CLINICAL TRIAL PROTOCOL

OPEN-LABEL EXTENSION OF THE HALT CARDIOMYOPATHY PROGRESSION IN DUCHENNE (HOPE-DUCHENNE) TRIAL

Protocol Number:	CAP-1002-DMD-03
Trial Phase:	Phase 2
Product Name:	CAP-1002 Allogeneic Cardiosphere-Derived Cells
IND Number:	[redacted]
Indication:	Duchenne Muscular Dystrophy
Sponsor:	Capricor, Inc. 8840 Wilshire Blvd., 2nd Floor Beverly Hills, CA 90211
Sponsor Contact:	[redacted]
Original Protocol:	08-Jan-2018
Amendment 1.0	12-Feb-2018

1.1. Investigator's Agreement

Trial Title:	Open Label Extension of the Halt cardiomyOPathy progrEssion in Duchenne (HOPE-Duchenne) Trial.
Short Title:	Halt cardiomyOPathy progrEssion in Duchenne (HOPE-OLE)
Protocol Number:	CAP-1002-DMD-03
Amendment 1.0:	12-Feb-2018

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

1.2. Sponsor Approval

Trial Title:	Open Label Extension of the Halt cardiomyOPathy progrEssion in Duchenne (HOPE-Duchenne) Trial
Protocol Number:	CAP-1002-DMD-03
Amendment 1.0:	12-Feb-2018

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

1.3. Procedures in Case of Emergency

Please reference the Manual of Procedures for detailed information on serious adverse event reporting.

Table 1: Emergency Contact Information

Role in Trial	Name	Address and Telephone Number
[redacted]	[redacted]	Capricor, Inc. 8840 Wilshire Blvd., 2nd Floor Beverly Hills, CA 90211 Tel: [redacted] Email: [redacted]
[redacted]	[redacted]	Capricor, Inc. 8840 Wilshire Blvd., 2nd Floor Beverly Hills, CA 90211 Tel: [redacted] Email: [redacted]

2. SYNOPSIS

Name of Sponsor: Capricor, Inc.	
Name of Investigational Product: CAP-1002 Allogeneic Cardiosphere-Derived Cells	
Name of Active Ingredient: Cardiosphere-Derived Cells	
Title of Trial: Open Label Extension of the Halt cardiomyOPathy progrEssion in Duchenne (HOPE-Duchenne) Trial	
Trial Name: Halt cardiomyOPathy progrEssion in Duchenne (HOPE-OLE)	
Trial Centers: Up to 3 (USA)	
Principal Investigators: This is a multi-center trial with multiple Principal Investigators.	
Studied Period: Approximately 6 months	**Phase of Development:** 2

Objectives:

Primary: To provide CAP-1002 to subjects who were randomized to the Usual Care Treatment Group of the HOPE-Duchenne trial and completed 12 months of follow-up.

Secondary: To explore the safety and efficacy of intravenous administration of CAP-1002 with repeat dose at Month 3.

Methodology: This Phase 2, multi-center, open label extension trial will provide CAP-1002 to subjects that were randomized to the Usual Care Treatment Group of the HOPE-Duchenne trial (CAP-1002-DMD-01) and explore the safety of two intravenous administrations of CAP-1002, each separated by three months. Subjects will undergo targeted tests and procedures 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 CAP-1002. Administration of CAP-1002 (Day 1) should occur within a maximum of 14 days following confirmation of eligibility; if a delay of more than 14 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.

All CAP-1002 infusions will be conducted in an outpatient setting at the investigative site on Day 1 and Month 3. 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.

A safety phone call will be performed 14 days (±3 days) after each CAP-1002 infusion, and 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.

Blood samples will be collected before each CAP-1002 administration (Day 1 and Month 3), after each CAP-1002 infusion (Week 4 and Month 4) and at Month 6, unless otherwise indicated, for donor specific antibody (DSA) testing and routine serum chemistries, hematology and cardiac enzymes. HLA

typing will occur before the first CAP-1002 administration on Day 1. Collection will occur either at the investigative site or remotely at a designated central laboratory patient service center.

Trial visits at the investigative site will occur at Months 3 and 6 (±14 days, respectively). Subjects will complete safety and efficacy assessments prior to CAP-1002 administration at the Month 3 trial visit.

The ***primary safety endpoints*** include the incidence of the following from baseline through the 6-month timepoint:

- Acute respiratory decompensation within 2 hours following IP administration
- Hypersensitivity reaction
  - Hypersensitivity reaction is defined as a clinical syndrome including, but not limited to, fever, leukocytosis, or rash with onset ≤ 2 hours post infusion and lasting < 24 hours, in the absence of clinical signs of concomitant infection.
- All-cause mortality
- Serious adverse events
- Treatment-emergent adverse events related to IP or administration procedure
- Immune sensitization syndrome
  - Immune sensitization syndrome shall be defined as: (a) clinical signs and symptoms consistent with systemic inflammation (e.g., fever, leukocytosis, rash, or arthralgia) with onset ≥ 24 hours post infusion and the absence of clinical signs of concomitant infection, **AND** (b) elevation of anti-human leukocyte antigen (HLA) antibodies against the donor cells (i.e., DSAs), detected ≤ 30 days following onset of syndrome, of (i) ≥ 2000 mean fluorescent intensity (MFI) if baseline MFI ≤ 1000, or (ii) ≥ 2 times baseline otherwise

The ***exploratory endpoints*** include the change from baseline to each assessment timepoint for the following assessments:

- All subjects
  - Mid-level (elbow) dimension of the Performance of Upper Limb (PUL) 1.2
  - Mid- and distal-level (elbow) dimension of the PUL 1.2
  - High-level (shoulder) dimension of the PUL 1.2
  - Left ventricular structure and function as assessed by cardiac MRI including regional systolic left ventricular wall thickening ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, regional wall thickness, and circumferential strain
  - Slow vital capacity (SVC), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak cough flow (PCF), and inspiratory flow reserve (IFR)
- Ambulatory subjects only

– 6-Minute Walk Test (6MWT)

Oversight of the trial will be provided by the trial Steering Committee, an independent Data Safety Monitoring Board (DSMB), and an independent, Clinical Events Committee (CEC) that will adjudicate all potential primary safety endpoints.

Number of Subjects: Approximately 10 subjects will be enrolled

Diagnosis and Main Criteria for Inclusion: Subjects randomly assigned to the Usual Care Treatment Group of the HOPE-Duchenne trial and who completed the 12-month follow-up period will be evaluated for eligibility to participate in the Open Label Extension trial. Eligibility criteria will be assessed within 30 days prior to first infusion on Day 1 unless otherwise noted.

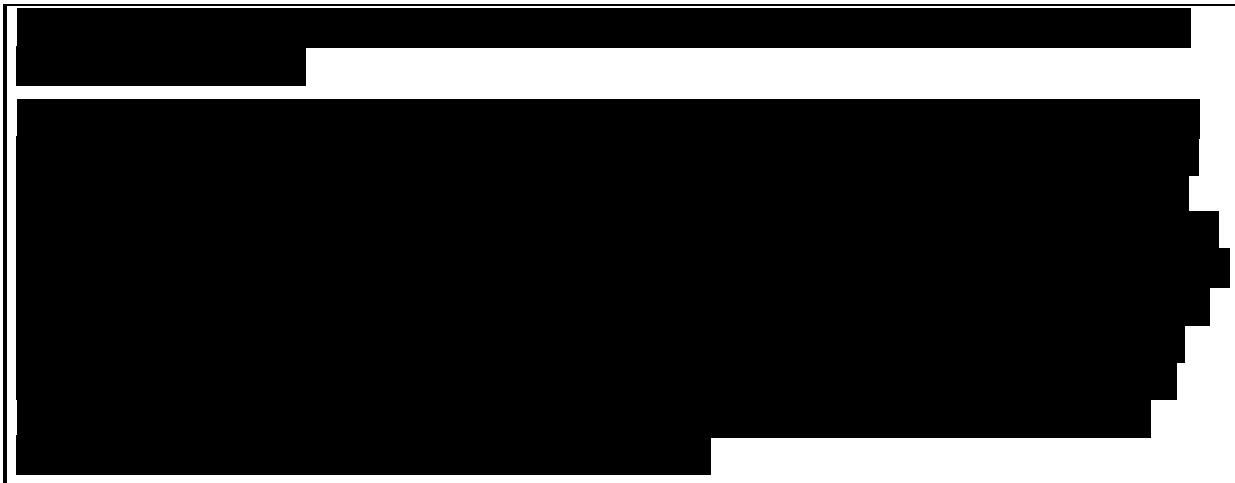
Inclusion Criteria:

1. Documented enrollment in the Usual Care Treatment Group of the HOPE-Duchenne 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 CAP-1002 infusions and routine blood collections 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. Left ventricular ejection fraction (LVEF) < 35% within 6 months of screening
2. Planned or likely major surgery in the next 6 months after planned first infusion
3. 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 at screening
4. History of non DMD-related chronic respiratory disease including, but not limited to, asthma, bronchitis, and tuberculosis
5. Acute respiratory illness within 30 days prior to screening
6. Known hypersensitivity to dimethyl sulfoxide (DMSO) or bovine products
7. Treatment with investigational product ≤ 6 months prior to first infusion
8. History, or current use, of drugs or alcohol that could impair ability to comply with participation in the trial
9. Inability to comply with the investigational plan and follow-up visit schedule for any reason, in the judgment of the investigator

Investigational Product, Dosage and Mode of Administration: [redacted]



Duration of Treatment: CAP-1002 is administered as a single intravenous infusion on Day 1 and at Month 3 for a total of 2 administrations.

Duration of Trial: All subjects will be followed for 6 months post Day 1 infusion.

Criteria for evaluation:

Safety

Safety assessments at Week 4 and Months 3,4 and 6, unless otherwise indicated, will include the following: vital signs, height, weight, physical examination, 12-lead ECG, adverse events, DSA assessment, and clinical laboratory testing (serum chemistries, hematology, and cardiac enzymes). Adverse events and concomitant medications will also be collected during each 14-day post-infusion safety phone call, or 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 subject.

Efficacy

The following efficacy outcome measures will be performed at Months 3 and 6 unless otherwise specified: PUL 1.2, spirometry, 6MWT when deemed appropriate by the Investigator, and cardiac MRI.

Statistical Methods:

Sample Size

Up to 10 subjects that were randomized to Usual Care Treatment Group and completed the 12-month follow-up period for the HOPE-Duchenne trial will be enrolled in this trial.

Analysis Populations

Intent-to-Treat (ITT) Population: All patients who meet the enrollment criteria and are enrolled in the trial. These patients will also constitute the Safety population.

Per Protocol (PP) Population: All enrolled subjects who have no protocol deviations/violations that could significantly impact completeness, accuracy, and/or reliability of the trial data. The list of subjects in the per protocol population will be compiled prior to database lock.

Safety Analysis

All primary safety endpoints 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. Primary safety endpoints that are adjudicated by the Clinical Events Committee (CEC) will be further described 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 1.2 scores (including the mid-level dimension, combined mid and distal-level dimensions, and high-level dimension), in left ventricular structure and function parameters (including ejection fraction, wall thickness, end-diastolic and end-systolic volumes, stroke volume, and circumferential strain, in pulmonary function (including SVC, FEV_1, FVC, MIP, MEP, PCF, and IFR) and in 6-minute walk test distance for ambulatory patients.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Term	Explanation
6MWT	Six-Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CDC	Cardiosphere-Derived Cells
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CK-MB	Creatine kinase MB Isoenzyme
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
DCM	Dilated Cardiomyopathy
DMD	Duchenne Muscular Dystrophy
DMSO	Dimethyl Sulfoxide
DSA	Donor-Specific Antibody
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture

Term	Explanation
ESR	Expedited Safety Report
ET	Early Termination
ETFE	Ethylene Tetrafluoroethylene
FDA	U.S. Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FVC	Force Vital Capacity
GCP	Good Clinical Practice
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
HLA	Human Leukocyte Antigen
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IFR	Inspiratory Flow Reserve
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous

Term	Explanation
IWRS	Interactive Web Response System
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
mITT	Modified Intent-to-Treat
mL	Milliliter
MOP	Manual of Procedures
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
PFT	Pulmonary Function Test

Term	Explanation
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
PUL	Performance of the Upper Limb
QOL	Quality of Life
RBC	Red Blood Cell
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
TLC	Total Lung Capacity
v/v	Volume to Volume
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

5. INTRODUCTION

5.1. 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).

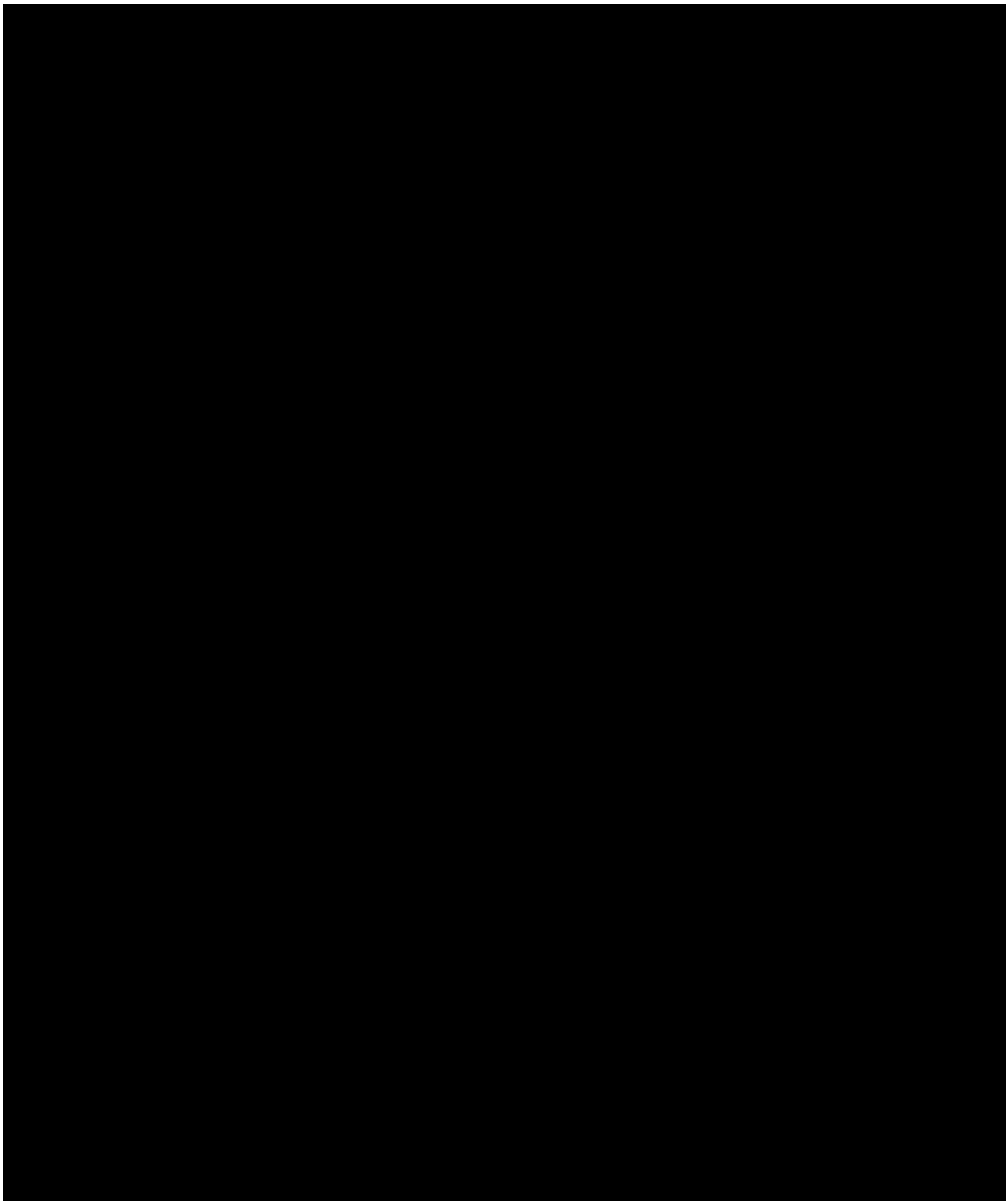
Dystrophin is a cytoplasmic protein encoded by the *dmd* gene, which links cytoskeletal actin filaments to membrane proteins. The dystrophin protein acts as a shock absorber during muscle fiber contraction by linking the actin of the contractile apparatus to the layer of connective tissue that surrounds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

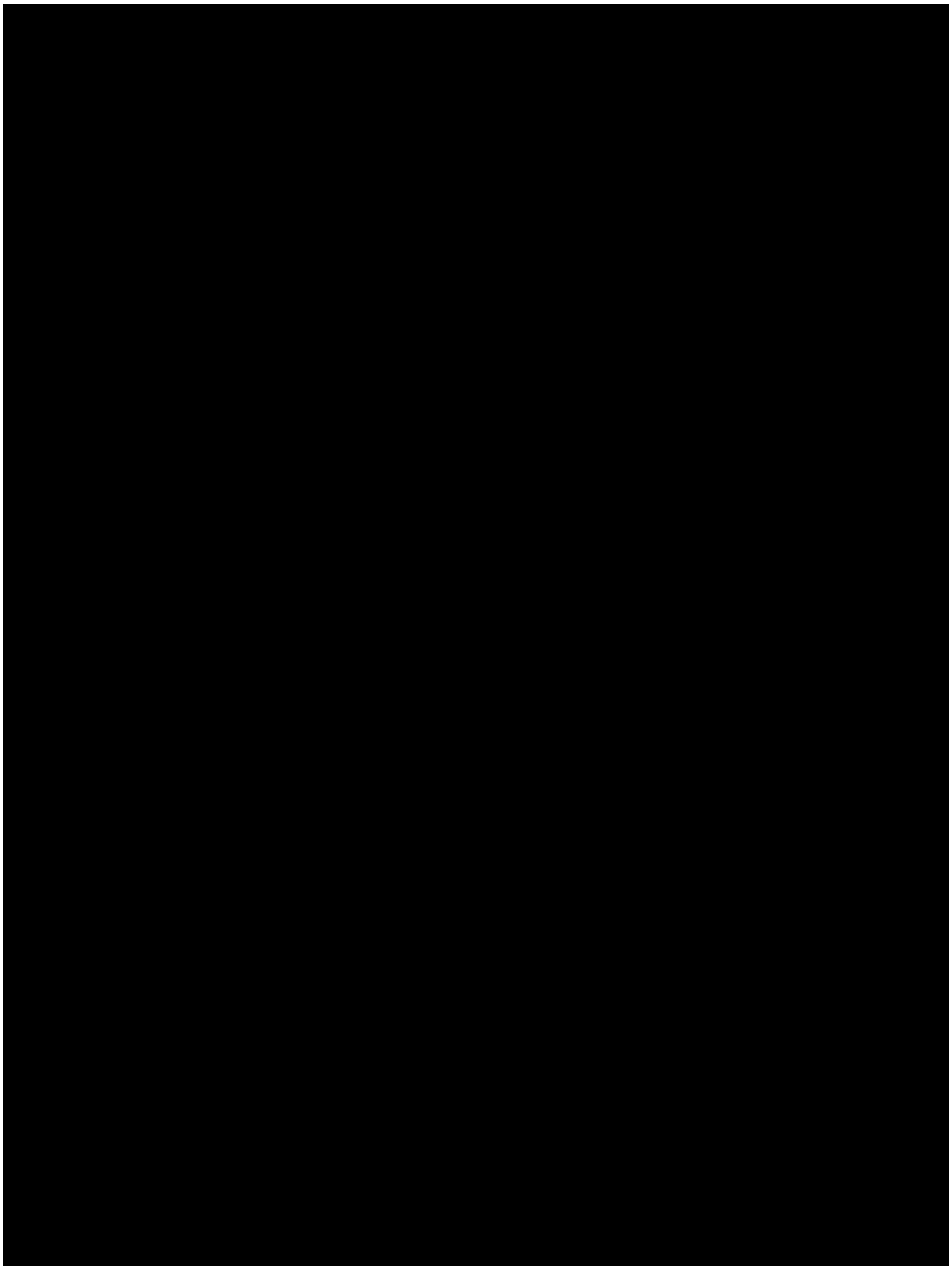
Due to the lack of dystrophin, the connection between the actin cytoskeleton and connective tissue is lost, inducing excessive membrane fragility and permeability, dysregulation of calcium homeostasis, and oxidative damage, which results in muscle cell necrosis and a chronic inflammatory state. Initially, 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).

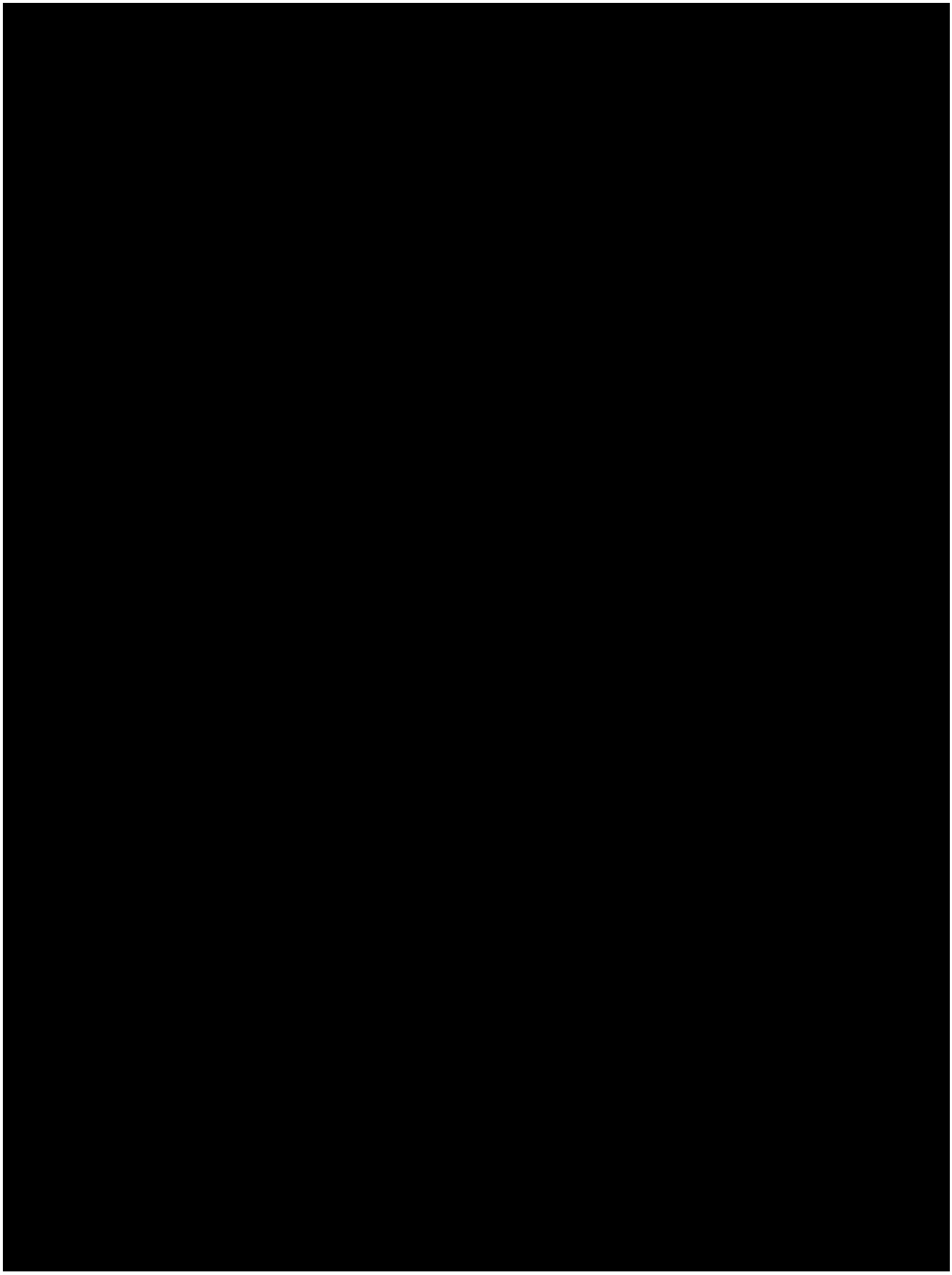
DMD symptoms begin in early childhood, with degeneration occurring progressively in the skeletal musculature and ultimately in the heart and respiratory muscles, resulting in premature death (Hendriksen et al., 2015). Progressive weakness and muscle atrophy caused by degenerating muscle fibers begins 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).

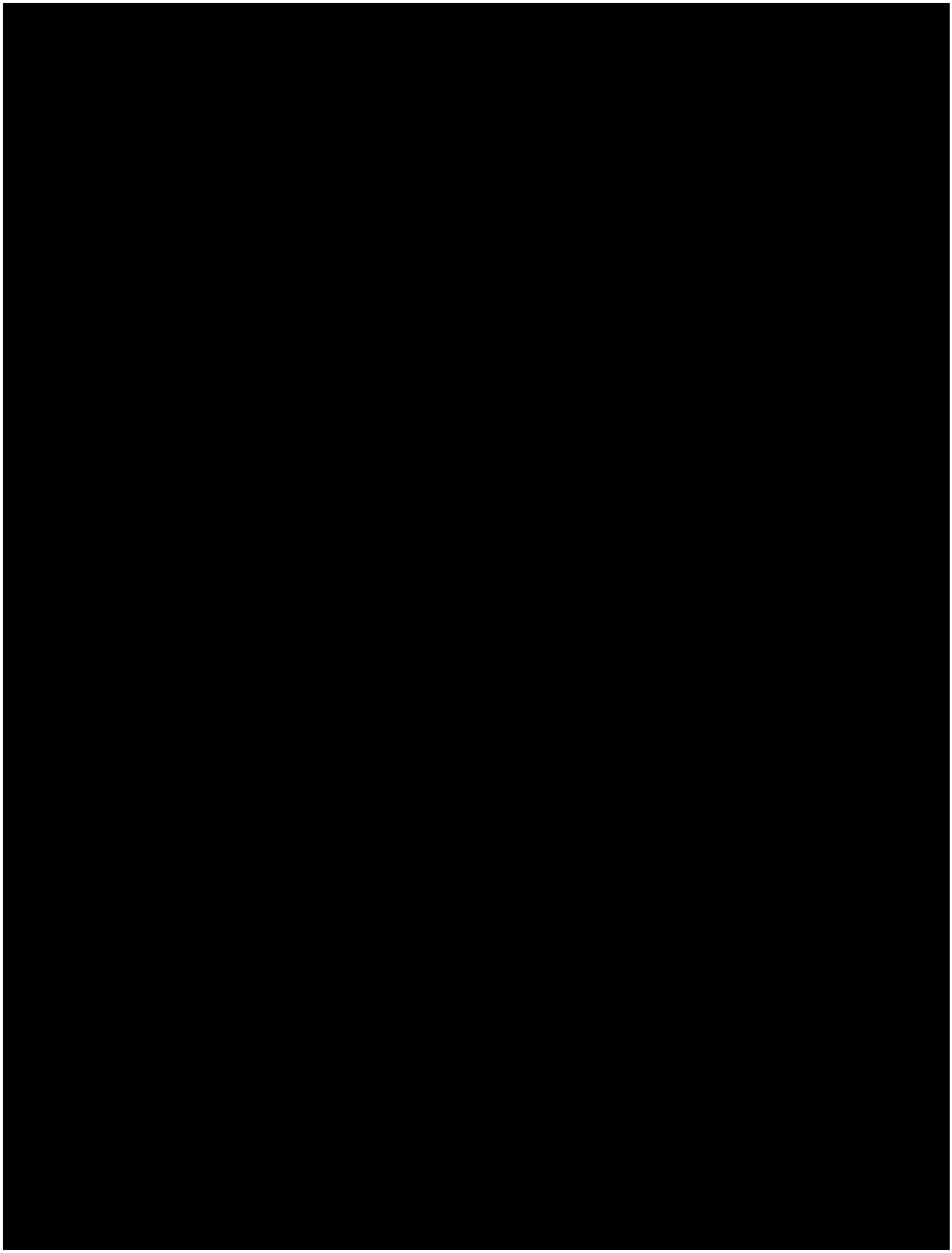
As the disease progresses, the muscles in the diaphragm that assist in breathing and coughing become weaker. Affected individuals experience breathing difficulties, respiratory infections, and swallowing problems. Almost all DMD patients will develop cardiomyopathy (Aartsma-Rus et al., 2016). Pneumonia, 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.









5.4. Risks and Benefits

In over 131 subjects treated with CAP-1002, the combination a favorable safety profile and preliminary indications of efficacy suggest a favorable risk-benefit profile of CAP-1002.

[redacted]

5).

Based on these data, the benefit-risk balance for CAP-1002 is considered favorable, and warrants additional clinical investigation.

5.5. Trial Rationale

The proposed open label extension (OLE) trial will enroll subjects randomized to the Usual Care Treatment Group in the HOPE-Duchenne trial (CAP-1002-DMD-01) and who completed the 12-month follow-up period. All subjects enrolled in the OLE will receive CAP-1002.

CAP-1002 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]

5.6. Dose Justification

5.6.1. Dosing Interval

Data from HOPE-Duchenne show a maintenance of benefit in PUL 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 in the proposed clinical trial, with a second dose administered after 3 months. [redacted]. Following a waning of the effect on cardiac function, repeat dosing of CDCs at an interval of 3 months led to a second improvement in cardiac function. 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.

5.6.2. Dose Selection

The [redacted] dose selected for testing in the open label extension trial was chosen because the dose already demonstrated preliminary efficacy via intracoronary infusion in the HOPE-Duchenne trial, and would be expected to be similarly efficacious via intravenous administration given what is known about cell biodistribution and engraftment post infusion by either route.

[redacted]

[redacted]

5.6.3. Repeat Administrations

The other element of safety relevant for the open label extension 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 CAP-1002 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. These collective data suggest that repeat administration of CAP-1002 should be reasonably safe in humans.

5.7. Trial Population

The target population for this trial is pediatric and adult males with a diagnosis of DMD who were randomized to the Usual Care Treatment Group of the HOPE-Duchenne trial and completed the 12-month follow-up period, and meet the OLE trial eligibility criteria (see Section 8) that focus on minimizing risk of participation in the extension trial.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this trial is to provide CAP-1002 to subjects who were randomized to the Usual Care Treatment Group of the HOPE-Duchenne trial and completed the 12-month follow-up period.

6.2. Secondary Objectives

The secondary objectives of this trial are to explore the safety and efficacy of intravenous administration of CAP-1002 with repeat dosing at Month 3.

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This Phase 2, multi-center, open label extension trial will provide CAP-1002 to subjects who were randomized to the Usual Care Treatment Group and completed 12 months of follow-up in the HOPE-Duchenne trial. The trial will assess the safety of CAP-1002, administered as two IV infusions, each separated by 3 months. All subjects will undergo targeted tests and procedures within 30 days prior to first infusion, unless otherwise stated, to confirm eligibility based on protocol inclusion and exclusion criteria.

Eligible subjects will undergo baseline safety and efficacy assessments (Table 3) prior to the first infusion of CAP-1002. Administration of CAP-1002 (Day 1) should occur within a maximum of 14 days following confirmation of eligibility; if a delay of more than 14 days between enrollment and CAP-1002 administration is unavoidable, a conversation between the Investigator and Medical Monitor should occur to determine the need for repeat assessments prior to infusion. For the purposes of this trial, enrollment is defined as the time consent is signed.

All intravenous infusions will be conducted in an outpatient setting at the investigative site on Day 1 and at Month 3. 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.

A safety phone call will be performed 14 days (±3 days) after each CAP-1002 infusion, and 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.

Blood samples will be collected at Week 4 and Month 4 (±7 days, respectively) for DSA testing and safety laboratory assessments. Collection will occur either at the investigative site or remotely at a designated central laboratory patient service center.

Subsequent trial visits at the investigative site will occur at Months 3 and 6 (±14 days, respectively). Subjects will complete safety and efficacy assessments at each of these visits and prior to CAP-1002 administration in the case of the Month 3 trial visit.

7.2. Trial Endpoints

7.2.1. Safety Endpoints

The ***primary safety endpoints*** include the incidence of the following from baseline through the 6-month timepoint:

- Acute respiratory decompensation within 2 hours following IP administration
- Hypersensitivity reaction
  - Hypersensitivity reaction is defined as a clinical syndrome including, but not limited to, fever, leukocytosis, or rash with onset ≤ 2 hours post infusion and lasting < 24 hours, in the absence of clinical signs of concomitant infection.
- All-cause mortality
- Serious adverse events

- Treatment-emergent adverse events related to IP or administration procedure
- Immune sensitization syndrome
  - Immune sensitization syndrome shall be defined as: (a) clinical signs and symptoms consistent with systemic inflammation (e.g., fever, leukocytosis, rash, or arthralgia) with onset ≥ 24 hours post infusion and the absence of clinical signs of concomitant infection, **AND** (b) elevation of anti-human leukocyte antigen (HLA) antibodies against the donor cells (i.e., DSAs), detected ≤ 30 days following onset of syndrome, of (i) ≥ 2000 mean fluorescent intensity (MFI) if baseline MFI ≤ 1000, or (ii) ≥ 2 times baseline otherwise

7.2.2. Exploratory Endpoints

The ***exploratory endpoints*** include the change from baseline to each assessment timepoint for the following assessments:

- All subjects
  - Mid-level (elbow) dimension of the PUL 1.2
  - Mid- and distal-level (elbow) dimension of the PUL 1.2
  - High-level (shoulder) dimension of the PUL 1.2
  - Left ventricular structure and function as assessed by cardiac MRI including regional systolic left ventricular wall thickening, ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, regional wall thickness, and circumferential strain
  - Slow vital capacity (SVC), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak cough flow (PCF), and inspiratory flow reserve (IFR)
- Ambulatory subjects only
  - 6-Minute Walk Test (6MWT)

7.3. Number of Subjects

Up to 10 subjects will be enrolled.

7.4. Treatment Assignment

All subjects will receive open-label CAP-1002 ([redacted] at Day 1 and Month 3 via IV infusion.

7.5. Dose Adjustment Criteria

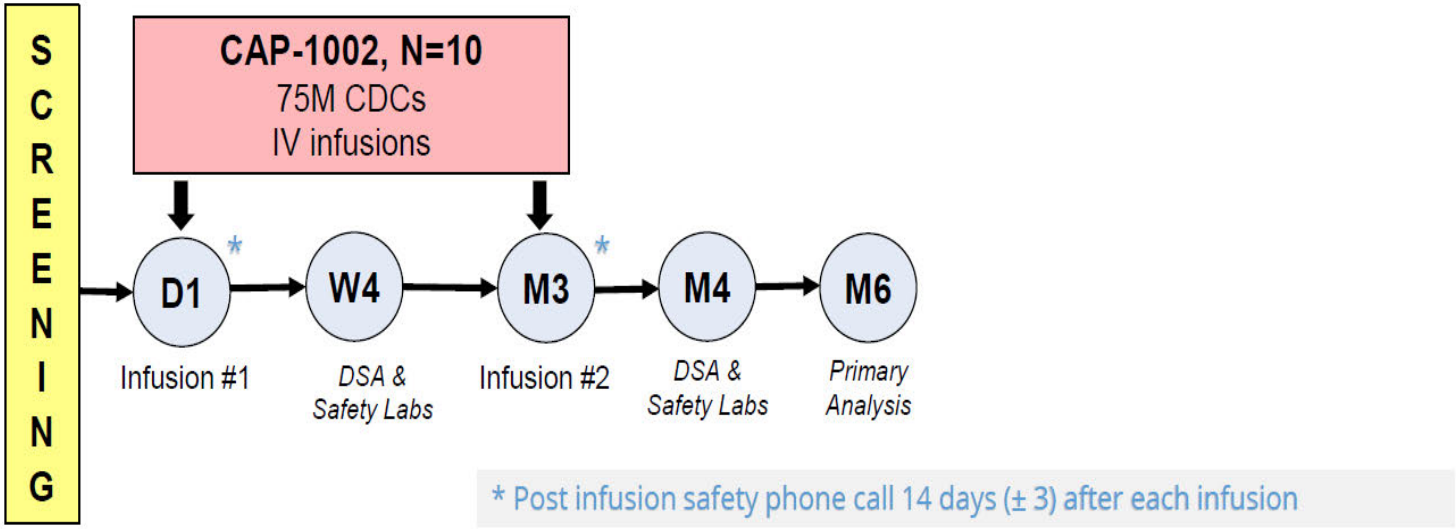
There are no planned dose adjustments. Should an acute toxicity arise during the infusion (e.g., hypersensitivity reaction, pulmonary decompensation, etc.), the infusion should be terminated immediately, and the actual total dose administered recorded. Any decision about re-challenging

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.

7.6. 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.

Figure 1: Trial Design



Safety Outcome Measures: AEs, PE, VS, WT & HT, ECG, CBC w/ diff, Hgb, HCT & plts, basic metabolic panel, comprehensive hepatic panel, CK, CK-MB, cTnI, DSA
Efficacy Outcome Measures: cMRI, PUL 1.2, 6MWT, core lab standardized PFTs (SVC, spirometry, MIP & MEP, PCF and IFR)

Table 3: Schedule of Assessments

Procedure / Event [1]	**Screening**	**Day 1 (Infusion #1)**	**Post-Infusion #1 Safety Monitoring**	**Week 4**	**Month 3 (Infusion #2)**	**Post-Infusion #2 Safety Monitoring**	**Month 4**	**Month 6 / Early Termination**[2]
Trial Day (Visit Window)	***≤ 30 days prior to Day 1***		***14 days (±3) after Infusion #1***	***30 days (± 7)***	***90 days (±14)***	***14 days (±3) after Infusion #2***	***120 days (± 7)***	***180 (±14)***
Informed Consent / Assent	X							
Eligibility Assessment	X	X						
Prior & Concomitant Meds	X	X	X		X	X		X
Medical History	X							
Medical Status Questionnaire		X			X			X
Adverse Events	X	X	X		X	X		X
CAP-1002 IV Infusion[3]		X			X			
Post-Infusion Safety Call [4]			X			X		
Vital Signs		X			X			X
Height / Ulna Length[5]		X			X			X
Weight		X			X			X
Physical Examination		X			X			X
12-Lead ECG		X			X			X
Serum Chemistry[6] [7]	X	X		X	X		X	X
Hematology[6] [8]		X		X	X		X	X
Cardiac Enzymes[6] [9]		X			X			X
HLA Typing[6]		X						

Procedure / Event [1]	**Screening**	**Day 1 (Infusion #1)**	**Post-Infusion #1 Safety Monitoring**	**Week 4**	**Month 3 (Infusion #2)**	**Post-Infusion #2 Safety Monitoring**	**Month 4**	**Month 6 / Early Termination**[2]
Trial Day (Visit Window)	***≤ 30 days prior to Day 1***		***14 days (±3) after Infusion #1***	***30 days (± 7)***	***90 days (±14)***	***14 days (±3) after Infusion #2***	***120 days (± 7)***	***180 (±14)***
Donor-Specific Antibodies[6]		X		X	X		X	X
PUL 1.2		X			X			X
6-Minute Walk Test[10]		X			X			X
Pulmonary Function Testing[11]		X			X			X
Cardiac MRI[12]	X							X

[1] Sites will complete assessments in the following sequence: 1) safety and other trial assessments, excluding blood collection (e.g., vital signs, height, weight, 12-lead electrocardiogram [ECG], etc.), 2) pulmonary function testing (PFT), 4) PUL 1.2, 5) 6MWT, 6) blood collection, 7) cardiac MRI (if applicable), and 8) CAP-1002 Infusion (if applicable). All efforts must be made for the same clinical evaluator to complete assessments for the same subject at the same time of day throughout the trial (preferably in the morning).

[2] All attempts must be made to perform the trial assessments indicated for the Month 6 visit (i.e., final comprehensive visit) for subjects that decide to early terminate early from the trial after starting at least one CAP-1002 infusion.

[3] All CAP-1002 infusions will be conducted in an outpatient setting at the investigative site. 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 local institutional policies related to parenteral infusions and post infusion monitoring.

[4] A safety phone call will be performed 14 days (±3 days) after each CAP-1002 infusion, and 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.

[5] If standing height cannot be measured, height will be calculated using a measurement of ulna length per Section 13.1.2.

[6] Blood samples will be collected using trial-specific laboratory kits, and then shipped to and tested at a central laboratory. Required sample collection for a visit may occur on multiple days; if the visit includes a CAP-1002 infusion, sample collections should occur prior to CAP-1002 administration.

[7] Basic metabolic panel (Glucose, Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Calcium), comprehensive hepatic panel (Albumin, Alkaline Phosphatase, Total Protein, ALT, AST, Direct Bilirubin, Total Bilirubin)

[8] CBC with WBC differential, hemoglobin, hematocrit and platelet count

[9] CK-MB and troponin I

[10] Ambulatory subjects

[11] PFT testing sequence: SVC, forced maneuver (FEV_1/FVC/PEF), MIP, MEP, PCF, and IFR.

[12]Subjects will undergo cardiac MRI if they are physically capable as determined by an Investigator. Subjects that cannot complete a cardiac MRI as part of the trial will complete an echocardiogram at screening using the site's local equipment, acquisition protocol, and evaluation procedures. The reported LVEF from a local interpretation, whether it's measured via cardiac MRI or echocardiogram, will be used to assess eligibility (exclusion criterion 1).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

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

8.1. 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 Usual Care Treatment Group of the HOPE-Duchenne 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 CAP-1002 infusions and routine blood collections in the judgement of the Investigator
4. Assessed by the Investigator as willing and able to comply with the requirements of the trial

8.2. Subject Exclusion Criteria

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

1. Left ventricular ejection fraction (LVEF) < 35% within 6 months of screening
2. Planned or likely major surgery in the next 6 months after planned first infusion
3. 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 at screening
4. History of non DMD-related chronic respiratory disease including, but not limited to, asthma, bronchitis, and tuberculosis
5. Acute respiratory illness within 30 days prior to screening
6. Known hypersensitivity to dimethyl sulfoxide (DMSO) or bovine products
7. Treatment with investigational product ≤ 6 months prior to first infusion
8. History, or current use, of drugs or alcohol that could impair their ability to comply with participation in the trial
9. Inability to comply with the investigational plan and follow-up visit schedule for any reason, in the judgment of the investigator

8.3. 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. All subjects, including screen failures, must be accounted for in the clinical database.

8.4. 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 the Month 6 visit (i.e., final comprehensive 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 CAP-1002 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 CAP-1002 infusion and then complete a final comprehensive visit.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Product

CAP-1002 consists of allogeneic cardiosphere-derived cells or CDCs in a cryogenic cell preservation solution. CCI

9.2. Treatment Compliance

CAP-1002 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.

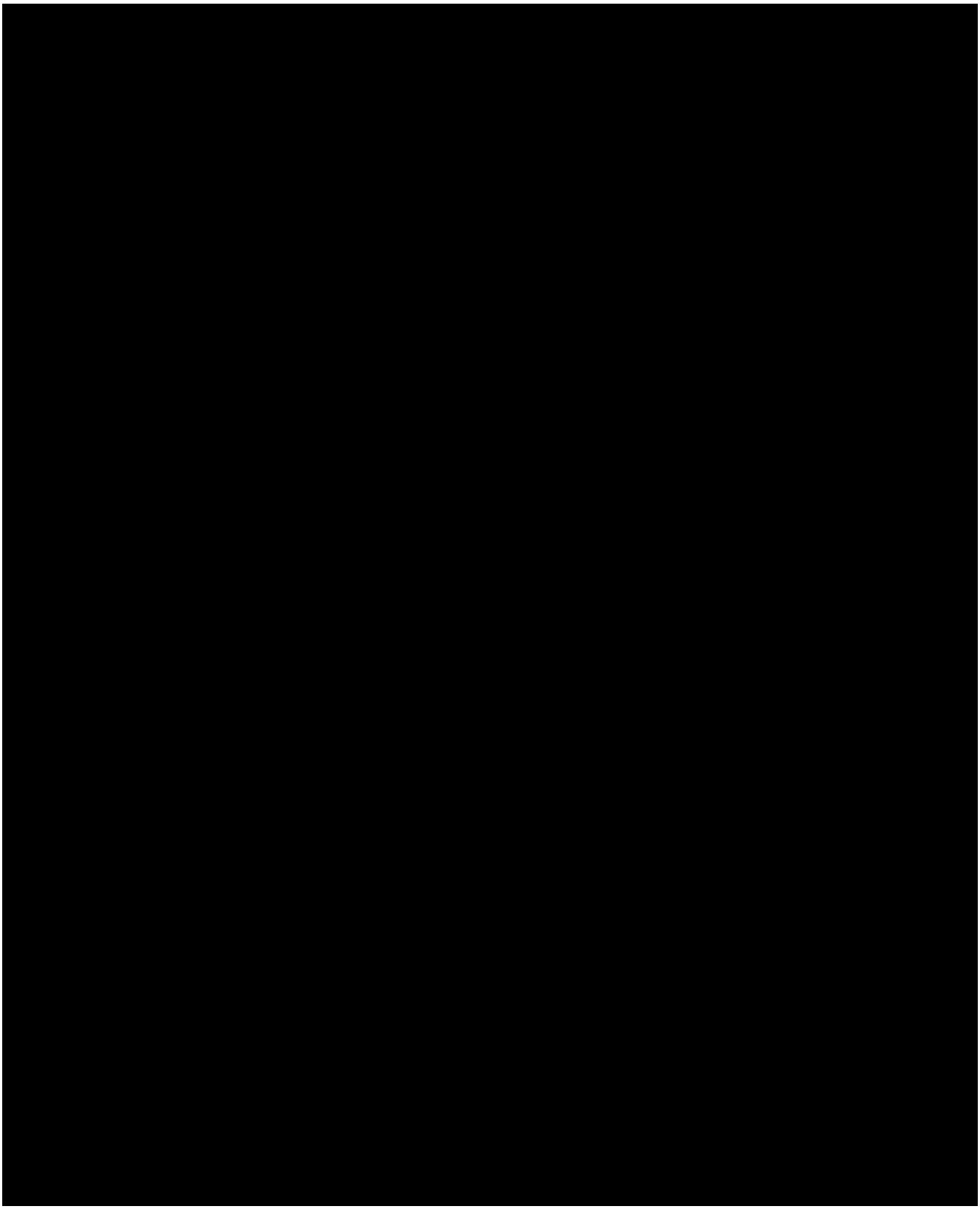
10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

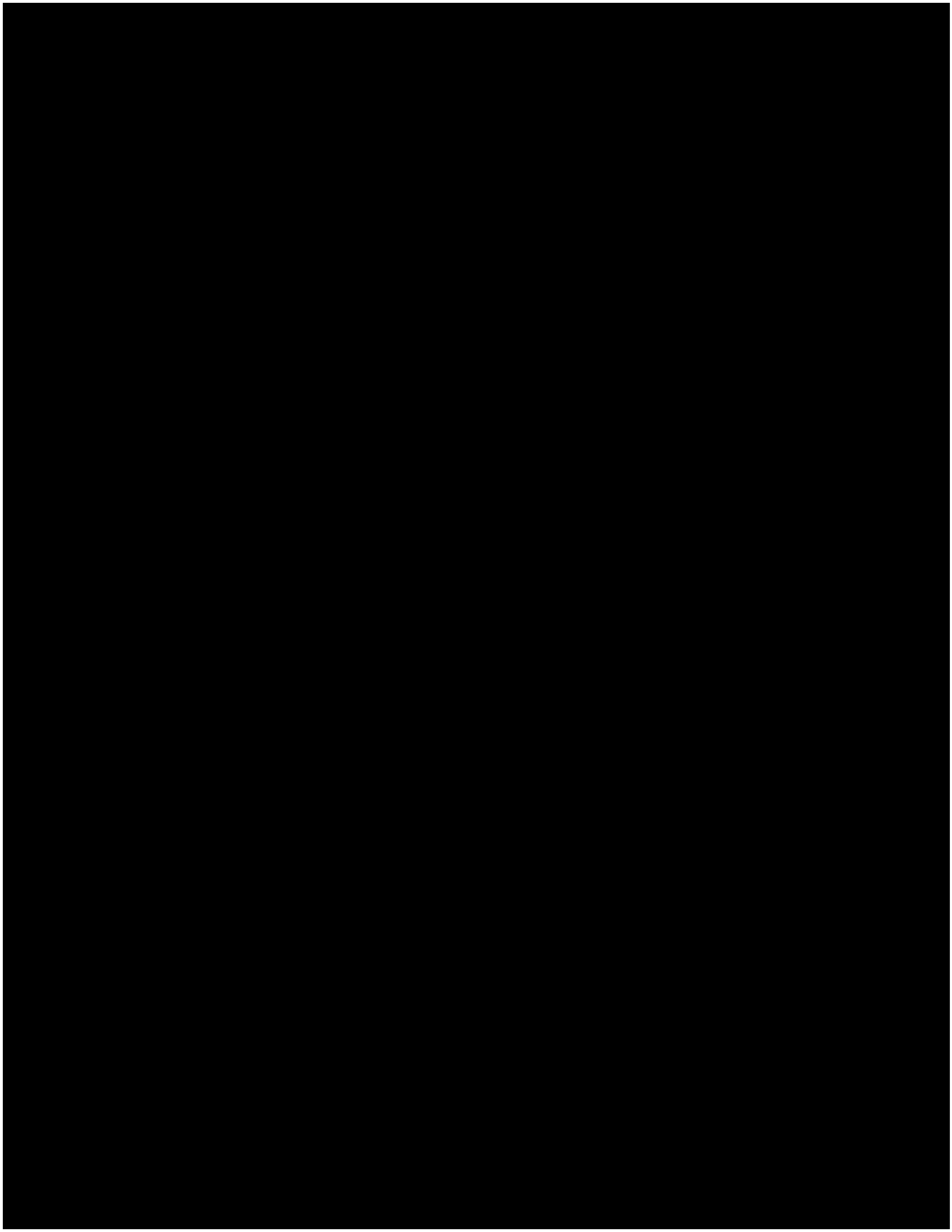
Detailed investigational product information can be found in the Investigator's Brochure (IB) and the Investigational Product Manual. Below and elsewhere in the protocol, reference is made to an investigational pharmacist which is typically a person licensed to dispense prescription medication usually within a special unit of the institutional pharmacy that handles all investigational products. CAP-1002 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, 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 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 CAP-1002 who may not be a licensed pharmacist.

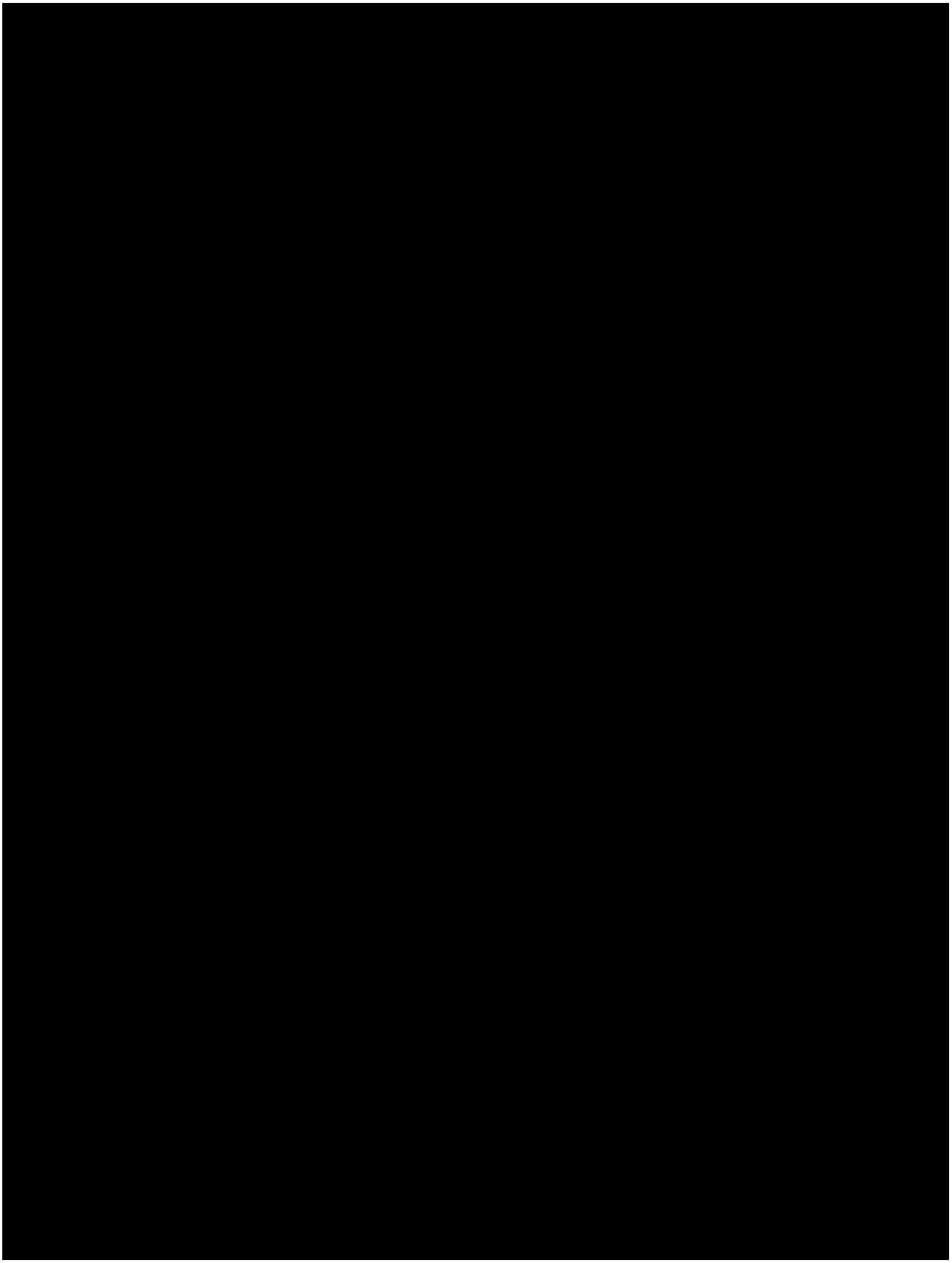
10.2. Master Cell Banks / CDC Donor

CDCs will be grown from a donor unrelated to the recipients. Subjects will receive CDCs produced from the same Master Cell Bank (MCB) without regard to pre-existing DSA levels and based on lot available inventory. A subject's anti-HLA antibody levels specific to the CDC

donor used for CAP-1002 production (i.e., DSA) will be assessed at screening and throughout the course of the trial per Section 13.1.5.



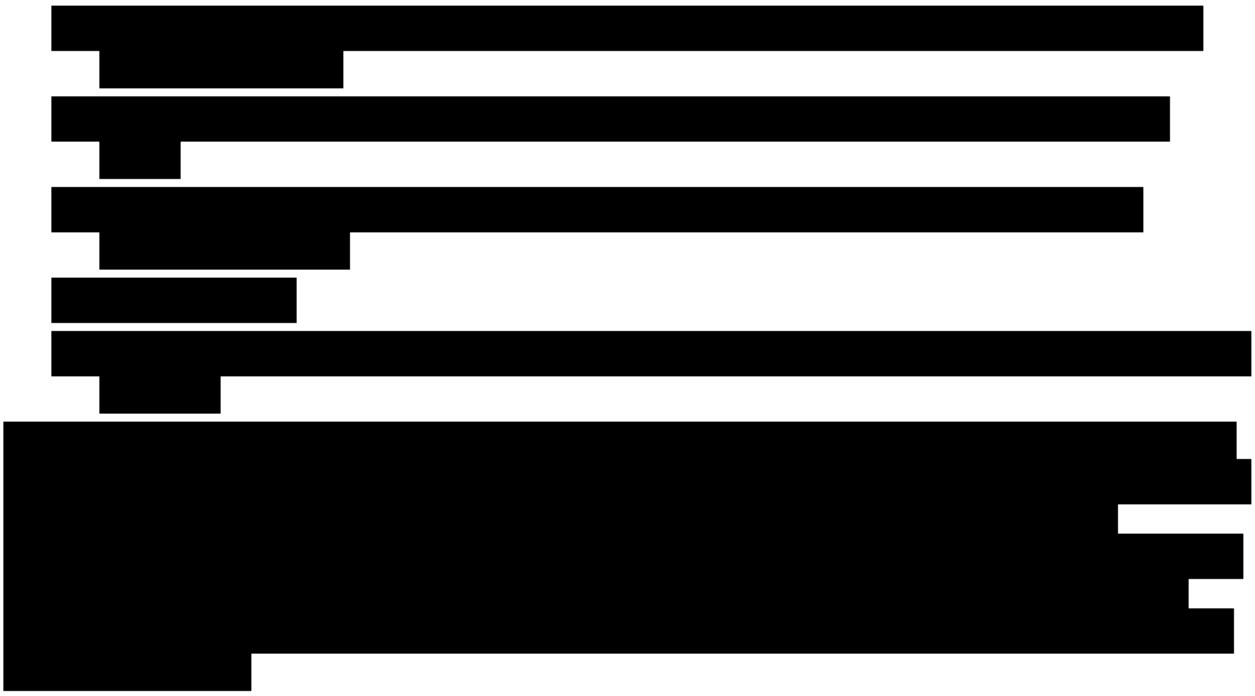




[redacted]

10.6. Administration

CAP-1002 will be administered in an outpatient setting at the investigative site on Day 1 and Months 3. Subjects must complete all other trial assessments prior to CAP-1002 infusion, excluding those related to the CAP-1002 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 an infusion rate of 4 mL/min. [redacted]



10.7. Post-Infusion Monitoring

Subjects will remain in the outpatient setting for at least 2 hours post infusion for observation. 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.

10.8. 14-Day Post-Infusion Monitoring

Subjects will complete a safety, follow-up phone call 14 days (±3 days) after each CAP-1002 infusion to document subject-reported AEs and new concomitant medications.

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.

10.9. 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 CAP-1002 received, prepared, administered and returned/destroyed. Therefore, CAP-1002 accountability must be maintained throughout the trial to show clear product traceability at all times. Details regarding CAP-1002 accountability will include dates, quantities, batch/serial numbers, expiration dates if applicable, storage conditions and the unique code assigned to the CAP-1002 and subjects. CAP-1002 accountability must adequately document that the subjects were provided the correct vial and

reconcile all CAP-1002 received from Capricor's drug depot. Further information on CAP-1002 accountability is found in the Investigational Product Manual.

10.10. Handling and Disposal

All CAP-1002 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 CAP-1002. 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.

11. ASSESSMENT OF EFFICACY

Assessments to evaluate efficacy will be performed at trial visits as indicated in Table 3.

11.1. Sequence of Assessments

Subjects will complete assessments in the following sequence and prior to IP infusion (if applicable):

- Safety and other trial assessments, excluding blood and urine collections (e.g., vital signs, height, weight, 12-lead ECG, physical exam etc.)
- Pulmonary function testing
- PUL 1.2
- 6MWT
- Blood and urine collections
- Cardiac MRI

At the Month 3 follow-up visit, subjects will complete the efficacy assessments designated for that visit prior to CAP-1002 administration.

11.2. Efficacy Assessment Training

Site personnel must complete trial-specific training prior to conducting efficacy assessments for the trial. Standardization and consistency are essential. All efforts must be made to have the same clinical evaluators conduct the PFT, PUL, and 6MWT assessments and the same imaging technologist conduct the cardiac MRI for a subject throughout the duration of the trial. Additional details regarding training requirements can be found in Section 17.1 and the trial's Manual of Procedures (MOP).

11.3. Performance of the Upper Limb

The Performance of the 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 of the 1.2 module using the same preferred arm throughout the course of the trial when PUL testing is required.

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

PUL equipment will be standardized across investigative sites and provided by Capricor. Additional details regarding the PUL requirements can be found in the trial's MOP.

11.4. Pulmonary Function Testing

Pulmonary function testing (PFT) in this trial will measure slow vital capacity (SVC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak cough flow (PCF), and inspiratory flow reserve (IFR). PFTs will be performed using equipment that meets or exceeds the minimal performance recommendations of the American Thoracic Society/European Respiratory Society and that will be provided by a centralized core lab.

Site personnel must complete a certification exam prior to conducting PFTs with a trial subject.

Subjects will complete PFTs in the seated position prior to any other functional outcome measurements (i.e., PUL 1.2, 6MWT, and cardiac MRI). Every effort should be made to complete a subject's PFTs at approximately the same time in the morning at each trial visit. Additional details regarding each PFT technique and requirements are included in the study reference manual provided by the centralized core lab. This manual should be followed for all pulmonary function testing.

11.4.1. Slow Vital Capacity

SVC maneuvers will be performed prior to spirometry (forced maneuvers) because of the potential for muscular fatigue and volume history effects.

Subjects will perform at least three acceptable SVC maneuvers (with no more than five total attempts) until the highest SVC is no more than 0.150 L greater than the next highest measurement. The largest acceptable SVC value will be reported.

11.4.2. Spirometry

At least three acceptable spirometry efforts (with no more than five attempts) will be obtained for FEV_1, FVC, and PEF determinations. Acceptable forced maneuvers will have a satisfactory start of test and end of test (i.e., a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons.

Quality control standards will be implemented within a testing session. The largest FEV_1, FVC, and PEF from the 3 acceptable efforts will be reported, even if they do not come from the same effort. The two largest accepted FVC values should be within ± 15% of each other. Additionally, the two largest accepted PEF values should be within ± 15% of each other.

11.4.3. Maximal Inspiratory & Expiratory Pressures

Maximal inspiratory pressure (MIP) and maximal expiratory mouth pressure (MEP) are simple tests in which patients generate as much inspiratory or expiratory pressure as possible against a blocked mouthpiece. Because lung volume cannot change significantly during measurement, results are to a large extent independent of the properties of the lungs. They are general tests of neuromuscular function of the combined diaphragm, abdominal, intercostal, and accessory muscles (Evans and Whitelaw, 2009).

Subjects will perform the MIP maneuvers (from residual volume (RV)) first, and the MEP maneuvers (from total lung capacity (TLC)) second.

There must be at least 3 acceptable maneuvers from a maximum of five per session.

The two largest accepted values should be within ± 15% of each other.

Subjects will sustain maximal efforts for a total of 3-4 seconds until a plateau in pressure is achieved for at least 1.5 seconds.

Site personnel must carefully judge outlier efforts, which need to be eliminated if the pressure reading showed no gradual increase to the plateau value, suggesting a sharp peak value.

11.4.4. Peak Cough Flow

Subjects will perform at least three cough maneuvers (with no more than five total attempts) from TLC for PCF determination. Site personnel must evaluate each maneuver to determine if it meets acceptability criteria. The largest, acceptable PCF value will be reported.

11.4.5. Inspiratory Flow Reserve

Subjects will perform at least three maximum inspiratory flow-volume maneuvers (with no more than five total attempts). From stable tidal breathing, subjects will expire to RV and then inspire to TLC with maximum effort. Site personnel must evaluate each maneuver to determine if it meets acceptability criteria. The largest, acceptable inspiratory flow reserve value will be reported.

11.5. 6-Minute Walk Test

Subjects assessed by the Investigator as capable of performing the 6MWT will do so on Day 1 and the protocol-specified follow-up visits. Subjects unable to perform the 6MWT on Day 1 will not be required to perform the test at any subsequent visit. Detailed information on performing the 6MWT are found in the trial MOP.

11.6. Cardiac MRI

Subjects will undergo cardiac MRI at the Screening and Month 6 visits (or, Early Termination Visit) if they are physically capable as determined by an Investigator. 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.

A subject's screening cardiac MRI case will require evaluation by a site's radiologist using institutional procedures. The reported LVEF from the local interpretation will be used to assess eligibility (exclusion criterion 1).

It is anticipated that the duration of each MRI session will be 45-60 minutes. Acquisition parameters and techniques are specified in the MRI Imaging Manual. The site-based MRI technologists will be trained and certified in the common acquisition protocol prior to initiation of enrollment at each site. 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.

Subjects that cannot complete a cardiac MRI as part of the trial will complete an echocardiogram at screening using the site's local equipment, acquisition protocol, and evaluation procedures.

The reported LVEF from the local interpretation will be used to assess eligibility (exclusion criterion 1).

12. OTHER TRIAL ASSESSMENTS

Other trial assessments will be performed as indicated in Table 3.

12.1. Medical Status Questionnaire

Subjects will be evaluated for the following at Day 1 and throughout the course of the trial:

- Frequency of manual/power wheelchair use
- Age permanently transitioned to a wheelchair full time
- Ventilatory support
- Frequency of falls

12.2. Medical History

Relevant and significant medical/surgical history will be confirmed at screening.

12.3. Prior and Concomitant Medications

All medications taken within one month prior to the screening visit through trial completion will be captured. Medications will be reviewed at each trial visit and any medication changes, including new and discontinuations, will be recorded.

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.

12.4. Planned Medical/Surgical Procedures

Data associated with any elective medical and/or surgical procedure (e.g., wisdom tooth extraction) that is not the result of an adverse event will also be captured.

For each procedure, the type of procedure, indication, and start date/time will be recorded. Any administered medication(s) related to the planned medical/surgical procedure(s) will be captured as a concomitant medication.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety assessments will be performed as indicated in Table 3.

13.1.1. 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 and before performing ECG and spirometry testing. A single set of values will be captured.

A subject's SpO_2 will be monitored for at least 30 minutes following each CAP-1002 infusion (see Section 10.7).

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

13.1.2. Weight and Height

Weight and height measurements 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.

If standing height cannot be measured, height will be calculated using a measurement of ulna length (Gauld et al., 2004). 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 for the purposes of calculating height.

Table 5: 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. If a subject is 18 years or older, enter "18" in the formula for age.

13.1.3. 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 13.2.1.

13.1.4. Electrocardiogram (ECG)

All ECG measurements will be obtained in the supine position with standardized equipment that meet institutional standards for clinical use. Site personnel must complete trial-specific training prior to ECG measurements. A 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained after measurement of vital signs and before spirometry testing.

The Investigator, a designated Sub-Investigator, or other appropriately trained site personnel will be responsible for performing 12-lead ECG assessments. The Investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation, or their over-read and reinterpretation.

ECG data will be electronically transmitted to an independent cardiologist, contracted by Capricor, and evaluated. The independent cardiologist, blinded to treatment assignment, will conduct an over-read of the ECG measurements required for the trial. Investigative sites will receive a report with the independent cardiologist's ECG interpretations that must be reviewed, signed, and dated by an Investigator.

13.1.5. Immunologic Assessments

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

DSA collection for the Week 4 and Month 4 (±7 days, respectively) visits will occur either at the investigative site or remotely at a designated central laboratory patient service center.

DSA samples may also be collected in the setting of clinical suspicion of immune sensitization syndrome in the judgment of the Investigator. See Section 7.2.1 for additional details regarding immune sensitization syndrome as a safety endpoint.

13.1.6. 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.

Instructions on collection, processing, storage and shipping the samples to the central laboratory are located in the Laboratory Manual.

13.1.6.1. Hematology

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

13.1.6.2. Serum Chemistry

Serum chemistry testing will include: basic metabolic panel (Glucose, Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Calcium), comprehensive hepatic panel (Albumin,

Alkaline Phosphatase, Total Protein, ALT, AST, Direct Bilirubin, Total Bilirubin), and Creatine Kinase

13.1.6.3. Cardiac Enzymes

Cardiac enzyme testing will include CK-MB and Troponin I

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. 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 13.2.4 or further details on event reporting.

13.2.1.2. 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.

13.2.1.3. Expected Adverse Events

As CAP-1002 is comprised of allogeneic cells, immunologic reactions to the product are a possible adverse event. However, to date, no significant immune system adverse events have been identified with any likelihood of relationship to CAP-1002.

There is some risk of developing transient DSA with the CAP-1002 allogeneic product. All subjects will be monitored during the trial for immune sensitization as outlined in Table 3.

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

13.2.1.4. 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 13.2.4.

13.2.1.5. 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.

13.2.2. 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.

13.2.3. 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 13.2.1.2. Both an AE and SAE can be assessed as severe. However, an AE of severe intensity may not meet SAE definition requirements.

13.2.4. Reporting Adverse Events

All adverse events are collected from the time of signing informed consent for trial participation until completion of 6 months or early termination, whichever occurs first. All AEs occurring after the initiation of the IV catheter placement for the initial dose of CAP-1002 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 and subsequent follow-up information must be reported to Capricor, or designee, via email or fax as outlined in the Manual of Procedures and Safety Plan.

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 ICG E2A guidelines.

For trials conducted under an investigational new drug (IND) application, FDA regulations require reporting of any suspected adverse reaction. 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 initial Expedited Safety Report (ESR) or MedWatch Form 3500A to the FDA within 5 business day of determination that the event qualifies for reporting.

13.2.5. Pregnancy Reporting

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 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.

13.2.6. 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 6 months 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 13.2.3 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.

14. STATISTICS

14.1. 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 is no formal hypotheses or statistical tests associated with trial endpoints. 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, without conclusions regarding statistical significance levels.
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.

14.2. Sample Size

Up to 10 subjects that were randomized to Usual Care Treatment Group and completed the 12-month follow-up period for the HOPE-Duchenne trial will be enrolled in this trial.

14.3. Analysis Population

Intent-to-Treat (ITT) Population: All subjects who meet the enrollment criteria and are enrolled in the study. These subjects will also constitute the Safety population.

Per Protocol (PP) Population: All enrolled subjects who have no protocol deviations/violations that could significantly impact the completeness, accuracy and/or reliability of the trial data. The list of subjects in the per protocol population will be compiled prior to database lock.

14.4. Safety Analysis

14.4.1. Safety Endpoints

All primary safety endpoints 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. Primary safety endpoints that are adjudicated by the Clinical Events Committee (CEC) will be further described by the relatedness to the study treatment and severity level.

14.4.2. Medications

A listing of prescription and over the counter medications used by individual trial subject will be prepared, including information on generic name. dosage, frequency of administration, reason for use, observed side effects, and any related adverse events. Study level summaries by type of medication may also be prepared.

14.4.3. Clinical Laboratory Evaluations

All laboratory evaluations will be documented. A listing of results by subject will be prepared, with any abnormalities noted at baseline or during the follow-up period.

14.4.4. Donor-Specific Antibodies

Donor-specific antibodies (DSA) will be assessed as screening and periodically during the follow-up period or upon clinical suspicion of an immune sensitization response, and will be summarized by the specific CDC donors contributing to the CAP-1002 doses used by individual subjects.

14.4.5. Physical Examination

Medical status and baseline physical exam results, including vital signs, 12-lead ECG, and weight, will be summarized using descriptive statistics and any observed abnormalities. Any changes over the follow-up period will be documented and reported.

14.5. Efficacy Analysis

Efficacy will be evaluated at the 3 and 6-month follow-up visit, with changes from baseline assessed for pre-specified exploratory endpoints. Analyses will be performed both in the ITT and PP populations.

14.5.1. Exploratory Efficacy Endpoints

Descriptive statistics will be used to summarize changes from baseline in the PUL 1.2 scores (including the mid-level dimension, combined mid and distal-level dimensions, and high-level dimension), in left ventricular structure and function parameters (including ejection fraction, wall thickness, end-diastolic and end-systolic volumes, stroke volume, and circumferential strain, in pulmonary function (including SVC, FEV_1, FVC, MIP, MEP, PCF, and IFR) and in 6-minute walk test distance for ambulatory subjects.

14.6. Statistical Methods

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

Mean changes from baseline in continuous measures (PUL 1.2, cardiac parameters, and pulmonary parameters) will be evaluated as a function of follow-up time. Variability in outcomes will be summarized with the associated 95% confidence intervals for the mean estimates. Statistical tests may be performed to assess whether observed mean changes are different than zero, but without assignment of statistical significance.

Additional analyses may be performed to examine the relationship of patient factors to study outcomes, to estimate the correlations between different study outcomes, or to examine the consistency of outcomes between subject subgroups or study sites.

Standard statistical tests for outliers may be performed in those cases where suspect lab tests or study outcomes are observed.

14.6.1. Multiplicity

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

14.6.2. Missing Data

There are no plans for imputation of missing data. 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.

15. TRIAL OVERSIGHT

15.1. Steering Committee

The Steering Committee will provide the overall scientific direction for the trial. The responsibilities of the Steering Committee are to: (a) maintain contact with trial Investigators to ensure high quality data collection; (b) approve and implement major protocol changes; (c) collaborate in data analysis, interpretations, and publications; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the trial.

15.2. Clinical Events Committee (CEC)

The purpose of CEC adjudication is to provide consistent and unbiased adjudication of clinical outcomes and specified events through the independent review of source documentation. The charge of the CEC is to review source documents and to adjudicate the classifications of all potential primary safety endpoint events. Sites will be provided instructions in the MOP on how to collect and submit event information required for CEC review. The CEC will remain blinded to subject treatment assignments. The individuals that serve on the committee will be appointed by Capricor, are independent from all other trial activities, and are not affiliated with any investigative site. The committee will consist of, at a minimum, a neurologist and pulmonologist with experience in treating patients with DMD. Additional experts in immunology will be consultants to the committee as necessary. The frequency of CEC meetings is detailed in the CEC Charter.

15.3. 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.

16. SOURCE DATA AND TRIAL DOCUMENTS

16.1. 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 Studys," 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.

16.2. 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, tests, 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.
- Infor 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.

16.2.1. Source Document Requirements

It is highly recommended that the investigative site uses the CRFs and schedule of assessments (Table 3) 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 their designee.

16.3. 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.

16.4. Retention of Records

The investigative sites must maintain all documentation relating to the trial for a period of two 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.

17. 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 16.3 for more details regarding the audit process.

17.1. 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.

Each investigative site MRI lab involved in image acquisition for this trial will be certified by the MRI core lab in accordance with the MRI Imaging Manual.

Each investigative site pulmonary function testing lab involved in conducting pulmonary function testing for this trial will be certified by the Pulmonary Function Core Lab as detailed in the Manual of Procedures.

Investigative site personnel delegated to perform the ECG assessment will be certified to perform and transmit the assessment by a centralized vendor.

All Investigators and coordinators will be trained by Capricor, or 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.

17.2. 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.

17.3. 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.

17.4. 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 designee, will conduct a site initiation prior to enrollment of the first subject. Investigators, study coordinator(s), investigational pharmacist(s), infusion suite personnel, clinical evaluator(s), MRI technologist(s), and laboratory personnel will be required to attend the initiation. All other site personnel who may be involved in the trial will be encouraged to attend.

17.5. Protocol Deviations

Efforts to maximize adhere 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 (in a blinded fashion) to determine whether data can reasonably be included in any trial analyses.

18. ETHICS

18.1. 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 correspondences 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.

18.2. 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 17 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 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

18.3. 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 individual, 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 their 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.

18.3.1. 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 guardian 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.

18.4. Subject Confidentiality

Confidentiality of all subject records will be maintained according to HIPAA guidelines. Investigators, investigative site IRBs, Capricor, CEC, 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.

19. 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 first anniversary 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 exploratory endpoints or other endpoints or 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.

20. REFERENCES

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21. APPENDIX

21.1. Summary of Changes – Amendment 1.0

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

Description of Change	Rationale / Justification	Sections Affected
Study Assessments		
Removed collection of CK-MB and troponin I at Week 4 and Month 4	Administration of CAP-1002 is no longer intracoronary	Table 3: Schedule of Assessments
Required sample collection for a visit may occur on multiple days; if the visit includes a CAP-1002 infusion, sample collections should occur prior to CAP-1002 administration.	Data collection clarification	Table 3: Schedule of Assessments
Replaced ~~extremities~~ with *musculoskeletal*	Clarification required to ensure appropriate data collection	13.1.3 Physical Examination
Addition: ~~All s~~Serum for DSA testing *and whole blood for HLA typing* will be collected	Required to ensure appropriate data collection for safety assessments	13.1.5 Immunologic Assessment Table 3: Schedule of Assessments
Investigational Product Materials and Management		
~~Only t~~*T*he Octapharma brand *(or equivalent) is preferred* ~~has been tested~~ for reconstitution of CAP-1002.	Align protocol with Sponsor recommendations for CAP-1002 preparation	10.5 Preparation
18- to 2*2*~~0~~-gauge infusion set ~~with a synthetic polymer ethylene tetrafluoroethylene (ETFE) peripheral venous~~	Align protocol with Sponsor recommendations for CAP-1002 administration	10.6 Administration

~~catheter, such as Nipro brand~~ IV catheter~~s~~ *that has been approved by Capricor*.		
Connect peripheral venous catheter to syringe using ~~polyvinyl chloride~~ *an* extension line, such as Smiths Medical Pressure Monitoring Line *or other extension line as approved by Capricor*.	Align protocol with Sponsor recommendations for CAP-1002 administration	10.6 Administration
Clarification / Corrections		
Addition of IND number	Administrative clarification	1. Title Page
Removed Agility Clinical Safety Department	Change with department structure	1.3 Procedures in Case of Emergency
Addition: *Please reference the Manual of Procedures for detailed information on serious adverse event reporting.*	Clarification regarding location of information	1.3 Procedures in Case of Emergency
Deletion: the peripheral ~~or central venous~~ access device	Internal consistency within protocol	2. Synopsis
Deletion: OAEs will be identified by the Medical Monitor during the evaluation of safety data for the ~~planned interim analysis and~~ Clinical Study Report.	Internal consistency within protocol	13.2.1.5 Other Adverse Event (OAE)