CLINICAL STUDY PROTOCOL

DRUG:	SRP-9001 (formerly referred to as rAAVrh74.MHCK7.micro-dystrophin)
STUDY NUMBER:	SRP-9001-101
STUDY TITLE:	Systemic gene delivery Phase I/IIa clinical trial for Duchenne muscular dystrophy using rAAVrh74.MHCK7.micro-dystrophin (microDys-IV-001)
IND Number:	CCI
EUDRACT Number:	Not Applicable
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	9.0 (Amendment 8) 25 August 2020
REPLACES VERSION DATE:	8.0 (Amendment 7), 26 June 2019

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	Systemic gene delivery Phase I/IIa clinical trial for Duchenne muscular dystrophy using rAAVrh74.MHCK7.micro-dystrophin (microDys-IV-001)
Study No:	SRP-9001-101
Current Version Date:	Version 9.0 (Amendment 8), 25 August 2020

This study protocol (Version 9.0, Amendment 8) was subject to critical review and has been approved by the appropriate protocol review committee of Sarepta Therapeutics, Inc. The information contained in this protocol is consistent with:

- The current benefit-risk evaluation of the study drug.
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312 and the European Clinical Trial Directive 2001/20/EC.

The Investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the study drug.

PPD

25-Aug-2020

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SRP-9001. I have read the SRP-9001-101 protocol (Amendment 8, Version 9 dated 25 August 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed about this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company:
Sarepta Therapeutics, Inc.
215 First Street
Cambridge, MA 02142 USA
Phone: +1-617-274-4000

Name of Investigational Product: SRP-9001

Name of Active Ingredient: micro-dystrophin

Title of Study: Systemic gene delivery Phase I/IIa clinical trial for Duchenne muscular dystrophy using rAAVrh74.MHCK7.micro-dystrophin (microDys-IV-001)

Study Center(s): Nationwide Children's Hospital (NCH)

Principal Investigator: Jerry R. Mendell, MD

Studied Period (years):	**Phase of Development:** Phase I/IIa
Estimated date first subject enrolled: 2018 Estimated date last subject completed: 2023	

Objectives:

Primary:

The primary objective of this study is the assessment of the safety of intravenous (IV) administration of rAAVrh74.MHCK7.micro-dystrophin for Duchenne muscular dystrophy (DMD) subject via peripheral limb vein.

Methodology: The proposed clinical study is an open-label single-dose study using rAAVrh74.MHCK7.micro-dystrophin for DMD subjects. Cohort A will include 6 subjects ages 3 months to 3 years, and Cohort B will include 6 subjects ages 4 to 7 years old. All subjects will receive IV micro-dystrophin vector (2×10^{14} vg/kg in approximately CCI). Cohort B subjects will be enrolled before Cohort A. Upon completion of Cohort B, the safety data will be presented to the Institutional Review Board and Data Safety Monitoring Board requesting permission to enroll Cohort A.

Although this study was originally designed to enroll 12 subjects into 2 cohorts as outlined above, as of this amendment (Version 9), a total of 4 subjects have been enrolled; all into Cohort B. No further subjects will be enrolled into the study.

Subjects will have infusions of rAAV carrying micro-dystrophin over approximately 1 to 2 hours in the Pediatric Intensive Care Unit at NCH. The Bayley-III Gross Motor Subtest will serve as the secondary outcome measure for all children in Cohort A (Bayley Scales of Infant and Toddler Development: Third Edition 2006 published by PsychCorp). The 100 Meter Timed Test (100m) will be a primary motor outcome and CCI The 100m will be the primary motor outcome for Cohort B. CCI . Functional assessments will be CCI as indicated in the Clinical Evaluator Manual. Pre- and post-treatment (90 day) needle muscle biopsies will be done on CCI muscles with appropriate anesthesia under advisement of anesthesiologist (or anesthetist). EMLA cream (or comparable lidocaine/prilocaine emulsion) and/or injectable anesthetic may be used at the site of biopsy. Micro-dystrophin gene expression will serve as a secondary

outcome measure. Quantification will be done using validated immunofluorescence [redacted]

Following gene transfer, the most recent Food and Drug Administration guidance will be followed with regard to long-term subject follow up.

Number of subjects (planned): 12 subjects were planned; however, the study will only enroll 4 subjects.

Diagnosis and main criteria for inclusion:

Inclusion criteria

1. Age of enrollment: Cohort A (n=6) is between 3 months to 3 years of age, inclusive; Cohort B (n=6) is between 4 to 7 years of age, inclusive.
2. Molecular characterization of the DMD gene with frameshift (deletion or duplication), or premature stop codon mutation between exons 18 to 58.
3. Indication of symptomatic muscular dystrophy:
   - CK elevation > [redacted] U/L **and**
   - Cohort A: Below average on the Bayley-III motor assessment for gross motor defined as a scaled score of ≤ [redacted]. Cohort B: Below average on the 100m defined as ≤ [redacted] predicted (Connolly 2013).
4. Males of any ethnic group will be eligible.
5. Ability to cooperate with motor assessment testing.
6. For Cohort A subjects: No previous treatment with corticosteroids. For Cohort B subjects: Stable dose equivalent of oral corticosteroids for at least 12 weeks prior to screening and the dose is expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the first year of the study.

Exclusion criteria

1. Active viral infection based on clinical observations.
2. Signs of cardiomyopathy, including echocardiogram with ejection fraction below [redacted]
3. Serological evidence of human immunodeficiency virus infection, or Hepatitis B or C infection.
4. Diagnosis of (or ongoing treatment for) an autoimmune disease.
5. Abnormal laboratory values considered clinically significant (gamma-glutamyl transferase [GGT] > [redacted] × the upper limit of normal, bilirubin ≥ [redacted] mg/dL, creatinine [redacted] mg/dL, hemoglobin < [redacted] or > [redacted] g/Dl; white blood cell count > [redacted] per cmm).
6. Concomitant illness or requirement for chronic drug treatment that in the opinion of the PI creates unnecessary risks for gene transfer.
7. Subjects with rAAVrh74 [redacted] antibody titers > [redacted] as determined by enzyme-linked immunosorbent assay (ELISA) immunoassay.

- If endpoint titer is positive at screening, testing may be repeated prior to exclusion.
- If infant and mother are positive for same antibody titers, mother will be asked not to breastfeed, and infant can be enrolled if antibodies CCI within 12 weeks.

8. Has a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability.
9. Severe infection (eg, pneumonia, pyelonephritis, or meningitis) within 4 weeks before gene transfer visit (enrollment may be postponed).
10. Has received any investigational medication (other than corticosteroids) or exon-skipping medications (including EXONDYS 51®), experimental or otherwise, in the last 6 months prior to screening for this study.
11. Has had any type of gene therapy, cell-based therapy (eg, stem cell transplantation), or CRISPR/Cas9.
12. Family does not want to disclose subject's study participation with primary care physician and other medical providers.

Investigational product, dosage and mode of administration:

The vector will be delivered via peripheral limb vein. Study subjects will receive sedation if deemed necessary for the procedure following the NCH dosing protocol. Six subjects in Cohort A and 6 subjects in Cohort B will receive IV micro-dystrophin vector (2×10^{14} vg/kg in CCI).

One day prior to gene transfer, subjects in Cohort A will be started on prednisolone (prednisone or deflazacort acceptable) 1 mg/kg and maintained for 30 days CCI. If the liver enzyme GGT is elevated at day 30, steroids will be maintained until GGT levels drop below CCI U/L.

Cohort B subjects receiving daily glucocorticoid medication will be maintained on a stable dose of corticosteroids throughout the first year of the study, but the dose may be increased for a short time if GGT is elevated >150 U/L or there are other clinically significant liver function abnormalities. Those on weekend dosing may receive an added daily dose equivalent to 1 mg/kg for up to 30 days.

Study duration: We will evaluate safety over a 5-year period. Subjects will be tested at baseline and return for follow up visits on days CCI, 30, CCI and months 3, CCI, 36, CCI, and 60. Unscheduled visits and additional blood draws (at NCH or local to subject's home) may occur if the PI determines they are necessary for the subject's safety and wellbeing. CCI

Reference therapy, dosage and mode of administration: None

Criteria for evaluation:

Primary outcome

Safety is the primary outcome for this clinical gene transfer study.

Additional outcomes

The following efficacy outcome measures will be done at designated time points:

- Time points for secondary outcomes: days 30, CCI, 90, CCI, months CCI, 36, CCI, and 60. CCI
- The Bayley Scales of Infant and Toddler Development Third Edition Gross Motor Subtest (Bayley-III) scores will serve as the secondary outcome measure for this study for Cohort A. Control data for DMD infants at this age using the Bayley-III Gross Motor Scale has been obtained and published from data collected in the MDA Network Clinical Centers (Mendell 2015). Ongoing data is being collected in boys up to 5 years of age with DMD in the MDA clinic at NCH. The Bayley-III is designed to assess the developmental functioning of infants and young children 1 to 42 months of age (Bayley N. Bayley Scales of Infant and Toddler Development: Third Edition 2006 published by PsychCorp).
- Physical Therapy Assessments: The 100m will be a primary motor outcome initiated for Cohort A as soon as the child is 3 years of age. CCI The 100m will be the primary motor outcome for Cohort B. CCI
- Baseline muscle biopsies with ultrasound guidance to assess micro-dystrophin expression will be done pre-treatment on all subjects. All subjects will have a post-treatment biopsy at day 90. Micro-dystrophin gene expression will be quantified (immunofluorescence and western blot analysis) and compared in pre and post muscle biopsies. Micro-dystrophin expression will also serve as a secondary outcome measure for both cohorts.
- CCI

Statistical methods:

Sample size

Twelve DMD subjects (Cohort A, n=6; Cohort B, n=6) will be enrolled at NCH for the gene transfer study. Subjects will encompass males of any ethnic or racial background. Cohort A will include subjects aged 3 months to 3 years, inclusive at the time of enrollment. Cohort B will include subjects aged 4 to 7 years, inclusive, at the time of enrollment and will preferentially be enrolled to receive gene delivery prior Cohort A.

Statistical analysis

This is a Phase I/IIa study, with safety as the primary measure. Bayley-III pre- and post-gene transfer will be the primary motor outcome for Cohort A. The 100m will be a primary motor outcome CCI [redacted]. The 100m will be the primary motor outcome for Cohort B. [redacted] As the sample size is small and the motor outcomes will differ between cohorts as well as over time for some subjects within Cohort A, all analyses will be descriptive in nature and will not employ inferential statistics.

The muscle biopsies will be processed in the CCI [redacted], which operates under a College of American Pathologists/Clinical Laboratory Improvement Amendments license for their diagnostic neuromuscular testing. There will be an assigned blinded identifier for each subject. Frozen sections will be stained for dystrophin using indirect immunofluorescence. CCI [redacted] will be used to quantify the intensity of dystrophin expression compared to normal controls. CCI [redacted] CCI [redacted]

Periodic safety and efficacy analyses are performed for safety monitoring reviews, Investigator's Brochure updates, regulatory submissions such as Development Safety Update Report and regulatory meeting briefing documents, and scientific disclosures. These periodic analyses are described in separate documents.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
100m	100 Meter Timed Test
AAV	adeno-associated virus
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBC	complete blood count
CFR	Code of Federal Regulations
CCI	CCI
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMD	Duchenne muscular dystrophy
DSMB	Data Safety Monitoring Board
ECHO	echocardiogram
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
HHD	hand-held dynamometry
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
IV	Intravenous(ly)
MRI	magnetic resonance imaging
NCH	Nationwide Children's Hospital
NSAA	North Star Ambulatory Assessment
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
PT	prothrombin time
PTT	partial thromboplastin time
SAE	serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TUG	Timed Up and Go modified for children
ULN	upper limit of normal

5. INTRODUCTION

5.1. Clinical Study Site

The study will be a single-center study carried out at The Research Institute at Nationwide Children's Hospital (NCH) in Columbus, Ohio. Dr. Jerry Mendell, Professor of Pediatrics and Neurology, will serve as the Principal Investigator (PI). Dr. Mendell brings to this study more than 40 years of clinical study experience in neuromuscular disorders. With regard to gene therapy, he was the first to do viral mediated gene transfer studies for muscular dystrophy as the PI in 2 viral mediated gene transfer studies, 1 in Duchenne muscular dystrophy (DMD) (Investigational New Drug CCI using a hybrid adeno-associated virus [AAV] consisting of AAV2 with 5 amino acid substitutions from AAV1, CMV promoter, and mini-dystrophin) (Mendell 2010), and the other in Limb Girdle Muscular Dystrophy, type 2D (LGMD2D, CCI, AAV1, tMCK promoter, and alphasarcoglycan- gene) (Mendell 2009). He conducted a gene therapy study using rAAV1.CMV.FS344 (CCI) in 2 groups, sporadic inclusion body myositis and Becker muscular dystrophy (BMD). The results of the BMD and sIBM studies have been published (Mendell 2017, Mendell 2015). He also conducted a gene therapy study in infants with SMA type 1 and showing significant efficacy (CCI). The results in this same group using the same dose for infusion have been safe (presented at the Presidential Symposium of the ASGCT 2016, and late-breaking abstracts WMS 2017) (Mendell 2016). Efficacy and safety have been documented, given that this dose of AAV delivering the SMN gene to 15 subjects has saved the lives of all participants and this study led to the approval in 2019 of this gene therapy for commercial use. As of the cutoff date of 07 August 2017, 13 have survived past 20 months (compared to 8% in natural history studies), 15 have reached 13.6 months (25% survival), and 15/15 have reached 10.5 months (50% survival). Furthermore, 7 are feeding themselves, 2 subjects are crawling, 4 are standing with support, and 2 subjects are walking independently.

5.2. Background and Significance

5.2.1. Disease and Characteristics

Duchenne muscular dystrophy is the most common, severe childhood form of muscular dystrophy. Inheritance follows an X-linked recessive pattern. Birth prevalence has been estimated at 1 in 5000 live male births (Mendell 2012). Approximately one-third of cases represent new mutations of the *DMD* gene with the remaining inherited on the X chromosome from a carrier mother. Questions usually begin to surface between ages 3 to 5 regarding reduced motor skills that alert a need for diagnostic evaluation. Earlier recognition results from delay in motor milestones or family history. Duchenne muscular dystrophy is relentlessly progressive with loss of ambulation by age 12 (Brooke 1983). Historically, patients died from respiratory complications. Now, a variety of factors protect the respiratory system related to improved supportive equipment, antibiotics, vaccines, and other ancillary methods (Eagle 2002). Prolonging life unmasks decline in cardiac function with complications of dilated cardiomyopathy. This poses further clinical challenges and a need for recognition and medical intervention that did not previously exist. Non-progressive cognitive dysfunction might be present in DMD and BMD.

5.2.2. Disease Pathogenesis

More than 20 years ago the DMD gene was cloned defining the molecular basis of the disease (Koenig 1987). The identification of dystrophin as the deficient protein followed closely on the heels of this discovery (Dent 2005). Dystrophin is a 427kDa cytoskeletal protein required for muscle fiber stability. Loss of this protein results in susceptibility to repeated cycles of necrosis and regeneration with satellite cell depletion, diminished regenerative capacity of the muscle, ending in fat and connective tissue replacement (fibrosis). The mutation spectrum within the DMD gene reveals that deletions of one or more exons are found in ~65% of cases clustered in 2 hotspot regions (Flanigan 2003). Detection of duplications represents 6% of the DMD mutations. Additional tools identify the full spectrum of mutations (deletions, duplications, splice-site and point mutations).

5.2.3. Treatment for Duchenne Muscular Dystrophy

Despite virtually hundreds of clinical studies in DMD, only one treatment has consistently demonstrated efficacy. Unequivocal evidence for glucocorticoid-induced improvement was established through a double-blind, randomized controlled study in a large cohort of subjects (n=103). Corticosteroids are now considered the standard of care; however, the side effect profile may preclude treatment for some boys. The only other treatment that seems to show an effect is exon skipping [redacted] (Mendell 2013). The treatment does not increase strength but slows the progression of the disease. This was demonstrated in a study done at NCH, and this oligonucleotide (eteplirsen) has been approved by the Food and Drug Administration (FDA) for the treatment of DMD (Mendell 2013).

Gene replacement therapy has been studied for the past 10-15 years and shows very favorable results in pre-clinical studies in mice and canine species deficient in dystrophin. In 2006, the first gene therapy clinical study in DMD was done at NCH, and the results were published in the New England Journal of Medicine because of the potential impact of the findings (Mendell 2010). Importantly, the dystrophin cDNA is 11kB and our vehicle for gene transfer, AAV can only hold 5 kB. Thus, the dystrophin gene must be scaled down in order to fit within the packaging constraints of AAV particles. This miniaturized transgene was termed mini-dystrophin and was delivered by intramuscular injection to DMD subjects ([redacted], closed). As this was a clinical study, subjects' immune systems were sensitive to the slight changes that occurred when the gene was expressed in their muscle. When this was done in 2006, we discovered that if you inject the gene into a subject with a deletion of the DMD gene as the cause of the disease, it could cause an immune response and reject the gene. This happened in 2 subjects with deletions in regions of dystrophin that were present in the Mini-Dystrophin gene. From this study, a new version of the truncated dystrophin gene was created termed micro-dystrophin, which retains different region of the native gene than mini-dystrophin. The micro-dystrophin transgene used in this study is the same that was used in a clinical study evaluating safety and expression of intramuscular injections of the product, rAAVrh74.MCK.micro-dystrophin ([redacted]). This construct demonstrated preliminary safety in the clinical study.

Our current design is relatively simple but carefully planned. We will ensure that the micro-dystrophin and the subject's mutation are compatible so that we can achieve expression of our transgene without inducing immune rejection. We will also pre-test subjects for pre-existing immunity to AAV, so that we can avoid rejection when we transfer the gene.

6. STUDY OBJECTIVES AND PURPOSE

The objective of this study is the assessment of the safety of intravenous (IV) administration of rAAVrh74.MHCK7.micro-dystrophin for DMD subjects via peripheral limb vein.

7. INVESTIGATIONALPLAN

7.1. Overall Study Design

The proposed clinical study is an open-label single-dose study using rAAVrh74.MHCK7.micro-dystrophin for DMD subjects. Cohort A will include 6 subjects ages 3 months to 3 years, and Cohort B will include 6 subjects ages 4 to 7 years old. All subjects will receive IV micro-dystrophin vector (2×10^{14} vg/kg in approximately CCI).
Cohort B subjects will be enrolled before Cohort A. Upon completion of Cohort B, the safety data will be presented to the Institutional Review Board (IRB) and Data Safety Monitoring Board (DSMB) requesting permission to enroll Cohort A.

Although this study was originally designed to enroll 12 subjects into 2 cohorts as outlined above, as of this amendment (Version 9), a total of 4 subjects have been enrolled; all into Cohort B. No further subjects will be enrolled into the study.

Subjects will have infusions of rAAV carrying micro-dystrophin over approximately 1-2 hours in the Pediatric Intensive Care Unit (PICU) at NCH. The Bayley-III Gross Motor Subtest will serve as the secondary outcome measure for all children in Cohort A (Bayley Scales of Infant and Toddler Development: Third Edition 2006 published by PsychCorp). The 100 Meter Timed Test (100m) will be a primary motor outcome CCI The 100m will be the primary motor outcome for Cohort B. CCI Pre- and post-treatment (90 day) needle muscle biopsies (Tarnopolsky 2011) will be done CCI muscles with appropriate anesthesia under advisement of anesthesiologist (or anesthetist). EMLA Cream (or comparable lidocaine/prilocaine emulsion) and/or injectable anesthetic may be used at the site of biopsy. Micro-dystrophin gene expression will serve as a secondary outcome measure. Quantification will be done using validated immunofluorescence CCI

The schedule of events is presented in Table 2.

CCI

[redacted]

7.2. Study Endpoints

7.2.1. Primary Endpoints

The primary endpoint of the study is safety as assessed by adverse events (AEs), changes in laboratory parameters (hematology, serum chemistry [Palmeria 2012, Rosales 2008], urinalysis), immunologic response to rAAVrh74 and micro-dystrophin, and reported history and observations of symptoms.

7.2.2. Other Endpoints

Efficacy assessed by gene expression is a critical secondary outcome measure judged by micro-dystrophin gene expression on muscle biopsies. In addition, efficacy will be measured by the Bayley-III Gross Motor Subtest (Cohort A only). The 100m will be a primary motor outcome CCI [redacted]. The 100m will be the primary motor outcome for Cohort B. CCI [redacted]. Baseline muscle biopsies with ultrasound guidance to assess dystrophin expression will be done pre-treatment on all subjects. All subjects will have a post-treatment biopsy at day 90. Micro-dystrophin gene expression will be quantified (immunofluorescence and western blot analysis) and compared in pre and post muscle biopsies. Dystrophin will also serve as a secondary outcome measure for both cohorts. CCI [redacted]

7.3. Study Committees

7.3.1. Data Safety Monitoring Board

The DSMB will act in an advisory capacity to review participant safety and study progress for the clinical study. Responsibilities of the DSMB are to:

- Review the research protocol, informed consent documents, and plans for data and safety monitoring;
- Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, study site performance, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on participant safety or the ethics of the study;
- Review study performance, make recommendations, and assist in the resolution of problems reported by the Sponsor;
- Protect the safety of the study participants;
- Review safety data to determine whether to recommend dose escalation;

- Ensure the confidentiality of the study data and the results of monitoring; and
- Assist by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

7.3.2. Data Safety Monitoring Board Reporting and Meetings

Reports describing the status of the study will be prepared by the Sponsor's staff and sent at the DSMB's request. The DSMB will meet prior to dosing the first subject. The DSMB will be provided with a report after subject [redacted] and a teleconference will occur after subject [redacted].

A meeting (either by teleconference or webcast) with the DSMB will be scheduled after CCI visit of the CCI subject, or at the DSMB's request. Reports will be submitted prior to a scheduled meeting for review by the DSMB.

Reports will include the following:

- A brief narrative of the study status, including the target enrollment, current and projected time to completing enrollment. Any significant events and/or difficulties should be briefly described in this narrative.
- A brief narrative for each participant describing gender, age, race and ethnicity and other relevant demographic characteristics. The narrative for each participant should briefly describe his/her study status (ie, dose level, visit number, AE information).
- A timeline outlining the study progress relative to visit number for each participant, as well as time points for each serious adverse event (SAE)/dose-limiting toxicity. A total for AEs for each participant should be included.
- A summary of AEs by severity levels.
- A listing of AE details grouped by participant.
- A listing of SAE details grouped by participant.
- A listing of deaths.
- A summary of clinically significant laboratory test results.
- A listing of protocol deviations.

7.3.3. Membership

The DSMB membership will consist of persons completely independent of the Investigator who have no financial, scientific, or other conflicts of interest with the study. Current or past collaborators or associates of Dr. Mendell must note any conflict of interest before their eligibility to serve on the DSMB is approved. The DSMB will include clinician translational scientists familiar with gene therapy.

Individuals invited to serve on the DSMB as either voting or non-voting members must disclose any potential conflicts of interest, whether real or perceived. Conflicts of interest can include professional, proprietary, and miscellaneous interests as described in the National Institutes of Health Grant Policy Statement and 21 Code of Federal Regulations (CFR) Part 54. Potential

conflicts that develop during a member's tenure on a DSMB must also be disclosed. Written documentation attesting to an absence of conflict of interest is required annually.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

A subject must meet all of the following criteria to be eligible to participate in this study:

1. Age of enrollment: Cohort A (n=6) is between 3 months to 3 years of age, inclusive; Cohort B (n=6) is between 4 to 7 years of age, inclusive.
2. Molecular characterization of the DMD gene with frameshift (deletion or duplication), or premature stop codon mutation between exons 18 to 58.
3. Indication of symptomatic muscular dystrophy:
   - CK elevation >CCI U/L **and**
   - Cohort A: below average on the Bayley-III motor assessment for gross motor defined as a scaled score of ≤CCI. Cohort B: below average on the 100m defined as ≤CCI% predicted (Connolly 2013).
4. Males of any ethnic group will be eligible.
5. Ability to cooperate with motor assessment testing.
6. For Cohort A subjects: No previous treatment with corticosteroids. For Cohort B subjects: Stable dose equivalent of oral corticosteroids for at least 12 weeks prior to screening and the dose is expected to remain constant (except for potential modifications to accommodate changes in weight) throughout the first year of the study.

8.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this study:

1. Active viral infection based on clinical observations.
2. Signs of cardiomyopathy, including echocardiogram (ECHO) with ejection fraction below CCI%.
3. Serological evidence of human immunodeficiency virus (HIV) infection, or Hepatitis B or C infection.
4. Diagnosis of (or ongoing treatment for) an autoimmune disease.
5. Abnormal laboratory values considered clinically significant (gamma-glutamyl transferase [GGT] >CCI the upper limit of normal [ULN], bilirubin ≥CCI mg/dL, creatinine ≥CCI mg/dL, hemoglobin <CCI or >CCI g/Dl; white blood cell count >CCI per cmm).
6. Concomitant illness or requirement for chronic drug treatment that in the opinion of the PI creates unnecessary risks for gene transfer.

7. Subjects with rAAVrh74 CCI antibody titers > CCI as determined by enzyme-linked immunosorbent assay (ELISA) immunoassay.
    - If endpoint titer is positive at screening, testing may be repeated prior to exclusion.
    - If infant and mother are positive for same antibody titers, mother will be asked not to breastfeed, and infant can be enrolled if antibodies drop ≤ CCI within 12 weeks.
8. Has a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability.
9. Severe infection (eg, pneumonia, pyelonephritis, or meningitis) within 4 weeks before gene transfer visit (enrollment may be postponed).
10. Has received any investigational medication (other than corticosteroids) or exon skipping medications (including EXONDYS 51®), experimental or otherwise, in the last 6 months prior to screening for this study.
11. Has had any type of gene therapy, cell-based therapy (eg, stem cell transplantation), or CRISPR/Cas9.
12. Family does not want to disclose subject's study participation with primary care physician and other medical providers.

8.3. Subject Withdrawal Criteria

Any subject can withdraw from study participation at any time for any reason. In addition, the Sponsor may decide to stop the study participation of any subject as deemed necessary. The Investigator may also stop the study participation of any subject at any time. Reasons for study withdrawal include but are not limited to:

- The subject was erroneously included in the study (ie, was found to have not met the eligibility criteria).
- The subject experiences an intolerable or unacceptable AE.
- The subject is unable to comply with the requirements of the protocol.
- The subject participates in another investigational study without the prior written authorization of the Sponsor.

The Investigator or study staff will document the reason(s) for treatment discontinuation on the case report form (CRF).

9. TREATMENT OF SUBJECTS

9.1. Treatment Administered

9.1.1. Gene Transfer Protocol

Subjects will be admitted to NCH for gene transfer, either PICU or Pulmonary PICU, the night before gene transfer and will be examined by either the PI or co-Investigator s (day -1). On the day of gene transfer (day 0), the pharmacy will prepare rAAVrh74.MHCK7.micro-dystrophin gene vector according to the Study Operations Manual. The research pharmacist will transport the vector to the clinical setting in a vector-containing syringe at room temperature, and the vector needs administered to the subject within 24 hours of preparation. The final volume will be administered to the subject by the PI or designee in the subject's hospital room. All subjects will receive IV micro-dystrophin vector (2×10^{14} vg/kg in volume of approximately CCI). This is the same volume that proved safe in the SMA infant gene therapy study. Documentation of the dilution will be completed by the pharmacy following standard pharmacy protocol, and handling of the rAAVrh74.MHCK7.micro-dystrophin gene will follow compliance standards for Biosafety Level 1 vectors.

9.1.2. Vector Administration Protocol

Vector administration will be through a peripheral limb vein. It is unlikely that conscious sedation or a sedative (like lorazepam) will be required, but this will be determined based on PI observation and consultation with parents. The skin over the injection site for gene transfer will be pre-treated with a lidocaine/prilocaine eutectic mixture incorporated in a cream base (EMLA cream) or a cellulose disk (EMLA patch). Comparable cream-based anesthesia such as xylocaine cream might be used. Intravenous catheter placement will be performed following NCH policy, and 2 IVs will be placed. One IV catheter will be for infusion and one for a secondary site in the event that there are complications with the first site. The total dose of vector in volume of approximately CCI to be infused will be 2×10^{14} vg/kg over approximately 1-2 hours. Monitoring of subjects during viral administration will include blood pressure, heart rate, respiratory rate and temperature.

Table 3: Treatment Cohorts

Cohort	Age	N	Vector Dose (vg/kg)	Volume (ml/kg)	Corticoid Steroids
A	3 – 47 months	6	2×10^{14}	CCI	1 mg/kg glucocorticoid maintained for 30 days post infusion unless GGT remains elevated
B	4 – 7 years	6	2×10^{14}	CCI	Stable dose of oral corticosteroids 12 weeks prior to and throughout the first year of the study

9.1.3. Dose-Limiting Plan

A dose-limiting toxicity is defined as any unanticipated SAE that is possibly, probably, or definitely related to the study drug. This would include any Grade [redacted] AE according to the definition provided in Section 12.3.2.

Study enrollment will be halted by the Investigators when any subject experiences 1 or more ≥Grade [redacted] AE toxicity that is unanticipated and possibly, probably, or definitely related to study drug. The event will then be reviewed by the DSMB and evaluated to determine if the study should be terminated early following the stopping/discontinuation rules.

Laboratory tests with values within the clinically significant range will be repeated during the same visit whenever possible. If the test result returns after the subject leaves the clinic, the subject will be immediately contacted. Local residents will be asked to return to the out subject clinic for a repeat test. For non-local residents, arrangements will be made to have the blood test re-drawn in a laboratory close to home or by their primary care physician. To avoid any confusion, the primary care physician will be informed (with permission from the subject) of the subject's participation in the study at the time of gene transfer. If the AE requires treatment, this will be carried out by the primary care physician or a doctor of choice selected by the subject. Copies of repeat laboratory tests and any relevant medical records will be obtained and added to the subject's research chart.

The Sponsor will fulfill the reporting responsibilities under 21 CFR 312.32(c), to notify the FDA in an IND safety report of potentially serious risks, as soon as possible, but no later than 15 calendar days after the Investigator receives the safety information and determines that the information qualifies for reporting. The Investigator will confer with the DSMB, IRB, and Center for Biologics Evaluation/FDA before continuing enrollment.

9.1.4. Stopping/Discontinuation Rules

An independent DSMB will monitor safety data on a continual basis throughout the study. The DSMB can recommend early termination of the study for reasons of safety. Study enrollment will be halted by the Investigators when any subject experiences **[redacted] or more Grade [redacted], or higher** AE toxicity that are **unanticipated** and **possibly, probably, or definitely related** to the study drug. This will include any subject death not related to underlying disease condition, important clinical laboratory finding, or any severe local complication in the injected area related to administration of the study agent. If after review by the DSMB, IRB, and FDA, the decision is made to continue, the study will proceed. If the liver enzyme GGT is elevated at day 30, steroids will be maintained until GGT levels drop below CCI U/L. CCI [redacted]

9.1.5. Dosing Schedule

There will be at least a CCI [redacted] dosing interval between subjects for Cohort B. There will be at least a CCI [redacted] dosing interval between subjects for Cohort A. Dose escalation will be considered in collaboration with FDA and DSMB.

The Investigators will confer with the IRB and DSMB on all Grade [redacted] or higher AEs with in CCI [redacted] that are unanticipated and possibly, probably, or definitely related to the study agent

before continuing enrollment. Based on the outcome of the safety and efficacy analysis of the event, decision will be made to proceed with additional subjects.

9.2. Randomization and Blinding

This study is open-label.

9.3. Concomitant Medications

All subjects will be asked to refrain from using concomitant medications that may interfere with the study objectives. This includes the FDA-approved exon skipping therapy EXONDYS 51. If, during the duration of this study, a subject begins use of EXONDYS 51 their data after use of an exon-skipping drug will no longer be included in study outcomes. We will ask that their study visits for safety assessments be continued for the remainder of the study.

9.4. Treatment Compliance

The vector will be administered under the direct supervision of trained staff.

10. IDENTITY OF INVESTIGATIONAL PRODUCTS

10.1. Description of Study Drug

SRP-9001 will be provided as a sterile frozen liquid in a single-use 2 mL vial containing rAAVrh74.MHCK7.micro-dystrophin gene vector. SRP-9001 will be thawed at room temperature prior to administration. Refer to the Study Operations Manual for further details.

10.1.1. Packaging and Labeling

Preparation should be completed in accordance with local/national aseptic techniques. Preparation of SRP-9001 should be completed on the same day as the dosing procedure.

The clinical pharmacist will prepare the SRP-9001 product aseptically in a Class II biosafety cabinet under sterile conditions. SRP-9001 vials are thawed at the hospital pharmacy at room temperature (20°C to 25°C).

Thawed vector vials are wiped with alcohol and placed in the biosafety cabinet. SRP-9001 for IV infusion will be supplied in a vial (2 mL per vial). The total vg dose will be calculated based on subject's body weight. The appropriate number of vials will be determined for each subject based on body weight at the equivalent of 2×10^{14} vg/kg as well as product titer for the specific SRP-9001 product lot of CCI [redacted]. The actual vg concentration per mL (vg/mL) will be provided on the Certificates of Analysis and the vial containing the Investigational Product.

10.1.2. Storage

SRP-9001 must be stored below -60˚C.

11. STUDY ASSESSMENTS

11.1. Pre-Treatment Assessments([redacted])

After obtaining informed consent and completing the registration procedures, a baseline subject history will be collected, including records of all medications and supplements that the subject is taking. The following assessments will be performed to confirm subject eligibility for this study. Baseline tests which must be completed prior to treatment administration include those listed below.

11.1.1. [redacted] Before Gene Transfer

- Physical examination
- Medical history
- Vitals
- Cardiac magnetic resonance imagining (MRI) (value of MRI of heart has been extensively studied in our MDA Clinic showing increased ability to detect fibrosis and more precise measures of ejection fraction)- Cohort B only
- Electrocardiogram (ECG)
- ECHO
- Chest X-ray
- Hepatitis B & C screen
- HIV screen
- Complete blood count (CBC)/differential/platelet with smear
- Total protein
- Serum GGT*
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Glucose
- Electrolytes (C02, Chloride, Potassium, and Sodium)
- [redacted]
- Creatinine/blood urea nitrogen (BUN)
- Cystatin C
- Alkaline phosphatase
- Amylase

- Prothrombin time (PT), Partial thromboplastin time (PTT), international normalized ration (INR)
- Urinalysis
- Serum antibody to rAAVrh74
- CCI
- Physical therapy assessments
- CCI
  ( )
- AE reporting
- Photograph of injection site
- Concomitant medications
  - Note: use of EXONDYS 51 will disqualify participants from inclusion in this study
- Muscle biopsy (to be completedday CCI)

* GGT will be used to monitor liver enzymes rather than ALT or AST because of the source of these enzymes from damaged muscle in DMD where levels can reach CCI X ULN. Alanine aminotransferase and AST can vary by CCI from day to day making interpretation difficult. Gamma-glutamyl transferase is not affected by muscle disease (Rosales 2008).

11.1.2. Pre-Treatment and Post-Treatment Muscle Biopsy CCI

Pre-gene transfer muscle biopsy with ultrasound guidance will be done after establishing eligibility including appropriate laboratory testing. If a previous muscle biopsy specimen was obtained within 1 year prior to enrollment, the PI will use discretion whether or not the first biopsy needs to be completed during the screening period. Needle CCI muscle biopsies with ultrasound guidance will be used to quantify transgene expression comparing baseline to day 90. The biopsies will be done on the opposite leg as the original biopsies. The muscles to be biopsied at both time points will either be the CCI , at the discretion of the Investigator. The biopsies will be done by the appropriate staff at NCH.

The muscle biopsies will be processed in the CCI , which operates under a College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) license for their diagnostic neuromuscular testing. There will be an assigned blinded identifier CCI for each subject. Blinded analysis will include polymerase chain reaction (PCR) analysis for viral DNA and quantitative Western blot on frozen muscle biopsy shavings. Quantitative protein analysis for micro-dystrophin using a validated Western blot method will be shipped to Sarepta Therapeutics to perform.

Frozen sections will be sectioned and stained for dystrophin using indirect immunofluorescence. CCI will be used to quantify the intensity of dystrophin expression

compared to normal controls. CCI [redacted]

11.1.3. Pre-Treatment Immunosuppressives

Subjects in Cohort A (not taking glucocorticoids upon enrollment per inclusion criteria) will be started on an oral dose of prophylactic prednisolone/prednisone (glucocorticoid) 1 day prior to gene transfer. In most cases this will be prednisolone, 1 mg/kg/day, but prednisone at the same dose is acceptable as well as a comparable glucocorticoid administered via IV if it were to be required. It is the intent for this to serve as an immunosuppressive to dampen host immune response to AAV or transgene. If GGT is below CCI U/L at day 30, steroids will be weaned over 1 week.

Subjects in Cohort B will remain on their stable dose of corticosteroids throughout the first year of the study but may be increased for short time if GGT level is > CCI U/L or there are other clinically significant liver function abnormalities. Those on weekend dosing may receive a daily dose of 1 mg/kg of glucocorticoid for approximately CCI days in addition to their regular weekend dosing.

11.1.4. Cardiac Magnetic Resonance Imaging

Cardiac MRIs will only be performed on subjects greater than 3 years of age (Cohort B) at the time of enrollment. The cardiac MRIs will be performed without any type of anesthesia. If this is not possible due to the ability of the subject, the MRI will not be completed. The cardiac MRI will occur at baseline, 6 months, and year 1 post gene transfer.

11.1.5. CCI

CCI [redacted]

11.2. Gene Transfer and Vector Administration Protocol

Refer to Sections 9.1.1 and 9.1.2.

11.3. Post Gene-Transfer Monitoring

11.3.1. CCI

CCI [redacted]

11.3.2. Extended Follow-up

Subjects will return for follow up visits on days CCI 30, CCI, 90, and CCI (biopsies will occur at CCI) and at months CCI, 36, CCI, and 60. Follow-up visits through day 30 will be done at NCH as will the muscle biopsy (pre- and post-gene transfer). Unscheduled visits may occur if the PI determines they are necessary for the subject's safety and wellbeing. CCI. Toxicity monitoring on each of these dates is described in the following sections of the protocol. We will follow the most recent FDA guidelines with regard to long-term subject follow up following gene transfer. CCI. We will, however, evaluate safety over a 5-year period that incorporates the active phase of the protocol (see assessment of endpoints below). If newly identified risks are associated with our product, or if the subjects suffer any adverse reactions during this period, we will initiate a long-term follow-up according to the FDA guidelines.

11.3.3. Assessment of Safety

11.3.3.1. CCI

CCI

Monitoring will occur at day CCI, 30, CCI, 90, and 180, and at months CCI, 36, CCI 60. A muscle biopsy will take place at day 90. The following parameters will be included at the monitoring evaluations:

- Physical examination
- Vitals
- Serum GGT
- ALT
- AST
- Total bilirubin
- Glucose
- PT, PTT, INR
- CBC/differential/platelet with smear

- CCI [redacted]
- Creatinine/BUN
- Cystatin C
- Alkaline phosphatase
- Amylase
- Electrolytes (C02, Chloride, Potassium, and Sodium)
- Total protein
- Urinalysis
- CCI [redacted]
- CCI [redacted]
- Cardiac MRI (at 6- and 12-month visit)- Cohort B only
- Photograph of injection site/surrounding area (up through day 30 visit)
- AE reporting
- Concomitant medications
- ECHO/ECG at day 30 and years 1, 2, 3, 4, and 5

11.3.4. Assessment of Efficacy

The Bayley-III Gross Motor Subtest will be scored for Cohort A on every follow up visit starting at day 30 and followed on day CCI [redacted], 90, and CCI [redacted], and at months CCI [redacted] 36, and serve as a secondary outcome for this study. Any subject that is 43-47 months of age, inclusive, at time of screening will have the scaled score calculated compared to normative data for 42 -month old children. The Bayley-III provides normative data for children 1-42 months of age.

The 100m will be a primary motor outcome CCI [redacted]. The 100m will be the primary motor outcome for Cohort B. CCI [redacted]

Muscle biopsies with ultrasound guidance will be used to quantify transgene expression comparing baseline to day 90. The biopsies will be done on the same leg as the original biopsies. However, in some cases at the discretion of the PI, the opposite extremity may be preferred if it will be less traumatic to the subject. It is also important to emphasize that the biopsies will be read blinded and will not be identified as pre- or post-treatment. The biopsies will be done by the appropriate staff at NCH.

The muscle biopsies will be processed in the CCI [redacted], which operates under a CAP/CLIA license for their diagnostic neuromuscular testing. There will be an

assigned blinded identifier for each subject. Frozen sections will be stained for dystrophin using indirect immunofluorescence. CCI will be used to quantify the intensity of dystrophin expression compared to normal controls. CCI

CCI

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1. Definitions of Adverse Events

12.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject that does not necessarily have a causal relationship with the study drug. An AE can, therefore, be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality that occurs during or after administration of a study drug, whether or not considered related to the study drug.

Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff
- The onset of new illness and the exacerbation of pre-existing medical conditions
- Test abnormalities (laboratory tests, ECG, etc.) deemed clinically significant

Abnormalities present at screening will be collected as part of medical history and are considered AEs only if they re-occur after resolution or worsen during the AE collection period.

12.1.2. Serious Adverse Event

An SAE is defined as any AE that results in any of the following:

- **Death**: The subject died as the result of the event.
- **Life-threatening event**: Any AE that places the subject, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred (ie, does not include an AE that, had it occurred in a more severe form, might have caused death).
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization.
  - Hospitalizations that are part of the study procedures are exempt unless the hospitalization is prolonged (based on the judgment of the Investigator) due to an event.
  - Pre-planned hospitalizations are not considered SAEs unless prolonged due to an AE.
- **Persistent or significant disability/incapacity**: An AE that results in persistent or significant disability or disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the study drug, or the partner of a subject exposed to the study drug.

Important medical event: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that

might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above.

12.1.3. Overdose

An overdose is defined as administration of a quantity of a medicinal product given that is above the maximum recommended dose according to the authorized product information.

12.1.4. Medication Error

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or subject harm while the study drug is in the control of the healthcare professional or, in certain cases, the subject. Such incidents may be due to healthcare professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, dispensing, nomenclature, compounding, distribution, administration, education, monitoring, and use.

12.1.5. Accidental/Occupational Exposure

Accidental/occupational exposure is the unintentional exposure to a study treatment as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (eg, study drug given to wrong subject).

12.2. Collection of Adverse Events

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be collected and documented in the electronic case report form (eCRF).

All AEs will be collected and recorded from the time of informed consent/assent through the last follow-up visit.

All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normal levels, the event has stabilized and there is a satisfactory explanation for the changes observed, the subject is lost to follow-up, or the subject has died.

All AEs will be followed until the resolution of the AE, completion of the subject's study participation, or study termination, whichever occurs first. All SAEs will be followed until resolution or until the condition stabilizes or returns to screening/baseline status.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF, as well as on the SAE Report Form's medical history section.

For subjects who are found to be ineligible for the study during the pre-infusion period and are not enrolled (ie, screen failures), only SAEs (Section 12.1.2) will be reported (Section 12.5).

If, at any time after the subject has completed participation in the study, the Investigator or study staff become aware of an SAE that the Investigator assesses as related to the study drug or

related to a study procedure (Section 12.3.1), then the event and any known details must be reported promptly to the Sponsor, no later than within 24 hours of awareness.

12.2.1. Clinical Laboratory Abnormalities

A laboratory abnormality deemed clinically significant by the Investigator should be recorded as an AE. Whenever possible, the underlying medical diagnosis (eg, anemia) should be recorded as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

12.3. Classification of Adverse Events

All AEs, whether serious or nonserious, will be classified by the Investigator according to the following rules and definitions.

12.3.1. Relationship to Study Agent, Study Procedures and the Subject's Pre-existing Disease

Association or relatedness to the study agent, study procedures and the subject 's pre-existing disease will be graded as follows: 5 = unrelated, 4 = unlikely, 3 = possibly, 2 = probably, and 1 = definitely related.

12.3.2. Severity of Adverse Events

The Investigator will assess the severity of all AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 5.0. Events **not listed** in the CTCAE will be assessed according to the following scale.

Grade 1:	Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated
Grade 2:	Moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care ADL
Grade 4:	With life-threatening consequences, urgent intervention indicated
Grade 5:	Death related to AE

Note that severity is not the same as "seriousness," which is defined in Section 12.1.2 and which serves as a guide for defining regulatory reporting obligations.

In addition, laboratory or vital signs-based events that are defined as Grade 4 in the CTCAE solely by laboratory or vital sign measurements are not automatically clinically life-threatening; the Investigator must make this clinical assessment regardless of grade.

12.3.3. Outcomes of Adverse Events

"Outcome" describes the status of the AE. The Investigator will provide information regarding the subject outcome for each AE. Outcome categories will include "recovered," "recovered with sequelae," "not recovered," "fatal," and "unknown."

12.3.4. Action Taken Regarding the Study Drug

The Investigator will provide information regarding the action taken with respect to the study treatment in response to the AE. Categories for action taken regarding study treatment will include "none," "drug interrupted," "drug withdrawn," and "not applicable."

12.3.5. Expectedness of Adverse Events

The expectedness of all AEs will be determined by the Sponsor according to the most recent version of the Investigator's Brochure for SRP-9001.

12.4. Recording Adverse Events

All AEs from the time of providing signed informed consent/assent through the last follow-up visit will be recorded in each enrolled subject's eCRF. All SAEs and other safety information, such as that pertaining to special situations (Section 12.6) will also be recorded on the Clinical Trial Safety Reporting Form and reported to the Sponsor via email to PPD within 24 hours of awareness.

Information recorded should include the following: a concise description of the event; date of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to study drug, study procedure, and underlying disease; and any action taken. Resolution occurs when the subject has returned to the baseline state of health, or when further improvement or worsening of the event is not expected.

Whenever possible, a diagnosis will be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. Several symptoms or laboratory results that are associated with the same diagnosis can thus be part of the same AE. A medical or surgical procedure is not an AE; rather, the condition leading to the procedure should be recorded as the AE.

Similarly, death is not an AE, but rather, the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then "death" must be reported as an AE. All causes of death are SAEs. In the event of death, every effort should be made to obtain a death certificate and if possible, an autopsy report. If the cause of death is unknown, death will be recorded as the event.

Any SAE assessed as related to the study drug, occurring after the subject completes the study, should be recorded on a Clinical Trial Safety Reporting Form and reported as per the instructions for SAEs provided immediately below.

12.5. Reporting Serious Adverse Events

12.5.1. Serious Adverse Events

The Investigator must report all SAEs via email to PPD within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE, as per the information printed on the Clinical Trial Safety Reporting Form and in the SAE Completion guideline.

12.5.2. Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SUSARs will be handled by appropriate Sponsor (or designee) personnel and reported within the required timelines, in an unblinded fashion, to regulatory authorities and the IRB, per the requirements of the concerned competent authorities.

12.6. Reporting Special Situations

12.6.1. Overdose

An overdose is not an AE. An overdose will be reported even if it does not result in an AE. An overdose will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

12.6.2. Medication Error

Any medication error is to be reported to the Sponsor on the Clinical Trial Safety Reporting Form sent via email to PPD within 24 hours of becoming aware, according to the process for reporting SAEs (Section 12.5).

12.6.3. Accidental/Occupational Exposure

Any accidental/occupational exposure is to be reported to the Sponsor on the Clinical Trial Safety Reporting Form sent via email to PPD within 24 hours of becoming aware, according to the process for reporting SAEs (Section 12.5).

12.7. Miscellaneous

12.7.1. Responsibilities of the Investigator

The responsibilities of the Investigator include, but are not limited to, the following:

- Monitoring and recording all AEs
- Determining the seriousness, severity, and relationship to study drug, study procedure, and underlying disease for each AE
- Determining the onset and end date of each event
- Providing the initial report of all SAEs and special situations to the Sponsor via email to PPD or designee within 24 hours of first knowledge
- Providing follow-up information on SAEs in a timely and proactive manner

- Responding to queries regarding AEs and SAEs in a timely manner
- Ensuring that source documentation for all AEs is accurate and complete
- Ensuring that the study is conducted as defined in this protocol and according to applicable regulations and guidelines

Investigators may also report improvement of pre-existing DMD conditions or unexpected therapeutic responses.

12.7.2. Responsibilities of the Sponsor

The responsibilities of the Sponsor include, but are not limited to, the following:

- Training of Investigator on AE/SAE definitions, safety assessments, and site obligations related to safety monitoring and reporting of AEs/SAEs
- Training with regard to the accurate and legal reporting of SAEs to all applicable regulatory authorities, IRBs, clinical study sites, and other parties, as appropriate and required within the regulated timing
- Ensuring accurate recording of AEs and SAEs
- Submission of expedited serious, unexpected, and related AEs to regulatory authorities per regulatory requirements
- Notification of blinded unexpected and related SAEs to sites
- Annual safety reporting to regulatory authorities and IRB according to regional requirements

13. STATISTICS

This is a Phase I/IIa study, with safety as the primary measure. Bayley-III pre- and post-gene transfer will be the primary motor outcome for Cohort A. The 100m will be a primary motor outcome [redacted]. The 100m will be the primary motor outcome for Cohort B. [redacted]. As the sample size is small and the motor outcomes will differ between cohorts as well as over time for some subjects within Cohort A, all analyses will be descriptive in nature and will not employ inferential statistics.

Periodic safety and efficacy analyses are performed for safety monitoring reviews, Investigator's Brochure update, regulatory submissions such as Development Safety Update Report and regulatory meeting briefing documents, and scientific disclosures**.** These periodic analyses are described in separate documents.

14. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

14.1. Regulatory and Ethical Considerations

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the International Council for Harmonisation (ICH) Good Clinical Practices Guidelines. The procedures outlined in the protocol and case report forms will be carefully reviewed by the PI and staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and wellbeing of subjects.

Amendments will be submitted to the NCH IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent Form will be revised and if applicable, subject 's consent to continue participation will again be obtained.

14.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow Sarepta to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

14.3. Informed Consent

Legally effective and properly executed written informed consent, in compliance with 21 CFR 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study or before any unusual or non-routine procedure is performed that involves risk to the subject. The informed consent will be signed prior to study procedures and will require IRB approval. Attention will be directed to the basic elements that are required for incorporation into the informed consent under US Federal Regulations for Protection of Human Patients [21CFR 50.25(a)]. The final IRB-approved document as well as any subsequent approved modified consent document(s) must be provided to correspondent agencies for regulatory purposes. If new information related to the study arises, subjects will be asked to sign a revised document. Signed consent forms will remain in each subject's research chart and will be available for verification by study monitors at any time. Subjects will be given a signed, dated copy of their consent form.

14.4. Data Management and Study Forms

All subjects will be given a unique sequentially assigned subject number. Subjects will be identified by number only to protect identity.

All data and observations will be documented on electronic CRFs from source documentation. A Study Monitor will have access to the data to monitor adherence to the protocol and to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. An electronic CRF will be completed for every subject that was registered for participation in the study. Case

report forms will be completed as information becomes available or within 3 days of a Study Visit.

Case Report Forms will be reviewed in detail by the study monitor on a regular basis for which the study monitor will have access to subject medical records, laboratory data, and other source documentation. The study monitor will make a decision as to whether the data are acceptable. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the eCRF in question will be queried.

The Investigator will sign the eCRFs. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form.

An external Contract Research Organization will also monitor the study in a regular basis to make sure the study is conducted in compliance with all regulatory aspects of the protocol.

14.5. Publication Policy

14.5.1. Study Reports

14.5.1.1. Final Study Report

The final study report will include data through the final study visit through Year 5.

14.5.1.2. Annual Study Reports

Within 60 days after the 1-year anniversary of the date on which the IND application went into effect, and after each subsequent anniversary until the study is completed, the Sponsor will submit information to the FDA set forth as follows:

a. Clinical Trial Information.

   – This will be a brief summary of the status of the study in progress or completed during the previous year. The summary will include the following information for the study: (1) the title and purpose of the study; (2) clinical sites; (3) the investigators; (4) clinical protocol identifiers , including the NCH IRB and IBCSC protocol numbers, and the FDA IND application number; (5) participant population (such as disease indication and general age group); (6) the total number of participants planned for inclusion in the study; the number entered into the study to date; the number whose participation in the study was completed; and the number who dropped out of the study with a brief description of the reasons; (7) the status of the study, eg, open to accrual of subjects, closed but data collection ongoing, or fully completed, and (8) if the study has been completed, a brief description of any study results.

b. Progress Report and Data Analysis.

   – Information obtained during the previous year's clinical and non-clinical investigations, including: (1) a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system; (2) a summary of all SAEs submitted during the past year; (3) a summary of SAEs that were expected or considered to have causes not associated with the use of the gene

transfer product such as disease progression or concurrent medications; (4) if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death; and (5) a brief description of any information obtained that is pertinent to an understanding of the gene transfer product's action, including, for example, information about dose-response, information from controlled studies, and information about bioavailability.

c. A copy of the updated clinical protocol including a technical and non-technical abstract.

15. LIST OF REFERENCES

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CCI

PPD

Signature:

Email:

Title:

Company: