers at the outset of the trial and during the trial follow-up period.

Capricor requires treatment of subjects prior to each infusion, as outlined in Section 9.7, to minimize the risk of a potential severe hypersensitivity reaction.

8.2.1. Permitted concomitant medications changes

Agamree® (vamorolone) has been approved by FDA as a steroidal anti-inflammatory agent. Patients may switch standard-of-care steroid therapy to vamorolone provided that the following conditions are met:

- Current steroid regimen must be administered daily. There is no data available as to the equivalency of non-daily (i.e., weekend, once a week, etc.) dosing of corticosteroids to vamorolone. Such participants on non-daily dosing may not be allowed to switch to vamorolone while on-study.
- Participants on daily dosing of corticosteroids may switch to an equivalent dose of vamorolone after the Month 12 visit at a maximum dose of 6.0 mg/kg, but not less than 2.0 mg/kg and not to exceed a total daily dose of 300 mg.
- Guidance for prednisone/deflazacort conversion is as follows:
  - Prednisone – 0.75 mg/kg/day = Vamorolone 6.0 mg/kg/day
  - Deflazacort – 0.9 mg = Prednisone 0.75 mg

- All other prescribing information considerations per the package insert must be followed (https://www.accessdata.fda.gov/spl/data/2a128ee3-956f-49eb-aa4e-9691bb4c1b5d/2a128ee3-956f-49eb-aa4e-9691bb4c1b5d.xml)
- Any switch to vamorolone dosing while on study must be approved by Capricor prior to making the switch.
- The switch cannot occur within 2 weeks of any given infusion.
- If the vamorolone dose cannot be tolerated, the patient may resume his original corticosteroid medication and dose.

8.3. Treatment Compliance

Deramiocel will be administered in a licensed infusion center, or other appropriate unit according to a site's institutional standards, by appropriately trained medical personnel who will document the actual volume administered at each infusion.

Deramiocel administration occurs every 3 months anchored from the previous infusion for a total of up to 20 infusions (Day 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36, Month 39, Month 42, Month 45, Month 48, Month 51, Month 54, and Month 57). Should a subject's infusion schedule need to be altered, please contact the Medical Monitor to discuss the subject-specific case and out-of-window administration of deramiocel.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

Detailed investigational product information can be found in the Investigator's Brochure (IB) and the Investigational Product Manual. Below and elsewhere in the protocol, reference is made to an investigational pharmacist which is typically a person licensed to dispense prescription medication usually within a special unit of the institutional pharmacy that handles all investigational products. Deramiocel is a cell-based investigational product, therefore the chain of custody and responsibility for preparation of the investigational product may reside within another institutional department or unit within institution or an outside laboratory designated for such purposes by institution, such as a center for cellular therapy or human cellular therapy laboratory or similar name, in which case "investigational pharmacy" shall mean the special center, laboratory or unit within or outside the institution designated to handle all cell-based therapies and "investigational pharmacist or other designee" shall mean the person delegated by the Principal Investigator as having the role in receiving, storing and preparing deramiocel who may not be a licensed pharmacist.

[redacted]

[redacted]

9.6. Discontinuation of Medications Prior to Infusion

If clinically acceptable in the judgement of the Investigator, beta blockers and angiotensin-converting enzyme inhibitors (ACEi) should not be administered on the day of infusion. Furthermore, since all subjects who are pre-treated with glucocorticoids, as determined by the Investigator as part of their pre-medications, will likely start pre-treatment with glucocorticoids beginning 12 – 14 hours prior to infusion (see Section 9.7), their standing steroid medications schedule may need to be adjusted. Specifically, standing glucocorticoids should not be administered in the setting of glucocorticoid pre-treatment within 24 hours prior to the time of scheduled infusion or on the day of the deramiocel infusion.

9.7. Pre-Infusion Guidance for Minimizing Risk of Potential Severe Hypersensitivity Reaction

As discussed in Section 8.2, Capricor requires treatment of all subjects prior to each deramiocel infusion to minimize the risk of a potential severe allergic reaction. It is strongly encouraged that pre-medication be administered according to the guidelines described in this section, including the administration of high-dose oral steroids, H1 and H2 blockers; however, investigative sites may use institutional protocols established for anaphylaxis prevention should they be at least physiologically comparable to the guidelines below.

Final decisions regarding the medication(s), dose(s) administered, and route(s) of administration are to be determined by the Investigator taking into consideration the subject's medical history. For any pre-treatment medication administered, the FDA approved label should be reviewed for information on potential side effects and/or drug interactions and followed for detailed instructions on weight-based dosing.

Please see Section 9.6 for recommendations on holding beta blockers, ACEi and standing steroid doses within 24 hours of scheduled infusion.

[redacted]

9.8. Administration

Deramiocel will be administered in an outpatient setting at the investigative site on Day 1 and Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57. Subjects must complete all trial safety assessments prior to the deramiocel infusion, excluding those related to the deramiocel infusion (e.g., post-infusion monitoring). CAP-1002 will be administered as an IV infusion using a commercially available syringe pump approved for human use at infusion rates of 1 mL/min to 3 mL/min. [redacted] to each infusion, it is recommended that site personnel meet to discuss the logistics for that specific infusion.

Capricor requires that subjects be treated prior to each deramiocel infusion with medications that minimize the risk of potential severe allergic reactions (see Section 9.7). [redacted]

9.9. Post-Infusion Monitoring

Subjects will remain in the outpatient setting for at least 2 hours post infusion for observation, or longer should that be warranted in the judgement of the treating clinician. Investigative sites will observe their local institutional policies for post parenteral infusion monitoring. The subject's pulse oximetry (SpO_2) will be monitored for at least 30 minutes post infusion. A site Investigator will assess the subject for adverse events and approve his discharge the same day if medically cleared.

If clinically indicated, an unscheduled in-person visit will be performed at the investigative site with targeted assessments based on presentation of signs and symptoms of the subject following infusion.

9.10. Accountability

Good Clinical Practice (GCP) and FDA regulations assign responsibility for investigational product accountability at the trial site with the Principal Investigator. The Investigator may elect to delegate this responsibility to the investigational pharmacist, or other designee, who is under the supervision of the Investigator.

The responsible person must maintain a record of deramiocel received, prepared, administered and returned/destroyed. Therefore, deramiocel accountability must be maintained throughout the trial to show clear product traceability at all times. Details regarding deramiocel accountability will include dates, quantities, batch/serial numbers, expiration dates if applicable, storage conditions and the unique code assigned to the deramiocel and subjects. Deramiocel accountability must adequately document that the subjects were provided the correct vial and reconcile all deramiocel received from Capricor's drug depot. Further information on deramiocel accountability is found in the Investigational Product Manual.

9.11. Handling and Disposal

All deramiocel materials will be disposed following each infusion. Site personnel will follow institutional policies on the proper disposal of containers and disposables coming into contact with the deramiocel. Generally, disposal like other biohazard red-bag trash that is ultimately

incinerated should be sufficient to meet local institutional policies and any other regulations or laws.

10. ASSESSMENT OF SAFETY

Assessments to evaluate safety will be performed at trial visits as indicated in Appendix B.

10.1. Safety Assessments

10.1.1. Vital Signs

Heart rate, systolic and diastolic blood pressure, respiratory rate, body temperature, and blood oxygen saturation (SpO_2) will be measured after the subject has rested for approximately 5 minutes. A single set of values will be captured.

A subject's SpO_2 will be monitored for at least 30 minutes following each deramiocel infusion (see Section 9.9).

Vital signs will be performed using equipment provided by investigative sites that has been properly calibrated per institutional guidelines.

10.1.2. Weight and Height

Weight and ulna length measurement for calculation of height will be performed.

Investigative sites will make every effort to perform a weight measurement without the subject's wheelchair or other assistive device (e.g., walker), if applicable.

Height will be calculated using the subject's ulna length (Gauld et al., 2004) for all subjects. It is critical to reduce variability in ulna length measurements across investigative sites. Therefore, site personnel must complete trial-specific training prior to measuring a subject's ulna length.

Table 4: Height Calculation from Ulna Length

Height (cm) = [4.605 x Ulna Length (cm)] + [1.308 x Age (years)] + 28.003

Centimeter and year entries must include decimal places to the tenth place. If a subject is 18 years or older, enter "18" in the formula for age.

10.1.3. Physical Examination

The physical exam (PE) is not considered a standard of care assessment as the examiner will be assessing for research events. Therefore, the physical exam is to be conducted only by an Investigator, or designated site personnel (e.g., nurse practitioners, physician assistants, research fellows) listed on the Delegation of Authority Log.

The physical examination will be a review of the major organ systems including general appearance, HEENT, lymphatic, respiratory, cardiovascular, chest, abdomen, gastrointestinal, and musculoskeletal.

Clinically significant findings prior to investigational product administration are to be captured as medical history.

Clinically significant findings after the start of investigational product administration are captured and reported as AEs, if they meet the definition of an AE per Section 10.2.1.

10.1.4. Immunologic Assessments

Serum for DSA testing will be collected following standard institutional procedures for blood collection and submitted to a central laboratory for analysis. Instructions on collection, processing and shipping the samples to the central laboratory are in the Laboratory Manual.

Elevation of HLA antibodies against the donor cells (i.e., DSAs) to determine a level considered clinically significant using mean florescence intensity [MFI]

10.1.5. Clinical Laboratory Assessments

All blood samples are to be collected following the standard institutional procedures for blood collection and submitted to a central laboratory for analysis. If central labs cannot be used, local labs can be used upon receipt of sponsor approval. Instructions on collection, processing, storage and shipping the samples to the central, or local if applicable, laboratory are in the Laboratory Manual.

10.1.6. Hematology

Hematological testing will include complete blood count (CBC) with white blood cell (WBC) differential, hemoglobin, hematocrit, and platelet count.

10.1.7. Serum Chemistry

Serum chemistry testing will include the following: basic metabolic panel (glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN], creatinine, calcium), comprehensive hepatic panel (albumin, alkaline phosphatase, total protein, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase (GGT), direct bilirubin, total bilirubin), and creatine kinase.

10.1.8. Coagulation Panel

Blood for a coagulation panel consisting of D-dimer, fibrinogen, PT/aPTT, INR, CRP, and ESR will be collected and analyzed locally at Months 48, 51, 54, and 57. During each visit, blood for the coagulation panel will be drawn pre-dose, 2-hours (± 30 minutes) post dose, and 24 hours (± 12 hours) post dose.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Events

10.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It may be indicated by physical sign, symptom, clinically significant laboratory abnormalities, and/or disease temporally associated with a medical (investigational) treatment, procedure, or product, whether or not related to the medical (investigational treatment, procedure or product. This definition includes intercurrent illnesses or injuries, exacerbation of pre-existing conditions, or events occurring due to abuse or overdose.

Any condition that was pre-existing is not an adverse event unless there is a change in the nature, severity, or degree of the condition.

Clinical laboratory abnormalities are considered AEs when deemed clinically significant by the Investigator and/or lead to a change in the subject's functional status.

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 trial 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.

All Investigators conducting investigative studies supported by Capricor must report both expected and unexpected SAEs to Capricor, or designee, and their individual Institutional Review Board (IRB) in compliance with their institutional policies. Please see Section 10.2.4 or further details on event reporting.

10.2.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the Investigator or Capricor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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 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 a hospitalization are AEs. When the hospitalization is prolonged due to the complication or the complication fulfills any other serious criteria, the event is reported as an SAE. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

10.2.1.3. Expected Adverse Events

As deramiocel is comprised of allogeneic cells, immunologic reactions to the product are a possible AE. In the completed randomized, double-blind, placebo-controlled HOPE-2 and open-label HOPE-OLE trials, 3 allergic reactions assessed as related to IP were reported as SAEs for 3 subjects. Allergic reactions during or after an infusion of cell products have been reported and can be prevented or mitigated by specific pre-treatment regimens, which were implemented in the HOPE-2 trial after these reactions occurred. A total of 42 deramiocel or placebo infusions were administered in the HOPE-2 trial after the introduction of the pre-treatment regimen and a single allergic reaction was reported. This subject experienced a likely allergic reaction requiring overnight observation during his third IV administration of IP, the event was assessed as not life-threatening. All 3 subjects that experienced an allergic reaction were observed overnight and discharged without any sequelae on the following day.

Other risks of the infusion procedure include those risks that are possible with the intravenous administration. These include risks related to infection, bleeding, pain, bruising and/or hematoma at the vascular access site(s).

10.2.1.4. Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed, if the Investigator's Brochure is not required or available, or if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Expedited reporting is required for serious unexpected AEs as discussed in Section 10.2.4.

10.2.1.5. Other Adverse Event (OAE)

OAEs will be identified by the Medical Monitor during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from the trial, will be classified as OAEs.

For each OAE, a narrative may be written and included in the Clinical Study Report.

10.2.2. Relationship to Investigational Product

The Investigator will assess the relationship (causality) of an AE to the investigational product and administration procedure.

Causality will be defined as follows:

- ***Probable***: adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the investigational product or administration procedure. The following characteristics will apply:

  - A reasonable temporal relationship exists between the event and the investigational product or administration procedure, and
  - The event is a known reaction to the investigational product or administration procedure, which cannot be explained by an alternative etiology commonly occurring in the population/individual.

- ***Possible***: adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the investigational product or administration procedure, but for which a connection has reasonable certainty. The following characteristics apply:
  - The event occurs after exposure to the investigational product or administration procedure, and
  - The event is not a known reaction to the investigational product or administration procedure, but cannot be explained by a commonly occurring alternative etiology, or
  - In the absence of a temporal relationship, the event cannot reasonably be explained by an alternative etiology.
- ***Unlikely***: adverse events that, after careful medical evaluation, do not meet the criteria for possible or probable relationship to investigational product or administration procedure and for which a connection is unlikely. The following characteristics will apply:
  - The event does not follow a reasonable temporal sequence from administration of the investigational product or administration procedure, or
  - May be explained by commonly occurring alternative etiology in the population/individual, or
  - May have been produced by environmental factors, and there is no apparent pattern of response to the investigational product or administration procedure.

An adverse event will be reported as "related" when causality is evaluated by an Investigator as probably or possibly related to the investigational product and/or the administration procedure. Related adverse events indicate a potential cause-and-effect relationship between the investigational product and/or administration procedure and the occurrence of the adverse event.

An adverse event will be reported as "unrelated" when causality is evaluated by an Investigator as unlikely related to the investigational product and/or administration procedure by the Investigator. Unrelated adverse events indicate no relationship between the occurrence of the adverse event and the investigational product and/or administration procedure.

10.2.3. Recording Adverse Events

Investigators will monitor all subjects for AEs during the trial and establish a diagnosis for an event based on signs, symptoms, and/or other clinical information. It is important to distinguish that individual signs and symptoms of the event are not adverse events and should not be reported.

For each AE, the Investigator will evaluate the causality and severity, report the action taken and event outcome and disclose whether or not it caused the subject to discontinue trial participation.

The following severity scale will be used as a guideline to differentiate the severity of adverse events:

- **Mild (Grade 1)**: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- **Moderate (Grade 2)**: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
- **Severe (Grade 3)**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required and often requiring hospitalization or prolongation of hospitalization
- **Life-Threatening or Disabling (Grade 4):** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required; hospitalization, prolongation of hospitalization, or hospice care
- **Fatal (Grade 5)**

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event. An event is described as "serious" when it meets one of the pre-defined outcomes noted in Section 10.2.1.2. Both an AE and SAE can be assessed as severe. However, an AE of severe intensity may not meet SAE definition requirements.

10.2.4. Reporting Adverse Events

All adverse events are collected from the time of signing informed consent for trial participation until completion of the Month 60 visit or early termination, whichever occurs first. All AEs occurring after the initiation of the IV catheter placement for the initial dose of deramiocel will be considered treatment emergent. Any ongoing adverse event that has not been resolved at the time of trial completion or early termination for a subject will be marked as ongoing on the adverse event case report form (CRF).

All AEs will be entered into the electronic data capture (EDC) system by trained site personnel at the investigative site.

Expected and unexpected SAEs must be reported to Capricor and entered into the EDC system within 24 hours of discovery of the event. For events that do not have complete information available at the time of initial report, the investigative site will submit all available information at the time of the submission. All SAE Report Forms must be signed by an Investigator and submitted with available source documentation. All source documentation must be de-identified prior to submission.

All SAEs must be reported to the respective IRB in accordance with the investigative site's policies. Copies of the submission will be collected by Capricor.

All SAEs will be reported to the DSMB at least semi-annually, or more frequently at the discretion of the Medical Monitor.

Capricor will promptly upon discovery, report serious and unexpected adverse events for which there is a reasonable possibility that the investigative therapy (i.e. administration product and/or investigative product) caused the events, to the Food and Drug Administration (FDA) in accordance with 21 CFR 312.32 regulations and ICH E2A guidelines.

For trials conducted under an investigational new drug (IND) application, FDA regulations require reporting of any serious suspected adverse reaction that is unexpected according to the current Investigator's Brochure. A serious adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug/biologic caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/biologic and the adverse event. Serious, unexpected suspected adverse reactions (SUSARs) are SAEs that are unexpected and are possibly or probably related to participation in the research. Expedited reporting is required for all SUSARs. Capricor will send an IND Safety Report to the FDA within 7 calendar days of receipt for fatal/life-threatening events, and within 15 calendar days of receipt for non-fatal/non-life-threatening events that qualify for expedited reporting.

10.2.5. Pregnancy Reporting

It is unknown if deramiocel could affect a baby. If the partner is able to become pregnant, one or both of the partners must use some form of effective birth control. Should a female be impregnated by a trial subject, investigative sites are required to notify Capricor within 24 hours of learning about the pregnancy. The investigative site will receive the Pregnancy Reporting Form to complete and submit to Capricor, or its designee.

All pregnancies will be followed until the pregnancy outcome is known. In addition, pregnancies that are ongoing at the time of trial completion will be followed until the outcome is known. The investigative site is responsible for outcome reporting via the Pregnancy Reporting Form, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications.

The pregnancy is not an adverse event for the male subject unless there is a suspicion that the investigational product interfered with the effectiveness of a contraceptive medication.

10.2.6. Adverse Event Follow-up

All AEs are followed by the investigative site until an outcome is known or the subject's participation in the trial concludes at either the Month 60 visit or early termination, whichever occurs first.

The investigative site is expected to review all ongoing AEs at each visit. AEs are followed until resolution or until no further changes in the event are expected (i.e., the point at which a subject experiencing an AE is treated successfully and stabilized even though he may continue to experience lingering sequelae that may never resolve), or it is agreed that further follow-up of the event is not warranted (e.g., non-serious, IP unrelated, ongoing at final visit). See Section 10.2.3 for reporting ongoing AEs at the end of trial participation.

For SAEs that were incomplete or ongoing at the time of initial submission, the investigative site is required to submit follow-up SAE Report Forms when event information is available to the research site personnel and/or an outcome is known.

11. OTHER TRIAL ASSESSMENTS

Other trial assessments will be performed as indicated in Appendix B.

11.1. Medical History

Relevant and significant new medical/surgical history since completion of HOPE-2 trial participation will be confirmed at screening.

Medical histories will also be assessed for upper body functionality (i.e., PUL 2.0) and Left Ventricular Ejection Fraction (i.e., cardiac MRI). The assessment periods will cover the time from the end of HOPE-2 to the beginning of HOPE-2-OLE.

11.2. Pre-Treatment Medications

All medications taken prior to each infusion as part of the pre-treatment regimen (see Section 9.7) will be captured.

For each medication, generic name, indication, dose, frequency, route, and starting and stopping dates/times (if applicable) will be collected. The trade name of the medication is to be reported for combination therapies (e.g., Alka-Seltzer, Advair, etc.).

All efforts should be made to maintain the same DMD medication regimen throughout the course of the trial. This should be discussed with the subject's primary medical doctor and caregivers at the outset of the trial and during the trial follow-up period.

12. ASSESSMENT OF EFFICACY

Site personnel must complete trial-specific training prior to conducting trial efficacy assessments. Standardization and consistency are essential. All efforts must be made to have the same clinical evaluators conduct the PUL 2.0 for a subject throughout the duration of a trial. Additional details regarding training requirements can be found in the trial's Manual of Operations.

12.1. Performance of Upper Limb

The Performance of Upper Limb (PUL) was designed specifically for assessing upper limb function in ambulant and non-ambulant DMD patients (Pane et al., 2014). All the tasks included in the PUL were selected to address patient prioritized activities of daily living that are typical regardless of age, including preschool children. The PUL includes an entry item to define the starting functional testing level for a subject. The remaining PUL items are divided into three regional dimensions: high-level (shoulder), mid-level (elbow), and distal-level (wrist and hand). Trial subjects will complete testing for PUL 2.0 in the same preferred arm throughout the course of the trial.

Elbow contractures will be measured in each arm of a subject prior to the start of PUL 2.0 testing at each visit that requires testing.

PUL equipment will be standardized across investigative sites and provided by Capricor. Every effort should be made to complete a subject's PUL 2.0 assessment at approximately the same time in the morning at each required visit. In addition, each subject should be assigned a single evaluator for testing. Additional details regarding the PUL 2.0 requirements can be found in the trial's Manual of Operations and Clinical Evaluator Binder.

Patients will undergo PUL 2.0 assessment at Day 1, Months 3, 6, 9, 12 (±14 days, each), 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 (±21 days, each). All attempts will be made to perform PUL 2.0 assessment at the specified visits. In the event a subject cannot complete the entire PUL 2.0 assessment, it should be marked as not done. For example, if a patient has a broken arm, the entire PUL 2.0 assessment should not be completed until such time that the broken arm resolves.

12.2. Cardiac MRI

Subjects will undergo cardiac MRI at the Month 24, Month 36, Month 48, and Month 60 visits (or, Early Termination Visit) if they are physically capable as determined by an Investigator. All attempts will be made to perform cardiac MRI assessment at the Month 24 visit, or as soon as possible thereafter. If the cardiac MRI at Month 24 needs to be delayed, then the cardiac MRI at Month 36, Month 48, and Month 60 should also be delayed accordingly to ensure an approximate 12-month gap between the two MRIs.

Subjects that complete the cardiac MRI will have sufficient attention span, ability to maintain a breath-hold, lack significant contractures that would otherwise make lying flat difficult, and fit properly within the MRI scanner.

It is anticipated that the duration of each MRI session will be 30-45 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. All trial images and applicable imaging data will be sent to and centrally read at an independent, central, imaging core by DMD cardiovascular MRI and imaging experts.

12.3. Retrospective Assessment of Upper Body Functionality and LVEF

Medical histories will be assessed for upper body functionality (i.e., PUL 2.0) and Left Ventricular Ejection Fraction (i.e., cardiac MRI). The assessment periods will cover the time from the end of HOPE-2 to the beginning of HOPE-2-OLE.

13. STATISTICS

13.1. General Considerations

1. Descriptive statistics will be used to summarize all subject baseline and outcome data collected during the trial. Continuous variables will be summarized using mean, standard deviations, medians, and ranges. Categorical variables will be summarized in frequency distributions or as rates.
2. Statistical analyses will be performed by validated software (e.g., SAS, IBM/SPSS, or Cytel Software).
3. There are no formal hypotheses or statistical tests associated with trial endpoints except as outlined in the SAP. Statistical tests will be performed, however, for informational value as part of summarizing trial results. Parametric and non-parametric tests will be used that are appropriate to the outcome measure being summarized. Reported p-values will be considered nominal and unadjusted for multiple testing.
4. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
5. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the case report forms (eCRF) will be provided for all key baseline, demographic and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

13.2. Sample Size

Up to 16 subjects who were enrolled in the HOPE-2 trial and completed the 12-month follow-up period will be enrolled in this trial.

13.3. Analysis Population

Enrolled Population: The enrolled population will include all subjects who signed the informed consent form and/or given assent.

Safety Population: The safety population will be defined as all subjects who received any amount of IP. All analyses will be based on the Safety Population.

13.4. Safety Analysis

13.4.1. Safety Endpoints

The primary safety endpoint and other observed adverse events will be documented and reported. Adverse events will be summarized by the incidence of events by type and by the percentages (rates) of subjects with those events.

13.4.2. Pre-treatment Medications

Prescription and over-the-counter pre-treatment medication use will be coded to drug class, preferred drug name, and generic/trade drug name using the World Health Organization drug

dictionary (WHO-DD). All reported pre-treatment medications will be listed. Frequencies and percentages of subjects reporting or receiving each medication will be summarized by WHO-DD drug class and preferred name within drug class.

13.4.3. Physical Examination

Observed status (e.g., normal, abnormal) and changes from baseline in body system-specific physical examination findings will be summarized by visit within each body system.

13.4.4. Safety Labs and DSA

Quantitative lab values and respective changes will be summarized across visits with mean, standard deviation, minimum and maximum. Categorical lab values will be summarized with observed status (e.g., normal, abnormal) and with tables showing shift from baseline to post-baseline visits.

13.5. Statistical Methods

All subject baseline and study outcomes for safety will be summarized using descriptive statistics. These descriptive statistics will be appropriate to the data type involved.

13.5.1. Multiplicity

There are no pre-specified test hypotheses or assignments of statistical significance to study results requiring a consideration of adjustments for multiple testing.

13.5.2. Missing Data

There are no plans for imputation of missing data, except to linearly impute missing item scores from the PUL 2.0, when those item scores are observed before and after the missing visit, and at least 50% of the other items in the PUL 2.0 total score are non-missing. The reasons for missing data will be documented. Sensitivity analyses, however, may be performed using various assumptions for missing data to assess the impact on summary results.

13.6. Efficacy Analysis

Efficacy will be evaluated at the 3, 6, 9,12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 month follow-up visits, with changes from baseline assessed for pre-specified endpoints.

Descriptive statistics will be used to summarize changes from baseline in the PUL 2.0 scores. Additional analyses will be conducted to assess the treatment effect and potential disease modification evidence, as outlined in the SAP.

13.7. Exploratory Analysis

Descriptive statistics will be used to summarize changes from baseline in the retrospective standard-of-care patient data from HOPE-2 and the beginning of HOPE-2-OLE and/or using an external comparator arm, pertaining to upper body functionality (i.e., PUL 2.0) and Left Ventricular Ejection Fraction (LVEF) (i.e., cardiac MRI).

14. TRIAL OVERSIGHT

14.1. Data Safety Monitoring Board

To meet the trial's ethical responsibility to its subjects, an independent Data Safety Monitoring Board (DSMB) will monitor results during the trial. The board consists of physicians and biostatistician(s) appointed by Capricor, who have no formal involvement or conflict of interest with the Investigators, investigative sites, subjects, or Capricor. The DSMB will act in a senior advisory capacity to Capricor regarding data and safety matters throughout the duration of the trial. 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. The DSMB will communicate their recommendations directly to Capricor. The investigative sites will have no contact with the members of DSMB and no voting member of the committee may participate in the trial as an Investigator.

15. SOURCE DATA AND TRIAL DOCUMENTS

15.1. Electronic Data Capture

All trial data will be entered into the EDC system. Site personnel requiring access will have their own Login/Password. Access to trial information will be based on individual roles and responsibilities. The application employs fine-grained role-based access control for data entry, viewing and reporting options. All trial data will be transmitted over an encrypted SSL (Secure Sockets Layer) connection that requires user authentication.

This application is designed to be in full compliance with the International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's CFR 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials," and Health Insurance Portability and Accountability Act (HIPAA).

EDC supports efficient data collection and management and facilitates rapid data closure. A strong advantage of web-based design is that Capricor, or designee, has immediate access to the data from all investigative sites so that queries can be generated and distributed to the sites in real-time and the frequency of missing data can be reduced.

15.2. Trial Monitoring

In accordance with 21 CFR 312.56, ICH- GCP, and local regulations, trial monitors will periodically complete on-site monitoring of data with a focus on safety, trial endpoints, data completion, data outliers and data integrity. Trial monitors will schedule an on-site visit with a site coordinator for an appropriate duration based on the scope of data anticipated to be collected. Prior to the visit, a confirmation letter will be sent to the investigative site, which will include a listing of which CRFs and source documents will be reviewed.

Site coordinators are to have all source documents up to date and easily accessible to a monitor.

During an on-site monitoring visit, trial monitors are to:

- Track the overall monitoring process including data collected and entered, visit schedules, and subject screening and enrollment.
- Verify and ensure compliance with the protocol according to GCP and HIPAA requirements.
- Ensure that appropriate data corrections are made, dated, explained, and initialed by the Investigator or representative.
- Assess the impact of any personnel changes on the investigative site's ability to conduct the trial.
- Verify a minimum of the following data points for all subjects: date of birth, signed informed consent, eligibility criteria, medical history, date of enrollment, serious AEs, and mortalities.
- Perform review of informed consent process and review documentation of informed consent for completeness and correctness.

- Perform on-site validation checks of recoded data by reviewing source documents to determine whether the data reported in the EDC system are complete and accurate. Source documents include medical charts, screening records and/or logs, research procedure records and/or files, and other trial related notes.
- Monitor subject safety by verifying that any AE, therapy modification, or concomitant medications are reported in accordance with the protocol.
- Determine whether all AEs, protocol deviations, and protocol violations are appropriately reported within the required time periods according to applicable regulatory requirements as outlined in the protocol and by regulatory agencies.
- Verify that any missed visits and examinations that were not performed, as well as trial withdrawals and/or dropouts are explained and clearly reported.
- Inform the site PI about any deviations from or violations of the trial protocol, GCP and/or regulatory requirements in order for appropriate actions to be taken to prevent recurrence of the deviation and/or violation.
- Inform the Investigator of any major data entry error, delays in data entry, omissions, or eligibility requirement errors.
- Verify that regulatory documentation is accurate, complete, current, and properly maintained.
- Very that PI oversight of trial conduct is documented via signature or initials and date on documentation regarding eligibility, AEs, and abnormal laboratory values.

The monitor may also inspect the investigative site's facilities to verify that proper space for study documents, equipment and investigational product is available.

A debriefing meeting with the PI, site coordinator(s), and the Monitor to review any notable findings will be scheduled toward the end of the on-site visit. The monitor will submit a written monitoring visit report to Capricor and send a follow-up letter with findings to the PI. The report and letter will include a summary of documentation reviewed by the monitor, any significant findings, AEs, protocol deviations and violations, missing regulatory documents and actions taken, to be taken or recommended to ensure compliance. The report and letter will include a list of action items. Investigative sites are expected to complete the list of actions items within 30 days of receipt.

15.2.1. Source Document Requirements

It is highly recommended that the investigative site uses the CRFs and schedule of assessments (Appendix B) to develop a plan for identifying and standardizing where source documentation for data verification will be collected across all trial participants at their site. As part of trial start-up and prior to first enrollment, investigative sites are encouraged to conduct a gap analysis to identify any data points that are not routinely documented in the medical record.

The medical record is the gold standard for source documentation. However, Capricor understands that there may be data points required for this trial that are not collected as routine practice at the investigative site in the medical record for this patient population. Investigative sites may use the provided source document worksheets or create source documents for the

purposes of collecting source data that are not included in the medical record. It is important to remember that "source" documentation is where the information is first recorded.

The investigative site must ensure that all subject source documentation is complete, orderly, and stored in a secure location. For electronic records, the investigative site should abide by the institutional policies for the storage of private health information (PHI). For any paper records containing any PHI, the investigative sites must ensure that the files are double-locked, that is, in a locked filing cabinet within a locked office or suite.

All source documentation is to be de-identified of all unique patient and hospital identifiers by the investigative site prior to review or submission to Capricor or its designee.

15.3. Audits and Inspections

Authorized representatives of Capricor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Capricor audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Capricor immediately if contacted by a regulatory agency about an inspection.

15.4. Retention of Records

The investigative sites must maintain all documentation relating to the trial for a period of five years after the last marketing application approval, or if not approved, two years following the discontinuance of the test article for investigation. If it becomes necessary for Capricor or the Regulatory Authority to review any documentation relating to the trial, the Investigator must permit access to such records.

16. QUALITY CONTROL AND QUALITY ASSURANCE

Capricor will implement and maintain quality control and quality assurance procedures to ensure compliance with the protocol, Good Clinical Practices, and all applicable regulatory requirements, and may conduct a quality assurance audit(s). Please see Section 15.3 for more details regarding the audit process.

16.1. Qualifications and Trainings

Clinical Investigators will be physicians with expertise in the clinical care of patients with DMD in a multi-disciplinary clinical setting that includes neuromuscular medicine, pulmonary, cardiology, and physical therapy.

All Investigators and coordinators will be trained by Capricor, or its designee, in the specifics of the protocol, investigational product and administration procedure at the site initiation visit in advance of the first subject enrollment. The Investigators and coordinators will also undergo a separate training to gain familiarity with the electronic data capture system.

16.2. Good Clinical Practices (GCP)

All Investigators, coordinators and other site personnel involved in care of trial subjects, and/or research data collection must provide certification that they have successfully completed their institutionally required GCP or other Human Subject Protection courses.

16.3. HIPAA or Other Privacy Training

All Investigators and coordinators must provide documentation that they have successfully completed the institutional requirements to ensure subject rights, privacy and security under HIPAA.

16.4. Site Initiation

IRB approval and the clinical trial agreement between the investigative site and Capricor must be signed and executed prior to the site initiation. Additionally, the completed Form FDA 1572, applicable CVs and other regulatory documents must be on file with Capricor prior to site initiation. A representative from Capricor, or its designee, will conduct a site initiation prior to enrollment of the first subject. Investigators, study coordinator(s), investigational pharmacist(s), and infusion suite personnel will participate on the site initiation webinar.

16.5. Protocol Deviations

Efforts to maximize adherence to the protocol will be made through careful and comprehensive training, review of trial data collected via the EDC, and routine communication with all site Investigators.

All protocol deviations and violations are to be documented and captured in the EDC. The investigative site is responsible for reporting deviations and violations to the IRB per the IRB's reporting guidelines. Capricor will ensure reporting to the proper local and federal regulatory authorities in accordance with all applicable federal and local regulations.

Capricor 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, and/or other appropriate courses of action. In addition, the Medical Monitor and biostatistician will review the circumstances of each deviation and violation to determine whether data can reasonably be included in any trial analyses.

17. ETHICS

17.1. Ethics Review

Investigative sites are required to follow their institutional guidelines for obtaining initial approval by the IRB and for submitting continuing reviews to the IRB. Subject enrollment at an investigative site will not commence until initial IRB approval documentation has been received and reviewed by Capricor. The composition and conduct of this committee must conform to the United States CFR and ICH E6.

The informed consent must be reapproved in accordance with the investigative site's IRB policies or at least annually.

Capricor will provide the investigative sites with DSMB approval letters, serious adverse drug reactions and any other applicable correspondence during the trial. Investigative sites are to follow their institutional policies for reporting these correspondences and documents to their IRB.

All IRB approvals and all materials approved/acknowledged by the IRB for this trial, including the subject consent/assent form, recruitment materials, or safety event notifications, must be maintained by the Investigator and made available for inspection.

17.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements. Please reference Section 16 for further information.

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

17.3. Written Informed Consent and Assent

The Investigator is responsible for ensuring that the informed consent process is conducted and documented appropriately by trained site personnel. A signed informed consent, which has been approved by Capricor and the individual site IRB, is required for trial participation. The consent form must incorporate a clinical research authorization for use and disclosure of private health information and a release of medical information that authorizes release of medical records to the trial Investigators, monitors, and Capricor. The Investigators or designated and qualified individuals, will provide a thorough explanation of objectives, subject responsibilities, risks and benefits of the trial, and will fully address all concerns raised by the subject and/or legal guardian. After all issues have been adequately resolved, and the Investigator confirms that the subject has been fully consented, the subject or his legal guardian will be asked to sign the informed consent. The consent process must be documented in the medical chart and a signed copy of the consent and/or assent must be given to the subject and/or legal guardian.

17.3.1. Obtaining Informed Consent and Assent

The Investigators at each center will ensure that the subject and legal guardian (applicable only if the subject is < 18 years of age) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. Subjects and legal guardians must also be notified that they are free to discontinue from the trial at any time. The subject and legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject must sign and date the informed consent form prior to performing any trial procedures. If the subject is <18 years of age, the subject must sign and date the assent form and a legal guardian must sign and date the informed consent form prior to performing any trial procedures. Specific requirements and guidelines for providing assent will be determined by the investigative site's IRB.

17.4. Subject Confidentiality

Confidentiality of all subject records will be maintained according to HIPAA guidelines. Investigators, investigative site IRBs, Capricor, and the FDA may review source documentation for enrolled subjects as necessary, but all unique patient and hospital identifiers will be removed prior to review. If the results of this trial are published, the data will be presented in aggregate, with all subject identifiers removed.

18. PUBLICATION POLICY

Recognizing the importance of communicating clinical trial results to the public and the medical and scientific communities in an accurate and complete manner, the first publication of the trial, to include results from all of the investigative centers in a multi-center publication, will be authored by the lead or national Principal Investigator, and/or other designees assigned by the Steering Committee, for publication in a peer-reviewed scientific journal. All participating Investigators, key site personnel, committees and committee members will be listed in an appendix as part of the main manuscript.

An individual Investigator has the right to publish his/her data after the multi-center publication, unless no such multi-center publication is so published before the eighteen months of the finalization of the multi-center database, in which case the Investigator may publish or submit for publication a manuscript without further delay according to the terms and conditions in the Clinical Trial Agreement.

Additional manuscripts targeting data not included in the first multi-center publication are anticipated and encouraged. In such cases, the Investigator(s) should submit ideas for these additional manuscripts to the Steering Committee that will serve as the clearing house to approve topics, ensure that activity between the Investigator(s) in analyzing the data is coordinated, prioritize data analyses and help determine authorship.

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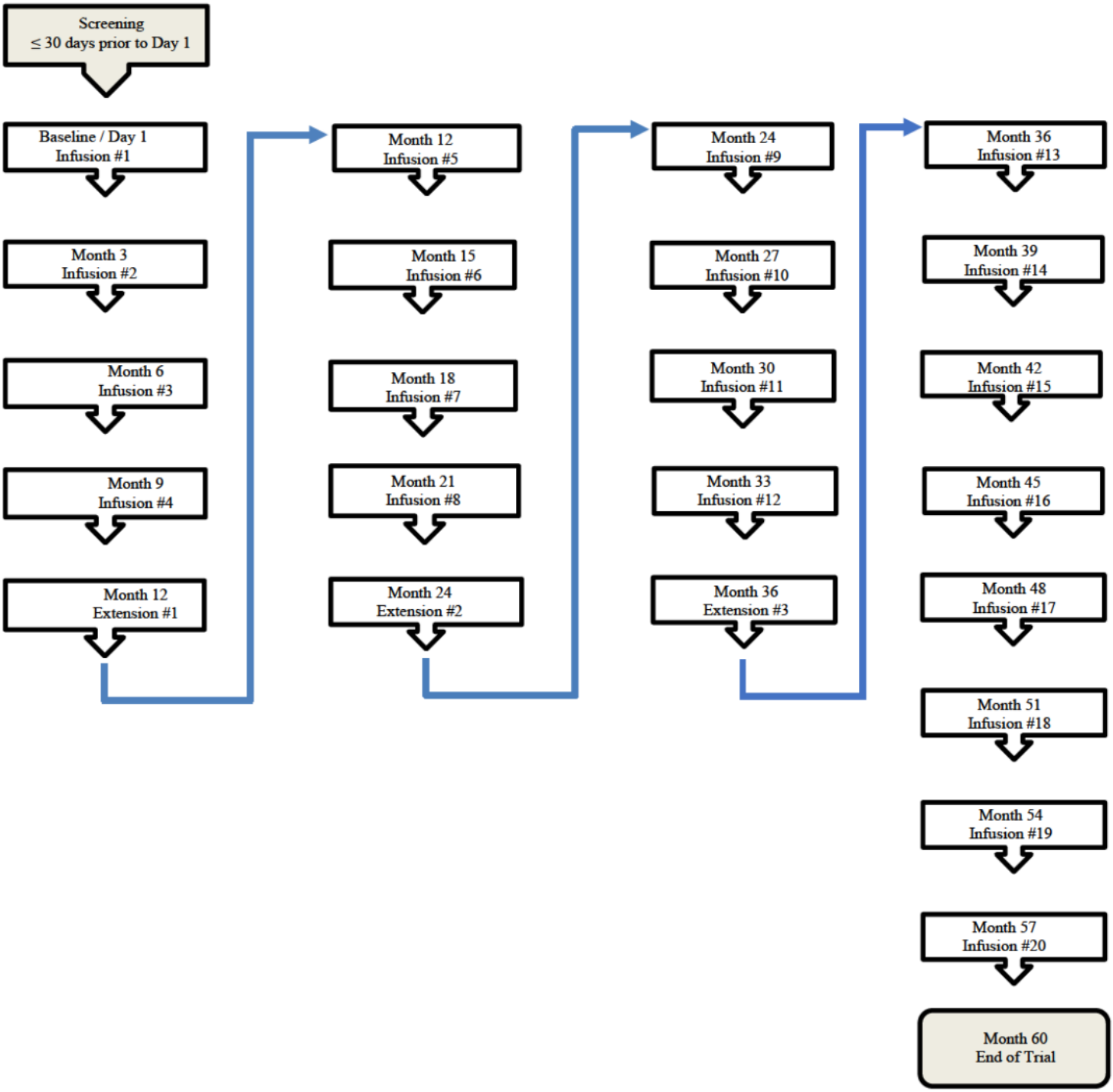
APPENDIX A. TRIAL DESIGN



APPENDIX B. SCHEDULE OF ASSESSMENTS

Procedure / Event	**Screening**[1]	**Baseline**[2] **/ Day 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**	**Month 36**	**Month 39**	**Month 42**	**Month 45**	**Month 48**	**Month 51, 54, 57**	**Month 60** Or Early Term
Trial Day (Visit Window)	*≤ 30 d prior to Day 1*	*1 d*	*(±14)*	*(±14)*	*(±14)*	*(±14)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*
Intravenous Infusion #		*#1*	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*	*#9*	*#10*	*#11*	*#12*	*#13*	*#14*	*#15*	*#16*	*#17*	*#18, 19 20*	
Informed Consent / Assent	X					X				X				X						
Demographics	X																			
Medical History[4]	X																			
Eligibility Assessment	X																			
Pre-Treatment Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Deramiocel (CAP-1002) Infusion[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulna Length[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[8 9]										X				X				X		X
Hematology[8 10]										X				X				X		X
DSA[8]										X				X				X		X
Coagulation Panel[12]																		X[12]	X[12]	
PUL 2.0		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac MRI	Standard-of-Care									X[11]				X[11]				X[11]		X[11]

[1] Some screening assessments may be conducted via telephone, but in-person assessments must be conducted prior to Baseline infusion.
[2] Baseline safety and efficacy assessments will be conducted prior to infusion on Day 1. Every effort should be made to have each subject complete all elements of the trial.
[3] If a subject has started at least one deramiocel infusion and withdraws prior to trial completion, all attempts must be made to perform a final comprehensive visit.
[4] Medical histories will be assessed for upper body functionality (i.e., PUL 2.0) and Left Ventricular Ejection Fraction (i.e., cardiac MRI). The assessment periods will cover the time from the end of HOPE-2 to the beginning of HOPE-2-OLE.
[5] A blood sample for tryptase should be obtained within 3 hours of the onset of allergic signs and symptoms and analyzed locally.
[6] All deramiocel infusions will be conducted in an outpatient setting at the investigative site. It occurs every 3 months anchored from the previous infusion for a total of up to 20 infusions (Day 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36, Month 39, Month 42, Month 45, Month 48, Month 51, Month 54, and Month 57). Prior to each deramiocel infusion, medications will be administered to the subject as determined by the Investigator based on pre-treatment guidelines provided by Capricor and/or institutional protocols to minimize risk of potential severe allergic reactions such as anaphylaxis. Subjects will be observed for at least 2 hours post-infusion, including pulse oximetry monitoring for at least 30 minutes post-infusion. Sites will observe institutional policies related to parenteral infusions and post-infusion monitoring.
[7] Ulna length will be measured in all subjects and height will be calculated using a measurement of ulna length.
[8] Blood samples will be collected using trial-specific laboratory kits and then shipped to and tested at a central or local laboratory. Required sample collection for a visit may occur on multiple days; if the visit includes an IP infusion, sample collections should occur prior to IP administration.
[9] Basic metabolic panel (glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium), comprehensive hepatic panel (albumin, alkaline phosphatase, total protein, ALT, AST, GGT, direct bilirubin, total bilirubin).
[10] CBC with WBC differentials, hemoglobin, hematocrit, and platelet count.
[11] Cardiac MRI will be taken on all subjects at Month 24 or as soon as possible thereafter, Month 36, Month 48, and approximately 12 months after (at Month 60).
[12] Blood for a coagulation panel consisting of D-dimer, fibrinogen, PT/aPTT, INR, CRP, and ESR will be collected and analyzed locally at Months 48, 51, 54, and 57. During each visit, the coagulation panel will be drawn pre-dose, 2-hours (± 30 minutes) post dose, and 24 hours (± 12 hours) post dose.

APPENDIX C. SUMMARY OF CHANGES

AMENDMENT 1.0

The following table presents a complete list of content changes in the protocol amendment.

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AMENDMENT 2.0

The following table presents a complete list of content changes in the protocol amendment.

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AMENDMENT 3.0

The following table presents a complete list of content changes in the protocol amendment.

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AMENDMENT 4.0

The following table presents a complete list of content changes in the protocol amendment.

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AMENDMENT 5.0

The following table presents a complete list of content changes in the protocol amendment.

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Description of Change	Rationale / Justification	Sections Affected
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]