CLINICAL PROTOCOL

A 48-Week, Open Label,
Study to Evaluate the Efficacy and Safety of
Casimersen, Eteplirsen and Golodirsen in Subjects with Duchenne
Muscular Dystrophy carrying eligible DMD duplications

NCH US IND: [redacted]
Sarepta Casimersen IND: [redacted]
Sarepta Eteplirsen NDA: [redacted]
Sarepta Golodirsen NDA: [redacted]

PROTOCOL VERSION: 6.0 (20APR2021)

IIS SUPPORTER: Sarepta Therapeutics

Sponsor-Investigator: Kevin M. Flanigan, M.D.

Abigail Wexner Research Institute
Nationwide Children's Hospital
Center for Gene Therapy

SIGNATURE PAGE

Study Title: A 48-Week, Open Label, Study to Evaluate the Efficacy and Safety of Casimersen, Eteplirsen and Golodirsen in Subjects with Duchenne Muscular Dystrophy carrying eligible DMD duplications

Financial Sponsor Sarepta Therapeutics

Protocol Version v6.0 20Apr2021

As Sponsor-Investigator, I agree to personally conduct this study in compliance with Principles of Good Clinical Practice as defined by federal, state, and local laws and regulations. I will abide by the current protocol (provided herein), including any protocol amendments that are approved by our institutional review board (IRB).

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Kevin M. Flanigan, MD
Sponsor-Investigator
Nationwide Children's Hospital

Contents

1 PROTOCOL SYNOPSIS

Title	A 48-Week, Open Label, Study to Evaluate the Efficacy and Safety of eteplirsen, casimersen and golodirsen in Subjects with Duchenne muscular dystrophy carrying eligible DMD duplications
Clinical Study Phase	Phase II
Number of Centers	Single-Center, Nationwide Children's Hospital, Columbus, Ohio
Study Objectives	Primary Study Objectives: • To evaluate the efficacy of casimersen (previously SRP-4045), eteplirsen (previously AVI-4658), or golodirsen (previously SRP-4053) on dystrophin expression as assessed by quantification of protein in muscle biopsy tissue by western blot. • To assess safety and tolerability in a population of subjects with relevant exon duplications using the following outcome measures. o Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs o Laboratory testing may include the following (See Section 9 for details): ▪ Hematology ▪ Coagulation ▪ Chemistry ▪ Urinalysis o Cardiac function including ECG and ECHO o Vital signs o Physical examination findings Secondary objectives will be to assess efficacy using the following outcome measures: • Expression of dystrophin as measured by immunofluorescent signal intensity and percent dystrophin positive fibers (PDPF) in muscle tissue sections in comparison to baseline values. • The efficiency of splicing alteration will be measured by RNA Sequencing (RNA-Seq) to establish *DMD* mRNA copy number and the exon-exon junction frequency quantified, with normalization to exon junction read values from an exon junction in regions distinct from the targeted exon. Exploratory objectives will be to assess efficacy using the following outcome measures: • Functional abilities of subjects in comparison to the expected natural history using the following measures: o Subjects between 6 to 36 months of age at enrollment: Bayley Scales of Infant Development - Gross motor functions and fine motor functions. o [redacted] o [redacted] o ACTIVE-seated for boys over 5 years of age.

	○ Forced vital capacity, as measured in absolute values and by % predicted forced vital capacity (FVC%) in patients ≥ age 10. ○ [redacted] ○ [redacted] • [redacted] • Adult PROMIS Upper Extremity Report for patients 18+ years. • Immune staining may be performed on biopsy specimens for members of the dystrophin-associated protein complex, such as the sarcoglycans, dystroglycans and n-Nos. • [redacted]
Methodology	This is a open-label, 48-week study to evaluate the efficacy and safety of three phosphorodiamidate morpholino oligomers (PMOs) (casimersen, eteplirsen, and golodirsen) in 6 subjects with genotypically confirmed Duchenne muscular dystrophy (DMD) with duplication mutations amenable to correction by skipping exon 45, 51, or 53, respectively. Subjects will be evaluated for inclusion during a screening period of approximately 8 weeks. Eligible subjects who have out-of-frame duplications of a single exon that may be corrected by skipping exon 45, 51, or 53 will receive once weekly intravenous (IV) infusions of 30 mg/kg casimersen, 30 mg/kg eteplirsen, or 30 mg/kg golodirsen respectively for 48 weeks. Upon qualification for the study based on Screening and Baseline assessments, all subjects will undergo a muscle biopsy for baseline assessment of dystrophin expression. All subjects will undergo a second biopsy at 48 weeks of treatment.. Efficacy, including the Bayley scale, NSAA, 100M, ACTIVE-seated and pulmonary function tests, will be assessed at regularly scheduled (12 week intervals) study visits and safety will be monitored on an ongoing basis for all subjects. Safety will be assessed through the collection of adverse events (AEs), serious adverse events (SAEs), deaths, discontinuation of study due to AEs, laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, physical examinations throughout the study as described in the Schedule of Events (see Sections 9 and 10).
Duration of Study	The total duration of the study will be up to 60 weeks based on the three parts below: • Screening/Baseline Period: Approximately 8 weeks • Treatment Period: Up to 48 weeks

	• Safety Follow-up: Subjects will be followed up with by phone call approximately 4 weeks (28 days) following last infusion to check for adverse events or other significant findings.
Number of Subjects	Approximately 6 subjects will be included in this study, to be enrolled by invitation.
Subject Population	**INCLUSION/EXCLUSION CRITERIA:** **Inclusion Criteria:** A subject must meet all of the following criteria to be eligible for this study. 1. Is a male with DMD and has an out-of-frame duplication of either exon 45, 51, or 53, with a normal copy number of all other *DMD* exons. 2. Is above age 6 months. 3. Has pulmonary function, that in the Investigator's opinion, is unlikely to decompensate significantly over the duration of the study. 4. Has sufficient muscle mass in a pair of bilateral muscles that will allow for pre- and post-treatment muscle biopsies per PI discretion. 5. If the subject is ambulant and 4 years old or greater and has been on a stable dose or dose equivalent of oral corticosteroids for at least 12 weeks prior to Week 1 the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: Subjects are allowed to take other medications (excluding other RNA antisense or gene therapy agents) including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β adrenergic blockers, potassium, and coenzyme Q, provided they have been on a stable dose for 12 weeks prior to Week 1. The dose is expected to remain constant throughout the study (modifications to doses to accomodate changes in weight are allowed). 6. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements. 7. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the subject to participate in the study. **Exclusion Criteria** A subject who meets any of the following criteria will be excluded from this study. 1. Any additional missing exon for DMD that cannot be treated with study drugs. 2. Subject has previously been treated with eteplirsen, casimersen, or golodirsen, or is currently being treated with other RNA antisense or gene therapy agents. 3. Current or history of liver disease or impairment including one of the following at Screening: a. an INR value above 1.5 b. a total bilirubin greater than 2 times the Upper Limit of Normal (ULN) or a GGT greater than 2 times the ULN 4. Screening platelet count below the Lower Limit of Normal (LLN) for age.

	5. Screening aPTT above the ULN 6. History of significant medical disorder which may confound the interpretation of either efficacy or safety data e.g., inflammatory disease. 7. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks prior to Week 1 that may have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids). 8. Current or previous treatment with any other experimental treatment within 12 weeks prior to Week 1. 9. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable. 10. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy. 11. Use of any aminoglycoside antibiotic or statin within 12 weeks prior to Week 1 or anticipated need for an aminoglycoside antibiotic or statin during the study. 12. QTcF ≥ 450 msec based on the Screening and/or Baseline ECG. 13. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the subject, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, subjects who seem unable/unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded. 14. Acute illness within 4 weeks of the first anticipated administration of study medication which may interfere with study assessments. 15. Symptomatic cardiomyopathy. If the subject is asymptomatic but has a left ventricular ejection fraction <40% at Screening, the investigator should discuss inclusion of subject in the study with the Safety Review Committee. 16. Use of anticoagulants, antithrombotics or antiplatelet agents within 4 weeks prior to anticipated study drug administration.
Dose/Route/Regimen (Test Article)	Eteplirsen, casimersen, or golodirsen (each at 30 mg/kg) will be administered as an IV infusion over 35-60 minutes once a week for 48 weeks.
Sample Size	The sample size for this study was based on the availability of subjects with these unusual mutations for this open label study, and not on power estimates of effect size.
Statistical Methods	**Efficacy Analyses:** The analysis of changes in dystrophin expression by western blot analysis will make use of published protocols for protein expression quantification in comparison to normal samples. Changes from baseline to week 48 will be assessed using a 1-sample permuation test. **Safety Analyses:** Treatment emergent adverse events (TEAEs) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group. Non-treatment emergent events will be recorded in the data listings. For all AE tables, the number and percentage of subjects reporting AEs will be grouped

	by SOC and PT. Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in the frequency tables. If a subject experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to study treatment will be used to summarize AEs by relationship and severity. Descriptive statistics for ECG, ECHO, vital signs, and safety laboratory parameters will be generated. Summary statistics for each parameter at specific time points, as well as the change from Baseline to that time point, will also be displayed. All safety data will be presented in the data listings.
Post-treatment Follow-up/Clinical Transition Period	Subjects will be followed up with by phone call approximately 4 weeks (28 days) following last infusion to check for adverse events or other significant findings. At the conclusion of the 48 week study period, subjects will be enrolled in the Sarepta Clinical Transition Program and will be followed clinically in the NCH DMD clinic for safety, specifically for monitoring of renal function as per the prescribing information for casimersen and golodirsen. All prescribing recommended testing will be performed for clinically monitoring only. Those subjects receiving golodirsen or casimersen via this program will be monitored by urine dipstick every month, and serum cystatin C and urine protein to creatinine ratio (UPCR) every 3 months There is no additional clinical safety testing recommended per the prescribing information for eteplirsen.- Additionally, through this program the subjects will be provided uninterrupted weekly drug access after conclusion of the 48 week study period. Subjects will remain on the Clinical Transition Program/SareptAssist until study samples can be analyzed and insurance authorization for the drug(s) can be obtained, or the efficacy of the drug is determined to not meet the standards for continuation. The threshold for study drug continuation in Sarepta's Clinical Transition Program/SareptAssist is a 10 percent increase in dystrophin positive fibers (defined as fibers with 30 percent of the circumference positive for dystrophin) as determined by immunofluorescence staining of the baseline and 48-week post-treatment muscle biopsies. Subjects will receive weekly drug infusions via home health care arranged by Sarepta Therapeutics and as noted above will be monitored clinically in the NCH DMD clinic.

2 ADMINISTRATIVE INFORMATION

2.1 Document History

Table 1: Document Record

Document	Version and Date	Submission Purpose
Clinical Protocol	V1.0 26Oct2018	IRB Submission
Clinical Protocol	V2.0 1Nov2018	IRB Modification/FDA IND Submission S/N 0000
Clinical Protocol	V3.0 13Dec2018	IRB Modification
Clinical Protocol	V4.0 06Dec2019	IRB Modification/IND Update Submission S/N 0001
Clinical Protocol	V5.0 17Feb2020	IRB Modification
Clinical Protocol	V6.0 20Apr2021	IRB Modification

2.2 Summary of Changes

The section below highlights content changes in this version of the protocol. Language deleted from the previous version of the protocol appears in ~~red/strikethrough~~. Language added to the previous version of the protocol appears in **bold**.

Table 2: Revision Record

Protocol Version	Description of Changes
V4.0 06Dec2019	• Administrative changes • ~~Removed language about the NSAA Revised and instead listed all applicable age ranges to receive the NSAA.~~ • ~~Removed the cognition and language skills portion of the Bayley.~~ • Clarified Exclusion Criteria #2 from: o Subject has been treated with eteplirsen, or is amenable to or is currently being treated with other RNA antisense or gene therapy agents. To o Subject has previously been treated with eteplirsen, casimersen, or golodirsen, or is currently being treated with other RNA antisense or gene therapy agents. • Replaced reference of a "Pharmacy Manual" with the "Clinical Study Manual of Operations"

	• In therapies not permitted during conduct of this trial, the item of "Systemic or oral steroids for non-DMD conditions" was amended to further include **"….that, in the Investigator's opinion, could interfere with study assessments and outcomes."** • **Changed weight based adjustments to be taken on a monthly schedule. This included adding weight to weeks 16, 20, 28, 32, 40, and 44** • ~~Removed height from weeks 1, 4, 8~~ • Moved Height from screening day 1 to screening day 2 • Updated table 1 and 2 • Clarified source of determining expectedness of adverse an adverse event. • ~~Removed reference to OBA~~ • **Addition of a summary of TEAE's to be include in safety reporting meetings** • Broadened the scheduling of port placement in case it cannot be completed at the same time as the muscle biopsy. • ~~Removed Immunogenicity studies~~ • Clarified Long-term Follow-up intentions. • Clarified that GGT and Amylase are not part of the CMP • **Added PROMIS for Upper Extremity Report for ages 18+** • **Added an upper age to the PODCI of 17 years.** • ~~The Safety Review Committee~~ was replaced with **the Data and Safety Monitoring Board.** • ~~Removed KIM-1 assay~~ • ~~Removed MMP-9 and miRNA analysis (Biobanking for biomarkers section removed)~~

	• Revised Section 11 to be in line with NCH IRB guidance
V5.0 17Feb2020	• ~~Removed pharmacokinetics (PK) testing from the study.~~ • ~~Removed KIM-1 from the Schedule of Events~~. • Updated contact information for study staff to ~~remove Rachel Heffern~~ and **add Maryann Kaler**.
V6.0 20Apr2021	• **Adding subject rollover to the Sarepta Clinical TransitionProgram.** • **Adding threshold of 10% dystrophin positive fibers for study drug continuation after completion of 48 week trial.** • ~~Removal of Anti-Dystrophin Antibodies.~~

2.3 Contact Information

Table 3: Study Team

Role in Study	Name	Address and Telephone Number
Sponsor Investigator	Kevin Flanigan, MD	WA3011 700 Children's Dr Columbus, OH 43205 Ph: 614-722-5615 megan.waldrop@nationwidechildrens.org
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Table 4: Data Safety Monitoring Board

Name	Address and Telephone Number

John Brandsema, M.D.	Children's Hospital of Philadelphia 3401 Civic Center Blvd Philadelphia, PA 19104 Ph: 215-590-1719 brandsemaj@email.chop.edu
Perry Shieh, M.D., Ph.D.	UCLA Neuro BOX 956975, B200, 300 Medical Plaza Los Angeles, CA 90095 Ph: 310-794-1195 pshieh@mednet.ucla.edu
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Table 5: Study Vendor Listing

Role in Study	Name	Address and Telephone Number
Monitor	IQVIA Biotech Terri Walker	580 N. 4th Street, Suite 270 Columbus, OH 43215 Ph: 614-954-0435 Terri.walker@iqvia.com
Lab for Immunofluorescence	Flagship Biosciences, Inc. Briana Kennedy	7575 W. 103rd Ave., Suite 102 Westminster, CO 80021 bkennedy@flagshipbio.com

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2D	2-dimensional
AAOS	American Academy of Orthopaedic Surgeons
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocking agent
AST	aspartate aminotransferase
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CD	compact disc
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG(s)	electrocardiogram(s)
ECHO(s)	echocardiogram(s)
EDC	electronic data capture
EF	ejection fraction
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
Injection	US nomenclature equivalent to Concentrate for Solution for Infusion
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous, intravenously

Abbreviation	Definition
IVR	interactive voice response
LDH	lactate dehydrogenase
LLN	Lower Limit of Normal
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities®
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
mRNA	messenger ribonucleic acid
NCS	not clinically significant
NSAA	North Star Ambulatory Assessment
QMT	quantitative muscle testing
PFT	pulmonary function test
PMO	phosphorodiamidate morpholino oligomer
PODCI	Pediatric Outcomes Data Collection Instrument
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
RBC	red blood cells
REML	restricted maximum likelihood
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	Upper Limit of Normal
US FDA	United States Food and Drug Administration
WBC	white blood cell

4 INTRODUCTION

4.1 Background of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a degenerative neuromuscular disease with an X linked recessive inheritance caused by mutations in the dystrophin gene, with a worldwide incidence of approximately 1 in 3500 newborn boys, irrespective of geographical region, race, or population density [1-3]. The mutations that cause DMD typically disrupt the mRNA reading frame and prevent production of dystrophin, a critically important part of the protein complex that connects the cytoskeleton of a muscle fiber to the cell membrane and extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contraction causes progressive muscle damage. The clinical effect of this disrupted dystrophin reading frame is progressive and ultimately fatal.

DMD is usually first diagnosed between the ages of 3 to 5 years[4], when toddlers develop a waddling gait, lordosis, toe walking, calf hypertrophy, and a difficulty in climbing stairs. Over time, ambulation becomes increasingly abnormal. By 8 years of age, most subjects have lost the ability to rise from the floor and to climb stairs, show an increasingly labored gait, and often fall while walking, which leads to use of mobility devices such as strollers and scooters. Subjects with DMD walk slower than healthy boys and spend less time walking[5] and they are significantly less active compared to healthy boys of similar age[5, 6]. By 10 to 14 years of age, most are wheelchair dependent. Weakness of the arms and increasingly limited upper limb function, contractures, decubitus ulcers, and scoliosis (which often requires surgery), occur frequently. While pulmonary and cardiac functions are generally normal during early childhood, cardiac and diaphragmatic muscles progressively weaken during late childhood and adolescence leading to eventual dependence on ventilation support. Historically, subjects typically died from respiratory or cardiac failure in their late teens or early 20s[7, 8]. Recent research suggests that use of ventilation support and steroids may increase life span by several years; however, DMD still has a mortality rate of 100%[9]. Corticosteroids used for palliative treatmemt of DMD can prolong ambulation and reduce the incidence of severe scoliosis; however, they are often associated with serious side effects[10, 11] and are not always employed.

4.2 Phosphorodiamidate Morpholino Oligomers (PMOs) for the Treatment of Duchenne Muscular Dystrophy

Antisense ribonucleic acid (RNA) therapeutics are compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and uracil or analogs) linked together on an oligomer backbone that hybridizes to complementary RNA targets. RNA therapeutics can be synthesized to bind to specific RNA sequences to regulate gene expression, thus they can be used to treat a wide range of diseases. A relatively new use of RNA therapeutics is to target a pre-mRNA sequence in the cell nucleus to influence the splicing process that creates the mature mRNA; this is referred as"exon skipping," as it determines which exons will be incorporated into the mature mRNA that is then translated into the protein product.

Phosphorodiamidate morpholino oligomers (PMOs) are a class of synthetic molecules based on a redesign of the natural nucleic acid structure. PMOs differ from 2′-*O*-methyl and other oligonucleotide therapeutic platforms because of their six-membered morpholino ring, which replaces the five-membered ribofuranosyl. Moreover, PMOs also have each morpholino ring bound to each other through an uncharged phosphorodiamidate moiety, as opposed other RNA therapeutics and backbones which have a negatively-charged phosphorothioate.

Several PMOs are being evaluated by Sarepta Therapeutics, Inc., (Sarepta) for the treatment of DMD. The investigational drug products, casimersen (previously SRP-4045), eteplirsen (previously AVI-4658), and golodirsen (previously SRP-4053), are charge-neutral PMOs that selectively bind to exon 45, 51, or 53, respectively, of dystrophin pre-mRNA and cause the exon to be skipped during processing. This restores the open reading frame in DMD subjects with mutations amenable to skipping exon 45, exon 51 or exon 53 of the dystrophin pre-mRNA, each of which represents approximately 8%, 13% and 8% of all DMD subjects, respectively[12]. This mechanism is expected to enable the production of an internally deleted, yet partially functional, dystrophin protein, similar to that observed in Becker muscular dystrophy (BMD), a much less severe form of dystrophinopathy. In contrast to DMD, most BMD subjects remain ambulatory and have a near-normal life expectancy[13, 14]. Treatment with casimersen. eteplirsen, or golodirsen is expected to result in sustained production of partially functional dystrophin protein and potentially improve the quality of life and prognosis for DMD subjects, essentially switching their clinical symptoms and prognosis to be more similar to those of subjects with BMD. Over time, treatment with casimersen, eteplirsen or golodirsen is expected to delay or potentially halt disease progression in boys with DMD who have gene mutations amenable to exon 45, exon 51 or exon 53 skipping, respectively. Nonclinical data for casimersen, eteplirsen, and golodirsen are described in the respective Investigator's Brochures.

4.3 Clinical Experience with Eteplirsen, Casimersen and Golodirsen

Available clinical data for the three PMOs is discussed here.

Eteplirsen

Eteplirsen is a charge neutral PMO that selectively binds to exon 51 of dystrophin pre-mRNA and it is conditionally approved for the treatment of subjects with DMD that are amenable to skipping exon 51.

Two Phase 1 clinical studies of eteplirsen have provided initial support and proof-of-concept for the safety and potential efficacy of eteplirsen in the treatment of DMD. In light of the positive findings from the 2 Phase 1 studies[15, 16], a 28-week, double-blind, placebo-controlled Phase 2 study (Study 4658-us-201)[17] was initiated to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of eteplirsen. Twelve patients aged 7 to 13 years were randomized to receive once-weekly intravenous (IV) infusions of eteplirsen (30 or 50 mg/kg) for 28 weeks, or once-weekly placebo infusions for 24 weeks followed by eteplirsen infusion (30 or 50 mg/kg) for 4 weeks. At Week 28, these same 12 patients were enrolled in the extension study (Study 4658-us-202)[18] where they continued open-label eteplirsen at the same dose they were receiving upon completion of the parent study. This extension study has been completed, and enrolled DMD patients received eteplirsen for more than 4 years. Four other eteplirsen studies have been conducted in patients with DMD:

- Study 4658-203[19], a Phase 2 study in patients 4 to 6 years of age
- Study 4658-204[20], a Phase 2 study in patients with advanced stage DMD
- Study 4658-301[21], a Phase 3 safety and efficacy study in a population of patients in late-ambulatory decline
- Study 4658-102[22], a Phase 2 study in patients aged 6-48 months

Based on the cumulative available safety data from these studies, eteplirsen has been shown to be well tolerated, with low rates of treatment-related serious or severe adverse events (AEs).

Analysis of biopsies taken at combined Study 201/202 Week 180 showed a significant increase in dystrophin protein by western blot in eteplirsen-treated subjects as compared to untreated controls ($p=0.007$) contributing to its approval by the FDA for use in subjects with deletion mutations amenable to exon 51 skipping[23].

Further, after 4 years on treatment in pivotal Study 201/202, subjects in the 30 mg/kg and 50 mg/kg eteplirsen cohorts experienced a decline on the six-minute walk test that was 165 meters less ($p=0.001$) than that observed in an external control group with comparable baseline characteristics that was identified using pre-defined filters of steroid use, age ≥7 and amenability to exon 51 skipping. Two of twelve eteplirsen-treated subjects lost ambulation versus 9 of 12 external control subjects.

Refer to the Investigator's Brochure for additional clinical data for eteplirsen.

Casimersen

Casimersen is being evaluated in 2 clinical studies:

- 4045-101[24] is a Phase 1, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and PK study in patients with DMD amenable to exon 45 skipping. The study is being conducted as a double-blind, placebo-controlled, dosetitration portion followed by an open-label extension.
- 4045-301[25] is a Phase 3, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of casimersen and golodirsen in patients with DMD who are amenable to skipping either exon 45 or 53, respectively.

No deaths or discontinuations from the study due to an adverse event (AE) have been reported. The majority of all TEAEs were nonserious, mild, and unrelated to study drug.

Refer to the Investigator's Brochure for additional clinical data for casimersen.

Golodirsen

Golodirsen is being evaluated in 2 clinical studies:

- 4053-101[26] is a Phase 1/2, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetic (PK) study evaluating golodirsen in patients with advanced-stage DMD who are amenable to exon 53 skipping. The study is being conducted in 2 parts: Part 1 consists of a double-blind placebo-controlled, dose-titration and Part 2 is an open-label safety and efficacy evaluation.
- 4045-301[25] is a Phase 3, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of casimersen and golodirsen in patients with DMD who are amenable to skipping either exon 45 or 53, respectively.

No deaths or discontinuations from the study due to an AE have been reported. The majority of all TEAEs were nonserious, mild, and unrelated to study drug.

In a Phase I/II clinical trial (4053-101) an analysis of biopsied muscle tissue at Week 48 of 4053-101 showed a significant increase in dystrophin protein by western blot ($p<0.001$) in golodirsen-treated subjects over their own pre-treatment muscle tissue. The study is ongoing and results from outcome measures of clinical efficacy are not available at this time.

Refer to the Investigator's Brochure for additional clinical data for golodirsen.

4.4 Rationale for the Current Study

DMD is a rare, serious, debilitating, and ultimately fatal, disease for which there is an urgent need to develop safe and effective therapies. In order to efficiently meet this urgency and the needs of the subject community, the study evaluates the efficacy and safety of casimersen, eteplirsen, and of golodirsen administration over approximately 1 year in DMD subjects with duplication mutations amenable to treatment by exon 45, 51 or exon 53 skipping. Skipping of a single copy of the duplicated exon is expected to result in a wild-type (WT) *DMD* transcript allowing the expression of a WT, full length dystrophin protein. Successful skipping of a single copy of the duplicated exon in *in vitro* and *in vivo* models has been reported in the literature[27-29]. Casimersen, eteplirsen, and golodirsen have the potential to be disease-modifying treatments for boys with DMD mutations amenable to exon 45, 51 and exon 53 skipping, respectively.

As summarized in Section 4.3 and in the casimersen and golodirsen Investigator's Brochures, the totality of the non-clinical data with these PMOs as well as AVI-4225 (targeting exon 23) and eteplirsen suggests that PMOs are well tolerated in the non-clinical setting. Moreover, treatment with eteplirsen (at 30 mg/kg and 50 mg/kg) has been well-tolerated by boys with DMD deletion mutations amenable to skipping exon 51.

The relatively low expected risk for subjects exposed to casimersen, eteplirsen, or golodirsen and the urgent medical need for a treatment for this subject population support the conclusion that the potential benefits of exposing subjects to casimersen, eteplirsen, or golodirsen outweigh the potential risks.

5 STUDY OBJECTIVES

5.1 Primary Objective

Primary objective are to evaluate the effect of either casimersen, eteplirsen, or golodirsen on:

- To evaluate the efficacy of casimersen (previously SRP-4045), eteplirsen (previously AVI-4658), or golodirsen (previously SRP-4053) on dystrophin expression as assessed by quantification of protein in muscle biopsy tissue by western blot.
- Safety and tolerability in a population of subjects with relevant exon duplications using the following outcome measures:
    - Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs
    - Laboratory testing may include the following (See Section 9 for details):
        - Hematology
        - Coagulation
        - Chemistry
        - Urinalysis
    - Cardiac function including ECG and ECHO
    - Vital signs
    - Physical examination findings

5.2 Secondary Objectives

Secondary objectives of this study is to evaluate the effect of either casimersen, eteplirsen, or golodirsen after 48 weeks of treatment on:

- Expression of dystrophin as measured by immunofluorescent signal intensity and percent dystrophin positive fibers (PDPF) in muscle tissue sections in comparison to baseline values.
- The efficiency of splicing alteration will be measured by RNA Sequencing (RNA-Seq) to establish *DMD* mRNA copy number and the exon-exon junction frequency quantified, with normalization to exon junction read values from an exon junction in regions distinct from the targeted exon.

5.3 Exploratory Objectives

Additional objectives are to evaluate the effect of casimersen, eteplirsen, or golodirsen analysing the changes from baseline to week 48 in the following:

- Functional abilities of subjects in comparison to the expected natural history using the following measures:
  - Subjects between 6 to 36 months of age at enrollment: Bayley Scales of Infant Development - Gross motor functions and fine motor functions.
  - Motor function as measured on the North Star Ambulatory Assessment (NSAA, ambulant boys age 3 years and older).
  - Ambulant subjects over age 3.5 years: endurance and muscle function as measured by the 100-Meter Walk / Run Test (100M)
  - ACTIVE-seated for boys over 5 years of age.
  - Forced vital capacity, as measured in absolute values and by % predicted forced vital capacity (FVC%) in patients aged ≥10 years
  - Peak expiratory flow as reported as % predicted by age and height (%PEF)
  - Timed functional tests for ambulant subjects 3 years or older:
    - time to complete 10-meter run
    - time to rise from the floor
    - time to climb 4 steps
    - time to descend 4 steps
- Pediatric Outcomes Data Collection Instrument (PODCI) for patients ages 2-17.
- Adult Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Report for patients 18+ years.
- Immune staining may be performed on biopsy specimens for members of the dystrophin-associated protein complex, such as the sarcoglycans, dystroglycans and n-Nos.
- Muscle morphometrics may also be performed, including fiber size histograms and quantification of central nucleation.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a open label, 48-week study to evaluate the efficacy and safety of three PMOs – casimersen, eteplirsen, and golodirsen – in 6 subjects with genotypically confirmed DMD with duplication mutations amenable to correction by skipping exon 45, 51, and 53, respectively.

Subjects will be evaluated for inclusion during a Screening period of approximately 8 weeks. Eligible subjects who have out-of-frame duplications of a single exon that may be corrected by skipping exon 45, 51, or 53 will receive once weekly intravenous (IV) infusions of 30 mg/kg casimersen, 30 mg/kg eteplirsen, or 30 mg/kg golodirsen respectively for 48 weeks.

Upon qualification for the study based on Screening and Baseline assessments, all subjects will undergo a muscle biopsy for baseline assessment of dystrophin expression. All subjects will undergo a second biopsy at 48 weeks of treatment.

Efficacy will be assessed at regularly scheduled (12 week intervals) study visits and safety will be monitored on an ongoing basis for all subjects.

Safety will be assessed through the collection of adverse events (AEs), laboratory tests, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs, and physical examinations throughout the study as described in the Schedule of Events (Table 6). A Safety Follow Up phone call will be placed approximately 4 weeks (28 days) after the last study infusion to check for new adverse events, to obtain any new information regarding ongoing AEs and/or any other noteworthy subject progress.

At the conclusion of the 48 week study period, subjects will be enrolled in the Sarepta Clinical Transition Program via the SareptAssist patient support program. Subjects will be followed clinically in the NCH DMD clinic for safety, specifically for monitoring of renal function as per the prescribing information for casimersen and golodrisen. All prescribing recommended testing will be performed for clinical monitoring only.Those subjects receiving golodirsen or casimersen via this program will be monitored by urine dipstick every month, and serum cystatin C and urine protein to creatinine ratio (UPCR) every three months. There is no additional clinical safety testing recommended per the prescribing information for eteplirsen.

Additionally, through this program the subjects will be provided uninterrupted weekly drug access after conclusion of the 48 week study period. Subjects will remain on the Clinical TransitionProgram/SareptAssist until study samples can be analyzed and insurance authorization for the drug(s) can be obtained, or the efficacy of the drug is determined to not meet the standards for continuation. The threshold for study drug continuation in Sarepta's Clinical TransitionProgram/SareptAssist is a 10 percent increase in dystrophin positive fibers (defined as fibers with 30 percent of the circumference positive for dystrophin) as determined by immunofluorescence staining of the baseline and 48-week post-treatment muscle biopsies.
Subjects will receive weekly drug infusions via home health care arranged by Sarepta Therapeutics and as noted above will be monitored clinically in the NCH DMD clinic.

6.2 Dose Selection Rationale

A dose of 30 mg/kg casimersen, eteplirsen, or golodirsen was selected to use in this study. Doses were chosen based on results from animal and phase 1 clinical studies with casimersen and golodirsen and on additional clinical data from eteplirsen. There are three ongoing clinical studies with golodirsen and casimersen in DMD patients (Study 4053-101, Study 4045-101 and Study 4045-301)[24-26].

As described in Section 4.3, clinical studies 4658-us-201[17] and 4658-us-202[18] with eteplirsen assessed the efficacy, safety, and tolerability of eteplirsen (50 mg/kg and 30 mg/kg) administered as IV infusions in twelve 7- to 13-year old pediatric subjects diagnosed with DMD with out of frame mutations amenable to treatment by skipping exon 51.

At Week 48, the increases in the percent of dystrophin-positive fibers were similar for subjects who had received weekly 30 mg/kg and 50 mg/kg eteplirsen without interruption from Week 1 (52% and 42% of normal respectively, or 47% for the combined groups). These data suggest that the effect of eteplirsen on the production of novel dystrophin is not significantly different between the two doses tested in this

study. Thus, the lower dose of eteplirsen (30 mg/kg) was selected for further clinical study, as it is a more conservative choice given that subjects would receive eteplirsen as a life-long treatment.

Like eteplirsen, the PMOs casimersen and golodirsen have been evaluated in non-clinical studies to assess their pharmacological activity, pharmacokinetic, safety, and toxicology/toxicokinetic proprieties. RT-PCR studies using cultured muscle cells and demonstrated strong exon 45 (casimersen) and exon 53 (golodirsen) skipping activities. Both casimersen and golodirsen have shown low protein binding activity and low potential for drug-drug interactions, since they did not interact with cytochrome P450 isoenzymes at biologically relevant concentrations *in vitro*.

The non-clinical safety profiles of casimersen and golodirsen are similar to other PMOs tested to date; no cardiovascular, respiratory or central nervous system effects, genotoxicity, male reproductive toxicity, or immunotoxicity have been detected. The kidneys were the main target organ in mice and monkeys after 12 weeks of repeat dosing (weekly IV injections of casimersen and golodirsen) which is consistent with the renal excretion being the major elimination pathway for PMOs. No adverse effect were observed in mice using 960 mg/kg and 120 mg/kg of casimersenand golodirsen, and the maximum feasible dose for IV administration in monkeys was of 320 mg/kg for both PMOs. Because the potential target organ of toxicity (the kidney) can be monitored in the clinic, doses of 30 mg/kg casimersen or golodirsen are considered safe for once weekly IV infusions in DMD subjects with mutations amenable to exon 45 or exon 53 skipping. Additional non-clinical data for casimersen and golodirsen are described in the respective Investigator's Brochures.

Further, 30 mg/kg/wk golodirsen treatment in clinical trial 4053-101 resulted in a significant mean increase in dystrophin protein from baseline (N=25, $p<0.001$) at Week 48.

Due to the expected similarities among investigational PMOs for the treatment of subjects with DMD, a 30 mg/kg dose for eteplirsen, casimersen and golodirsen was selected for evaluation in this study.

6.3 Study Endpoints

6.3.1 Safety Endpoints

The safety and tolerability of casimersen and golodirsen will be assessed through a review and evaluation of the following:

- Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs
- Laboratory testing may include the following (See Section 9 for complete details):
  - Hematology
  - Coagulation
  - Chemistry
  - Urinalysis
- Cardiac function including ECG and ECHO
- Vital signs
- Physical examination findings

6.3.2 Efficacy Endpoints

6.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Change from Baseline to Week 48 in dystrophin expression quantified by western blot in muscle biopsy tissue.

6.3.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Change from Baseline to Week 48 in expression of dystrophin as measured by immunofluorescent signal intensity and percent dystrophin positive fibers (PDPF) in muscle tissue sections in comparison to baseline values.
- The efficiency of splicing alteration will be measured by RNA Sequencing (RNA-Seq) to establish *DMD* mRNA copy number and the exon-exon junction frequency quantified, with normalization to exon junction read values from an exon junction in regions distinct from the targeted exon.

6.3.2.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are based on the change from Baseline to Week 48 in the following measures:

- Subjects 6 to 36 months of age at enrollment: Change from baseline in scores on the Bayley Scales of Infant Development – gross motor functions and fine motor functions.
- Change from Baseline to Week 48 in NSAA (subjects 3 years or greater).
- Change from Baseline to Week 48 on the 100M in ambulant subjects over the age of 3.5 years.
- Change from Baseline to Week 48 in ACTIVE-seated for boys over 5 years of age.
- Changes in FVC and FVC% predicted in patients aged ≥ 10 years.
- Peak expiratory flow as reported as % predicted by age and height (%PEF).
- Timed functional tests for ambulant subjects 3 years or older:
    - time to complete 10-meter run
    - time to rise from the floor
    - time to climb 4 steps
    - time to descend 4 steps
- Pediatric Outcomes Data Collection Instrument (PODCI) for patients ages 2-17.
- Adult Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Report for patients 18+ years.
- Immune staining may be performed on biopsy specimens for members of the dystrophin-associated protein complex, such as the sarcoglycans, dystroglycans and n-Nos.
- Muscle morphometrics may also be performed, including fiber size histograms and quantification of central nucleation.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Number of Subjects

Six subjects will be included in this study to be enrolled by invitation. They will receive either casimersen, eteplirsen, or golodirsen according to their genotype.

7.2 Subject Inclusion Criteria

A subject must meet all of the following criteria to be eligible for this study.

1. Is a male with DMD and has an out-of-frame duplication of either exon 45, 51, or 53, with a normal copy number of all other *DMD* exons.
2. Is above age 6 months.
3. Has pulmonary function, that in the Investigator's opinion, is unlikely to decompensate significantly over the duration of the study.
4. Has sufficient muscle mass in a pair of bilateral muscles that will allow for pre- and post-treatment muscle biopsies per PI discretion.
5. If the subject is ambulant and 4 years old or greater and has been on a stable dose or dose equivalent of oral corticosteroids for at least 12 weeks prior to Week 1 the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study.

   Note: Subjects are allowed to take other medications (excluding other RNA antisense or gene therapy agents) including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β adrenergic blockers, potassium, and coenzyme Q, provided they have been on a stable dose for 12 weeks prior to Week 1. The dose is expected to remain constant throughout the study (modifications to doses to accomodate changes in weight are allowed).
6. Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.
7. Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide written informed consent for the subject to participate in the study.

7.3 Subject Exclusion Criteria

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

1. Any additional missing exon for DMD that cannot be treated with study drugs.
2. Subject has previously been treated with eteplirsen, casimersen, or golodirsen, or is currently being treated with other RNA antisense or gene therapy agents.
3. Current or history of liver disease or impairment including:
   a. an INR value above 1.5
   b. a total bilirubin greater than 2 times the Upper Limit of Normal (ULN) or a GGT greater than 2 times the ULN
4. Baseline platelet count below the Lower Limit of Normal (LLN) for age.
5. aPPT above the ULN.
6. History of significant medical disorder which may confound the interpretation of either efficacy or safety data e.g., inflammatory disease.
7. Use of any pharmacologic treatment (other than corticosteroids) within 12 weeks prior to Week 1 that may have an effect on muscle strength or function (e.g., growth hormone, anabolic steroids).
8. Current or previous treatment with any other experimental treatment within 12 weeks prior to Week 1.
9. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.
10. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
11. Use of any aminoglycoside antibiotic or statin within 12 weeks prior to Week 1 or anticipated need for an aminoglycoside antibiotic or statin during the study.
12. QTcF ≥ 450 msec based on the Screening and/or Baseline ECG.
13. Prior or ongoing medical condition that could, in the Investigator's opinion, adversely affect the safety of the subject, make it unlikely that the course of treatment would be completed, or impair the assessment of study results. Additionally, subjects who seem unable/unwilling to comply with the study procedures, in the Investigator's opinion, are to be excluded.

14. Acute illness within 4 weeks of the first anticipated administration of study medication which may interfere with study assessments.
15. Symptomatic cardiomyopathy. If the subject is asymptomatic but has a left ventricular ejection fraction <40% at Screening, the investigator should discuss inclusion of subject in the study with the medical monitor.
16. Use of anticoagulants, antithrombotics or antiplatelet agents, previous treatment with investigational drugs within 4 weeks prior to anticipated study drug administration.

NOTE: Potential subjects with abnormal laboratory values may be re-screened for specific laboratory tests within the screening period (the 45 days prior to dosing) before being designated a screen failure. Repeat values within the normal range will be acceptable for inclusion. Additionally, if a subject should have an acute illness within 4 weeks of the first anticipated dose, the PI will discuss with the DSMB about the potential to delay treatment until the illness has resolved.

7.4 Completion of a Subject's Participation in the Study

The length of a subject's participation will be from the time the informed consent form is signed until completion of the End of Study (Week 48) visit (up to 60 weeks).

7.5 Subject Withdrawal Criteria

Any subject can withdraw from study participation at any time for any reason. In addition, the Study Sponsor/Investigator may 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 (i.e. was found to have not met the eligibility criteria).
- 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 Study Sponsor.
- The subject experiences an intolerable or unacceptable AE.

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

Subjects who have received at least (1) one dose of study treatment and who are withdrawn from treatment within 28 days after a functional assessment visit will not be asked to return for an End of Study visit (to complete the Week 48 assessments. Subjects who receive at least one (1) dose of study treatment who are withdrawn from treatment more than 28 days after a functional assessment visit will be asked to complete all early termination (Week 48) assessments within approximately 28 days of withdrawal.

Subjects withdrawn from treatment will not be replaced.

7.6 Study Discontinuation

If the Study Sponsor/Investigator, the DSMB, the study monitor, institutional review board/independent ethics committee(s) (IRB), and/or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Study Sponsor/Investigator, IRB and the DSMB.

Conditions that may warrant termination of the study or an individual site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision by the Drug Manufacturer to suspend or discontinue testing, evaluation, or development of the IP
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB or appropriate regulatory authorities

- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the DSMB, the study monitor, IRB or regulatory authorities
- Insufficient adherence to protocol requirements consistent with 21 CFR 312 or the European Clinical Trial Directive 2001/20/EC

Study termination and follow-up will be performed in compliance with the conditions set forth in International Conference on Harmonisation (ICH) E6 on Good Clinical Practice (GCP) as well as 21 CFR 312.56b and the European Clinical Trial Directive 2001/20/EC which require an Investigator's compliance with these requirements and to promptly secure a plan for compliance or discontinue shipment of the IP to the Investigator and end the Investigator's participation in the study.

8 TREATMENT OF SUBJECTS

8.1 Investigational Products

The Investigational Products (IPs) (casimersen, eteplirsen, and golodirsen injection) are supplied as concentrated sterile solutions, which are diluted with 0.9% sodium chloride injection prior to administration via an IV infusion.

Casimersen, eteplirsen, and golodirsen injections are sterile, clear, colorless, isotonic, phosphate-buffered saline (PBS) solutions supplied in single-use 2-mL glass vials containing 2 mL of casimersen, eteplirsen, or golodirsen at a concentration of 50 mg/mL.

8.1.1 Packaging and Labeling

Please refer to the Clinical Study Manual of Operations for information on packaging and labeling. The label text for the study treatments will comply with applicable regional, national, and local laws and regulations and will include at a minimum the contents of the vial, the appropriate regional cautionary statements, lot number, storage conditions, and the name of the Drug Provider (Sarepta Therapeutics, Inc.).

8.1.2 Storage

Store the study treatment at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store in the original carton until ready for use.

Vials of study treatment must be stored in a secured, limited-access area with appropriate temperature recording, controls, and monitoring. Details for study treatment handling, storage and for preparation of the diluted study treatment for administration can be found in the study-specific Clinical Study Manual of Operations.

8.2 Treatments Administered

Eligible subjects will receive a weekly IV infusion of study treatment (30 mg/kg of casimersen, eteplirsen, or golodirsen, according to genotype) for up to 48 weeks. Subjects will be transitioned to the Sarepta Clinical TransitionProgram/SareptAssist after the study period for continuous weekly drug access while study sample analysis is pending.

The dose of casimersen, eteplirsen, or golodirsen will be calculated based on the most recent subject weight obtained at the site prior to the current visit. Infusion solutions of casimersen, eteplirsen, or

golodirsen are to be prepared by following the steps detailed in the study-specific Clinical Study Manual of Operations.

- Study treatment will be administered as an IV infusion over a period of approximately 35 to 60 minutes. Patients are to be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (e.g. lidocaine 2.5%, prilocaine 2.5%, LMX4 cream, or other per the Investigator's discretion) be applied to the infusion site prior to each administration of study treatment. Additional administration and IP details are available in the study-specific Clinical Study Manual of Operations.

An implanted venous access port may be inserted for study treatment administration at the discretion of the Investigator. After study treatment administration and the saline flush, the port may be flushed with heparin to heplock the port prior to removal of the infusion line. If study treatment is administered into an existing IV line, the line must be flushed with normal saline before and after administration of study treatment.

Subjects will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. At each infusion, conconmittant medications and adverse events will be reviewed.

No other medications may be administered concomitantly during the study treatment infusion. All subjects will be observed for at least 1 hour following the end of each infusion.

The following guidelines for the timing of dosing are to be followed throughout the study:

1. Subjects should receive study treatment once every 7 days starting at the Week 1 Visit.
2. After the first infusion, a window of ±2 days around the scheduled weekly dosing date (referenced back to the first dose at Week 1) is acceptable.
3. Subjects may not receive 2 separate doses of study treatment within the same 60-hour period.
4. The Principal Investigator is to be contacted in the event of a missed dose.

8.2.1 Dose Modification, Reduction, or Delay

There is no provision for dose alteration in this study. If a subject experiences an AE that requires interruption of administration for ≥2 consecutive doses, the Investigator will consult with the DSMB to determine whether the subject may resume treatment.

8.3 Prior and Concomitant Medications

Oral corticosteroids, including but not limited to prednisolone and prednisone, for treatment of DMD are required for boys older than 5 years during the course of this study. Subjects entering the study on corticosteroids must have been on a stable dose (or dose equivalent) of oral corticosteroids for at least 12 weeks prior to the first administration of study treatment at Week 1. If clinically necessary, subjects may be allowed to change the corticosteroid compound as long as equivalent dosing is maintained. Doses of corticosteroids are expected to remain constant (except for modifications to accommodate changes in weight) through the completion of study to the degree that is clinically feasible.

Provided they have been on a stable dose for at least 12 weeks prior to Week 1 and the dose is expected to remain constant throughout the study, subjects are allowed to take other medications including:

- Oral ACE inhibitors, including but not limited to perindopril and lisinopril
- Oral β adrenergic blockers, including but not limited to carvedilol and atenolol
- Angiotensin-receptor blockers, including but not limited to losartan, irbesartan, valsartan, and candesartan
- Oral laxatives, including but not limited to lactulose, Senokot, and Movicol
- Vitamin D and calcium supplements
- Alendronate (Fosamax) or other bisphosphonates used to treat osteoporosis/osteopenia by inhibiting osteoclasts
- Over-the-counter preparations such as herbal supplements, vitamins, minerals, and homeopathic preparations

Other concomitant medications (excluding other RNA antisense or gene therapy agents) may also be taken if, in the opinion of the Investigator, they do not interfere with study assessments and outcomes. The Investigator is to contact the DSMB if he/she is unsure of the impact of a concomitant medication on study assessments and outcomes. Every attempt should be made to keep the dosage constant throughout the treatment period (i.e. through Week 48), although modifications to accommodate changes in weight are permitted.

It is recommended that introduction of new physiotherapy interventions during the course of the study be avoided unless the best interests of the subject are at stake. Should a contracture develop during the course of the study, and it is considered in the best interest of the subject to treat the contracture, then any of the following interventions may be used to reduce the contracture, but they must be clearly documented:

- Stretching exercises (passive, active, self)
- Night splints
- Contracture control device
- Serial casting

The following therapies are **not permitted** during the conduct of this study:

- Systemic or oral steroids for non-DMD conditions that, in the Investigator's opinion, could interfere with study assessments and outcomes
- Other investigational agents for the treatment of DMD
- Any medication with the potential to affect muscle mass, strength, and/or function, such as, but not limited to, growth hormone and PDE-5 inhibitors
- Immunosuppressants (other than oral or systemic corticosteroids, as outlined)
- Systemic aminoglycoside antibiotics (unless discussed and agreed upon with the Investigator and the DSMB)
- Statins (unless discussed and agreed upon with the Investigator and DSMB)

8.4 Treatment Compliance

Treatment compliance will be assessed via compliance with scheduled weekly infusions.

9 STUDY VISITS

The schedule outlining the study assessments and times of assessments is shown in Section 9.9 and all procedures are described in detail in Section 10. **All assessments scheduled on the same day as study treatment administration are to be completed prior to initiation of study treatment infusion.**

9.1 Screening and Baseline (Approximately 8 weeks prior to Week 1)

9.1.1 Informed Consent

Subjects and/or parent(s)/legal guardian(s) will be invited to review and sign the Informed Consent Form (ICF) and assent (if applicable) to participate in this trial prior to the collection of any data and any study related procedures. Overall study requirements and details surrounding Screening and Baseline assessments are reviewed by the subject and their parent(s)/guardian(s) during this process. Baseline measures from subjects will be obtained prior to infusion.

If there are changes to the study that affect the consent or assent, parents and or the subject will be reconsent/assented at their next visit.

9.1.2 Screening

The screening evaluations will take place over two visits to allow time for assessement of all available criteria before the subject undergoes sedation.

9.1.2.1 Screening Day 1

The following assessments will occur at this visit:

- Informed Consent
- Assent, if applicable
- Medical history
- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Weight

The following blood lab work will occur at this visit:

- Hepatitis B, C and HIV
- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehydrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C
- Genotyping of *DMD,* if not previously done

The following urine lab work will occur at this visit:

- Urinalysis

9.1.2.2 Screening Day 2

The following will be assessed at this visit:

- Adverse Events
- Concommitant Medications
- ECHO
- ECG
- Bayley scale of Infant Development (6 to 36 months of age)
- 100M – ambulant subjects (3.5 years until non-ambulant)
- NSAA (3 years to non-ambulant)
- Active-seated – non ambulant subjects (5 years and older)
- Pulmonary functional test (PFT) (10 years and older)
- Timed functional tests for (ambulant subjects 3 years and older)
- Pediatric Outcomes Data Collection Instruments (PODCI, ages 2-17)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extermity Report (ages 18+)
- Assessment of inclusion and exclusion criteria
- Height

9.1.3 Baseline

The baseline visit should occur 3-5 weeks after screening is completed and will occur over two days.

9.1.3.1 Day 1

The following assessments will occur at this visit:

- **Confirmation of eligibility**
- Medical history
- Adverse Events
- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Height
- Weight
- ECG
- Bayley scale of Infant Development (6 to 36 months of age)
- 100M – ambulant subjects (3.5 years until non-ambulant)
- NSAA (3 years to non-ambulant)
- Active-seated – non ambulant subjects (5 years and older)
- Pulmonary functional test (PFT) (10 years and older)
- Timed functional tests for (ambulant subjects 3 years and older)
- Pediatric Outcomes Data Collection Instruments (PODCI, ages 2-17)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extermity

Report (ages 18+)

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.1.3.2 Day 2

A baseline open muscle biopsy will be performed in one gastrocnemius muscle or alternate muscle. (Note that the rationale and methods of muscle biopsy site selection and performance for this and subsequent biopsies are discussed in Section 10.2.1). If in the discretion of the principal investigator, an implanted venous access port needs to be placed prior to infusion, this placement may occur at the same time as the muscle biopsy. RNAseq analysis will be completed on tissue from this muscle biopsy.

If in the opinion of the Principal Investigator, a PORT placement is indicated, all attempts will be made to have this occur during this same sedation event (see Section 8.2 for full details), but if it is not feasible, a separate visit will be scheduled to place the port.

9.2 Week 1

Week 1 should occur within 4 weeks of the Baseline Functional Assessment Visit. If the Week 1 visit is > 4 weeks after Baseline, the subject is required to repeat the Baseline functional assessments to reconfirm eligibility.

Infusion with the study drug will begin at Week 1 and will occur weekly through the week 48 visit. For details regarding the infusion, please see Section 8.2.

The following assessments will occur at this visit:

- **Confirmation of eligibility**
- Medical history
- Adverse Events
- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Weight

- Infusion

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.3 Week 4 (+/- 1 week)

The following assessments will occur at this visit:

- Medical history
- Adverse Events
- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Weight
- Infusion

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.4 Week 8 (+/- 1 week)

The following assessments will occur at this visit:

- Medical history
- Adverse Events
- Concommitant Medications
- Brief Physical Exam
- Vital Signs
- Weight
- Infusion

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.5 Weeks 12 and 36 (Functional Assessment Visits) (+/- 1 week)

The following assessments will occur at this visit:

- Medical history
- Adverse Events
- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Height
- Weight
- ECG
- Bayley scale of Infant Development (6 to 36 months of age)
- 100M – ambulant subjects (3.5 years until non-ambulant)
- NSAA (3 years to non-ambulant)
- Active-seated – non ambulant subjects (5 years and older)
- Pulmonary functional test (PFT) (10 years and older)

- Timed functional tests for (ambulant subjects 3 years and older)
- Pediatric Outcomes Data Collection Instruments (PODCI, ages 2-17)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extermity Report (ages 18+)
- Infusion

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.6 Weeks 16, 20, 28, 32, 40 and 44 (+/- 1 week)

The following assessments will occur at this visit:

- Medical history
- Adverse Events
- Concommitant Medications
- Brief Physical Exam
- Vital Signs
- Weight
- Infusion

9.7 Week 24 (Functional Assessment Visit) (+/- 1 week)

The following assessments will occur at this visit:

- Study drug infusion
- Medical history
- Adverse Events
- Concommitant Medications
- Full Physical Exam
- Vital Signs

- Height
- Weight
- ECHO
- ECG
- Bayley scale of Infant Development (6 to 36 months of age)
- 100M – ambulant subjects (3.5 years until non-ambulant)
- NSAA (3 years to non-ambulant)
- Active-seated – non ambulant subjects (5 years and older)
- Pulmonary functional test (PFT) (10 years and older)
- Timed functional tests for (ambulant subjects 3 years and older)
- Pediatric Outcomes Data Collection Instruments (PODCI, ages 2-17)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extermity Report (ages 18+)

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.8 Week 48 (or Early Termination Visit, if more than 28 days after a Functional Assessment Visit) (+/- 1 week)

Early termination assessments are the same as Week 48 assessments. An Early Termination visit is required if the patient discontines more that 28 days after a Functional Assessment visit (Week 12, 24 or 36) The evaluations will take place over two visits.

9.8.1 Day 1

The following assessments will occur at this visit:

- Medical history
- Adverse Events

- Concommitant Medications
- Full Physical Exam
- Vital Signs
- Height
- Weight
- Infusion
- ECHO
- ECG
- Bayley scale of Infant Development (6 to 36 months of age)
- 100M – ambulant subjects (3.5 years until non-ambulant)
- NSAA (3 years to non-ambulant)
- Active-seated – non ambulant subjects (5 years and older)
- Pulmonary functional test (PFT) (10 years and older)
- Timed functional tests for (ambulant subjects 3 years and older)
- Pediatric Outcomes Data Collection Instruments (PODCI, ages 2-17)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Upper Extermity Report (ages 18+)

The following blood lab work will occur at this visit:

- Complete Metabolic Panel (CMP)
- Amylase
- Gamma-glutamyl transpeptidase (GGT)
- Complete Blood Count (CBC)/Differential
- Coagulation Measures
- Uric Acid
- Lactate dehudrogenase (LDH)
- C-reactive Protein (CRP)
- Creatine Kinase (CK)
- Cystatin C

The following urine lab work will occur at this visit:

- Urinalysis

9.8.2 Day 2

A post-treatment open muscle biopsy will be performed in one gastrocnemius muscle. (Note that the rationale and methods of muscle biopsy site selection and performance for this and subsequent biopsies are discussed in Section 10.2.1). RNAseq analysis will be completed on tissue from this muscle biopsy.

Subjects should have the muscle biopsy performed following the Week 48 infusion and functional assessments. The biopsy at Week 48 must occur within 2 weeks after the Week 48 visit and at least 48 hours after the most recent infusion.

9.9 Schedule of Events

Table 6

TREATMENT WITH CASIMERSEN, ETEPLIRSEN, OR GOLODIRSEN STUDY TIMELINE																
Study Period	**Screening[g]**		**Baseline[g]** (3-5 weeks after Screening)	**Treatment Period**												
Week #	**Approximately 8 Weeks prior to Week 1**			**1[a]**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ ET[b,e]**
Visit #	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent/Assent[f]	X															
Assess Inclusion/Exclusion Criteria		X														
Confirm Eligibility			X	X												
Medical History	Continuous (Weekly)															
Adverse Events		Continuous (Weekly)														
Concomitant Medications	Continuous (Weekly)															
Study Treatment				Once Weekly[g]												
Port Placement			X[f]													
Muscle Biopsy			X													X[h]
RNAseq			X													X
Full Physical Exam	X		X	X	X		X			X			X			X
Brief Physical Exam						X		X	X		X	X		X	X	
Vital Signs[c]	X		X	Once Weekly												
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X	X				X			X			X			X
ECHO		X								X						X
ECG		X	X				X			X			X			X
Antibody testing Hep. B, C and HIV	X															
CMP	X		X	X	X	X	X			X			X			X
Amylase	X		X	X	X	X	X			X			X			X
GGT	X		X	X	X	X	X			X			X			X
CBC/Diff	X		X	X	X	X	X			X			X			X
Coagulations	X		X	X	X	X	X			X			X			X
Uric Acid	X		X	X	X	X	X			X			X			X
Lactate dehydrogenase (LDH)	X		X	X	X	X	X			X			X			X
C-reactive Protein (CRP)	X		X	X	X	X	X			X			X			X
Creatine Kinase (CK)	X		X	X	X	X	X			X			X			X
Cystatin C	X		X	X	X	X	X			X			X			X
Genotyping for *DMD* mutation, if not previously done	X															
Urinalysis	X		X	X	X	X	X			X			X			X
Bayley Scale of Infant Development		X	X				X			X			X			X
100 M		X	X				X			X			X			X
NSAA		X	X				X			X			X			X
Active Seated		X	X				X			X			X			X
Timed Function Tests		X	X				X			X			X			X
PFT		X	X				X			X			X			X
PODCI		X	X				X			X			X			X
PROMIS		X	X				X			X			X			X

a. Week 1 should occur within 4 weeks of the Baseline Functional Assessment Visit. If the Week 1 visit is > 4 weeks after Baseline, the subject is required to repeat the Baseline functional assessments to reconfirm eligibility.

b. Early termination assessments are the same as Week 48 assessments. An Early Termination visit is required if the patient discontinues more that 28 days after a Functional Assessment visit (Week 12, 24 or 36)

c. During infusion visits, vitals will be measured approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. At all other visits, vitals will be measured only once.

d. If there are changes to the study that affect the consent or assent, parents and or the subject will be reconsented/assented at their next visit.

e. Visit will occur over multiple days

f. A PORT will be placed per Principal Investigator discretion.

g. All assessments that are to occur on the same day as an infusion will be completed prior to the infusion.

h. The week 48 muscle biopsy must occur withing 2 weeks of the week 48 visit and at least 48 hours post the most recent infusion.

9.10 Muscle and Strength Test Schedule

Table 7

	6 mos - 3 yrs	3 - 3.5 yrs	3.5 - 4.9 yrs	5 - 9.9 yrs	10 yr Until Non-Ambulant	Non-Ambulant
Bayley						
Timed Functional Tests						
NSAA						
100 meter						
ACTIVE						
PFTs						
Number of Assessments	1	3	3	4	5	3

10 STUDY PROCEDURES

10.1 Safety Assessments

10.1.1 Adverse Events

The collection of adverse events is described in Section 11.

10.1.2 Clinical Laboratory Evaluations

The following routine clinical laboratory tests will be performed at the time points specified in Section 9. Safety samples will be collected analyzed by an accredited central laboratory:

Hematology:	White blood cells (WBC), hemoglobin, hematocrit, platelets, red blood cells (RBCs), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and any abnormal cells
Coagulation:	Prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
Chemistry:	Complete Metabolic Panel [CMP, including: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase)], amylase, gamma-glutamyl transferase (GGT), uric acid, lactate dehydrogenase (LDH), C-reactive protein (CRP), creatine kinase (CK), and serum cystatin C
Immunology:	Hepatitis B, C and HIV
Urine:	Urinalysis (including: specific gravity, pH, cytology, hemoglobin, protein, glucose, and ketones)

** For subjects taking drugs that potentially induce GGT synthesis through the cytochrome P450 system, the clinically significant range will be estimated at two times the levels obtained from the baseline screening test.*

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will determine whether abnormal assessment results are clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from Baseline levels is noted, the Investigator will continue to monitor the subject with additional assessments until:

- Values have reached normal range and/or Baseline levels

10.1.3 Electrocardiogram

Twelve-lead ECGs will be obtained at the time points specified in Section 9. ECGs will be performed at a consistent time of day throughout the study. ECGs will be performed only after the subject is in the supine position, resting, and quiet for a minimum of 15 minutes. The ECG will be manually reviewed and interpreted by medically qualified personnel according to pre-specified criteria. The Investigator will review the results and determine if the findings are clinically significant.

10.1.4 Echocardiogram

A standard 2-dimensional (2D) ECHO will be obtained at the time points specified in Section 9. ECHOs will be performed at a consistent time of day throughout the study. The ECHO will be reviewed and interpreted by medically qualified personnel according to pre-specified criteria. Ejection fraction (EF) will be noted. The Investigator will review the results of the ECHO report and determine if the findings are clinically significant.

10.1.5 Vital Signs, Weight, and Height

Vital signs (blood pressure, heart rate, respiration, and temperature) and weight will be measured at the time points specified in Section 9.

For infusion visits, vital signs are to be collected within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion. All assessments will be performed after subjects have remained seated for 5 minutes. Heart rate and respiratory rate are to be measured over 1 minute.

Temperature is to be recorded in degrees Celsius (°C).

Weight is to be recorded in kilograms. If a subject's weight varies by more than 10% from the prior visit, the subject is to be re-weighed to confirm the result, and an explanation of the change must be documented.

Height will be measured at the time points specified in Section 9. Height is to be measured with shoes off. If standing height cannot be obtained, height is to be calculated using the following equation[30]:

$$\text{Height (cm)} = 4.605U + 1.308A + 28.003$$

where U is the length of the ulna in centimeters measured using an anthropometer or calipers, and A is the subject's age in years.

10.1.6 Adverse Events

Adverse Events will collected by the Investigator or qualified staff at the time points specified in Section 9.

10.1.7 Medical History

A full medical history will be conducted by the Investigator or qualified study staff at the time points specified in Section 9. Special attention will be paid to any fracture history.

10.1.8 Physical Examination

Physical examinations, full and brief, will be conducted at the time points specified in Section 9. Physical examinations will be performed by the Investigator or qualified study staff.

10.1.8.1 Full Physical Exam

Full physical examinations will include examination of general appearance, head, eyes, ears, nose, and throat (HEENT), heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems.

10.1.8.2 Brief Physical Exam

Brief physical examinations will include examination of general appearance, HEENT, heart, chest, abdomen, and skin.

10.1.9 Concomitant Medications and Therapies

The PI will encourage participants to maintain the medication and supplements they are on at enrollment through the course of the study. Subjects on aspirin or drugs that could affect coagulation will continue their medication as indicated. Several investigations show that preoperative aspirin ingestion and intravenous heparin therapy can be administered safely without concerns about the risk of postoperative bleeding and should not lead to modification or cessation of such therapy.

10.2 Efficacy Assessments

10.2.1 Functional Assessments

Details about how each assessment is performed is provided in the Clinical Evaluator Manual.

10.2.1.1 Bayley Scales of Infant Development

The Bayley Scales of Infant & Toddler Development – 3rd edition is a standardized, norm-reference assessment of infant and toddler development. It is intended for use between the ages of 1 to 2 months, inclusive (to be used only if age of enrollment is 1 to 36 months). It can also be used as a developmental checklist in older children with developmental delay, such as boys with Duchenne Muscular Dystrophy. It has five domains of development (cognitive, receptive and expressive communication and gross and fine motor).

10.2.1.2 North Star Ambulatory Assessment (NSAA)

The NSAA will be performed at the time points specified in Section 9. The NSAA is a clinician-administered scale that rates subject performance on various functional activities[31]. For subjects older than 3 years old, the NSAA will be administered as long as the subject remains ambulant.

During this assessment, subjects will be asked to perform 17 different functional activities, including a 10 m walk/run, rising from a sit to stand, standing on 1 leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. Subjects will be graded as follows: 2 = achieves goal without any assistance; 1 = modified method but achieves goal independent of physical assistance from another person; and 0 = unable to achieve goal independently. A revised scored is provided for children from 36 to 60 months.

10.2.1.3 100-Meter Walk / Run Test (100M)

The 100M will be performed at the time points specified in Section 9 starting at ages 3.5 years until nonambulant. In the 100-metre Walk/Run Time test the subject is asked to complete 4 laps on a 25 m track, for a total of 100 meters as quickly as safely possible. If the subject is able to run, he is encouraged to do so. The total time spent to complete the task is recorded.

10.2.1.4 ACTIVE-Seated Test

The ACTIVE-Seated Test will be performed at the time points specified in Section 9 for subjects 5 years and older.

10.2.1.5 Pulmonary Functional Testing (PFT):

The PFT will be performed at the time points specified in Section 9 in subjects 10 years and older. The PFT involves assessing maximal lung function with both a spirometer and respiratory pressure meter. The Forced Vital Capacity (FVC) is reported on the subject's CRF.

10.2.1.6 Timed Functional Test

Timed functional tests will be conducted in subjects 3 years and older.

10.2.1.6.1 Time 4-Step Test

The Timed 4-Step Test will be performed at the time points specified in Section 9. Timed 4-stair climb quantifies the time required for the patient to ascend and descend four standard stairs (6" height for each step).

10.2.1.6.2 10-meter Walk Run (10MWR)

The 10MWR will be performed at the time points specified in Section 9. The time it takes the subject to move will be recorded.

10.2.1.6.3 Rise Time

Rise Time will be recorded at the time points specified in Section 9. The time it takes the subject to rise from supine will be recorded.

10.2.2 Quality of Life Assessment: PODCI

Quality of life will be evaluated for subjects at the time points specified in Section 9using the PODCI, a parent-reported measure of quality of life for children with acute or chronic illnesses. The PODCI has been used to evaluate health-related quality of life in subjects with DMD[32, 33]. The 86-item instrument generates 8 scales including upper extremity and physical function scale, transfer and basic mobility scale, sports/physical functioning scale, pain/comfort scale, treatment expectations scale, happiness scale, satisfaction with symptoms scale, and global functioning scale[32, 34].

10.2.3 Quality of Life Assessment: PROMIS

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a collection of patient-reported measures assessing various domains of physical, mental, and social health. PROMIS tools were developed in collaboration with NIH and are considered psychometrically-sound instruments created to be relevant across conditions and symptoms. The PROMIS Upper Extremity questionnaire assesses self-reported performance of 16 upper extremity tasks with higher scores indicating higher function with a maximum score of 80 points.

10.2.4 Muscle Biopsy

Upon qualification for the study based on Screening and Baseline assessments, all subjects will undergo two muscle biopsies at Baseline and Week 48.

The Baseline muscle biopsy may be obtained as soon as eligibility is confirmed (i.e. Baseline assessment is complete and genotype is confirmed), prior to the first dose of study treatment. The first dose of study treatment must be within 4 weeks of the Baseline Functional Assessment visit. Muscle biopsy surgery must be performed within the 4-week window between the Baseline Functional Assessment visit and Week 1. Subjects will not begin to receive study treatment until after the Baseline muscle biopsy has been performed.

The Baseline muscle biopsy will be obtained from one gastrocnemius muscle and the subsequent muscle biopsy will be obtained from the contralateral muscle. A previously unbiopsied alternative upper leg muscle may be used if the gastrocnemius has been biopsied previously. If an alternative muscle is used, the same contralateral muscle will be biopsied at the subsequent muscle biopsy.

The Biopsy at Week 48 must occur within 2 weeks after the week 48 visit and at least 48 hours after the most recent infusion.

All analyses related to quantification of dystrophin protein will be performed at the conclusion of the study.

Tissue samples may be stored for a maximum of 15 years and may be used for research at a later time (Long term follow-up).

10.2.4.1 RNAseq Analysis

The efficiency of splicing alteration will be assessed by RNA Sequencing (RNA-Seq). Data will be analyzed to establish DMD mRNA copy number, and the exon-exon junction frequency quantified, with normalization to exon junction read values from exon junctions in regions distinct from the targeted exon.

10.3 Additional Assessments

10.3.1 Genotype Confirmation

If a subject does not have a previously acceptable genetic report stating their mutation, blood will be collected to send out for genetic mutation analysis of *DMD*.

11 ADVERSE EVENTS AND SAFETY REPORTING

11.1 Collection of Adverse Events

Over the entire duration of the study, site personnel will ensure that all AEs are recorded appropriately. If an AE occurs, the primary concern is for subject safety, and the Investigator will use his/her judgment and expertise to determine the appropriate course of action.

All AEs from the time of informed consent through the End of Study visit (or early termination from the study) will be recorded in each individual subject's CRF. For subjects who prematurely discontinue the study (see Section 7.5), AEs will continue to be recorded until 28 days after the last study treatment infusion.

11.2 Definition of Adverse Events

11.2.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with the investigational drug. An AE can, therefore, be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality that occurs during or after administration of an IP whether or not considered related to the IP. Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at Screening are considered AEs only if they reoccur after resolution or worsen during the AE collection period.

11.2.2 Serious Adverse Event (SAE)

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 Sponsor-Investigator, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.
    - **Required or prolonged insubject hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.
    - **Persistent or significant disability/incapacity**: An AE that results in a substantial 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 IP.

- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.3 Classification of Adverse Events

Each AE whether serious or non-serious will be classified by the Investigator according to the following rules and definitions.

11.3.1 Relationship to Investigational Product

For each AE, the Investigator will determine whether there is a reasonable likelihood that the AE may have been caused by the study treatment according to the categories below:

Unrelated:	The event is clearly not related to the study treatment
Possibly/probably related:	The event could be related/is likely to be related to the study treatment
Definitely related:	The event is clearly related to the study treatment

11.3.2 Relationship to Study Procedures

For each AE the Investigator will determine whether there is a reasonable possibility that the AE may have been caused by the study procedures according to the categories below:

Unrelated:	The event is clearly not related to the study procedures
Possibly/probably related:	The event could be related/is likely to be related to study procedures
Definitely related:	The event is clearly related to the study procedures

11.3.3 Relationship to Underlying Disease

For each AE the Investigator will determine whether there is a reasonable possibility that the AE may be related to the underlying disease according to the categories below:

Unrelated:	The event is clearly not related to the underlying disease
Possibly/probably related:	The event could be related/is likely to be related to the underlying disease

Definitely related:	The event is clearly related to the underlying disease

Events of disease progression may be considered AEs, based on the Investigator's discretion.

11.3.4 Severity of Adverse Events

Note that severity is not the same as "seriousness," which is defined in Section 11.2.2 and which serves as a guide for defining regulatory reporting obligations.

The Investigator will assess the severity of all AEs as Mild, Moderate, or Severe, based on the following definitions:

Mild:	The event does not interfere with the subject's usual activities.
Moderate:	The event interferes with the subject's usual activities.
Severe:	The event prevents the subject from undertaking their usual activities and requires therapeutic intervention or cessation of the study treatment.

11.3.5 Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the subject outcome of each AE.

11.3.6 Action Taken Regarding the Investigational Drug Product

The Investigator will provide information regarding the action taken with respect to the study treatment in response to the AE.

11.3.7 Expectedness of an Adverse Event

The expectedness of all AEs will be determined according to the most recent versions of the Investigator's Brochures for casimersen and the prescribing information for eteplirsen and golodirsen.

11.3.8 Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

11.3.9 Adverse Event Reporting

Only Treatment Emergent Adverse Events (TEAEs) will be summarized in reports. Non-emergent events will be recorded in data listings. For all AE tables, the number and percent of subjects reporting AEs (grouped by the Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class [SOC] and Preferred Term [PT]) will be summarized by treatment group. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs. Treatment-related TEAEs will be defined as those that the Investigator considers possibly/probably or definitely related to the study treatment.

Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in frequency tables. If a subject experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship and maximum severity to study treatment will be used to summarize AEs by relationship and severity.

The following summary tables will be produced:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Treatment-related TEAEs by severity
- SAEs
- Deaths

In addition, all SAEs regardless of their treatment-emergent status will be summarized by SOC and PT.

The following listings will be produced:

- Non-treatment emergent AEs
- All TEAEs
- AEs leading to discontinuation
- SAE

11.4 Recording Adverse Events

All AEs/SAEs experienced from the time of informed consent/assent to the last follow-up visit will be recorded within each subject's CRF. For patients who prematurely discontinue from the study (Section 7.6), AEs will continue to be recorded until 28 days after the last study treatment infusion.

Information should include: a concise description of the event; date of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to IP or study procedure or underlying disease; and any action taken will be recorded. Resolution occurs when the subject has returned to his Baseline state of health or 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 related to 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 is 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 AEs will be followed until the resolution of AE, completion of the subject's study participation, or study termination, whichever occurs first. SAEs will be followed until resolution or until the condition stabilizes or returns to Baseline status.

11.5 Safety Reporting

The investigator or his designee will report all serious adverse events according to the following:

DSMB: The Investigator or his/her designee will report SAEs to the DSMB within the below timeframe:

- Any serious adverse event that is **fatal or life-threatening** and possibly, probably, or definitely related to one of the investigational products, regardless of expectedness, will be reported to the DSMB within **5 business days** of initial receipt of the information.
- Any serious adverse event that is unexpected and possibly, probably, or definitely related with the use of one of the investigational products (SUSAR), but is **not fatal or life-threatening**, will be reported within **5 business days** of initial receipt of the information.

FDA: The Investigator or his/her designee will report SAEs to their FDA Investigator-Initiated IND within the below timeframe:

- Any serious adverse event that **is fatal or life-threatening** and unexpected and possibly, probably, or definitely associated with the use of one of the investigational products (SUSAR) will be reported as soon as possible, but in no case later than **7 calendar days** after initial receipt of the information.
- Any serious adverse event that is unexpected and possibly, probably, or definitely associated with the use of one of the investigational products (SUSAR), but is **not fatal or life-threatening**, will be reported as soon as possible, but in no case later than **15 calendar days** after initial receipt of the information.
- If, after further evaluation, an unexpected serious adverse event that is initially considered not to be associated with the use of one of the investigational products is subsequently determined to be associated, then the event will be reported as soon as possible, but in no case later than **15 calendar days** after the determination is made.

IRB: The Investigator or his/her designee will report SAEs to the IRB within the below timeframe:

- Any serious adverse event that is unexpected and possibly, probably, or definitely related will be reported to the IRB within **5 business days** of initial receipt of the information.

Sarepta: The Investigator or his/her designee will report SAEs to Sarepta within the below timeframe:

- Any serious adverse event that is unexpected and possibly, probably, or definitely related (SUSAR) will be reported to Sarepta within **24 hours** of initial receipt of the information. All follow-up information on SUSARs will be reported to Sarepta within **24 hours** of initial receipt of the information.
- All other serious adverse events and Special Situation listings will be reported to Sarepta **monthly**, regardless of expectedness, relatedness, or if they meet the definition for unanticipated problems to the clinical trial.

Sarepta will be responsible for submitting expedited reports to their respective FDA INDs and NDAs, as applicable, all ex-US regulatory authorities, and to Investigators in ongoing studies of casimersen, eteplirsen or golodirsen.

Changes in the FDA reporting schedule will be permitted only where, under the **FDA IND** regulations [21 CFR 312(c) (3)], changes in this reporting schedule have been approved by the FDA and are reflected in the protocol. Nationwide Children's Hospital will be responsible for reporting to their Investigator-Initiated FDA IND for the product.

Relevant follow-up information will be submitted concurrently to the **FDA, IRB, DSMB, and Sarepta**, as applicable, as soon as the information is available and will be identified as such, i.e., "Follow-up IND Safety Report."

If a serious adverse event occurs after the end of a clinical trial, the event will be reported to the **FDA, IRB, DSMB** and Sarepta according to the criteria and timelines defined above for reporting SAEs during the trial.

Should a serious adverse event deemed possibly, probably or definitely related to one of the investigational products occur during administration, the product will be discontinued, appropriate treatment will be given under medical supervision and the subject will be examined as frequently as necessary thereafter until symptoms cease or stabilize.

11.5.1 Serious Adverse Event Reporting: Content and Format

The serious adverse event report will include, but need not be limited to: (1) the date of the event; (2) designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports; (3) clinical site; (4) the Principal Investigator; (5) FDA's Investigational New Drug (IND) application number; (6) Drug name; (7) route of administration, e.g., intramuscular; (8) dosing schedule; (9) a complete description of the event; (10) relevant clinical observations; (11) relevant clinical history; (12) relevant tests that were or are planned to be conducted; (13) date of any treatment of the event; and (14) the suspected cause of the event.

This report will be sent to the IRB, FDA, DSMB and Sarepta according to regulatory requirements described in section Safety Reporting.

11.5.2 Special Situations

All occurences of pregnancy, overdose, medication error, and accidental or occupational exposure with study treatment (regardless of whether an AE or SAE has occurred) must be reported to the DSMB within 24 hours of notification and to Sarepta on monthly line listings.

11.5.2.1 Pregnancy

If the female partner of a treated male subject becomes pregnant, the male subject must notify the Investigator within 24 hours of learning of the pregnancy. The Investigator must make every effort to ensure that the pregnant female is aware of the need to notify her healthcare provider regarding her male partner's participation in this clinical trial and his potential exposure to casimersen, eteplirsen or golodirsen.

The study site must complete a pregnancy form within 24 hours of learning of the pregnancy and send to the DSMB. The study site will make every effort to follow the pregnancy until outcome is known.

11.5.2.2 Overdose

An overdose is defined as administration of a dose that is >10% higher than the assigned dose per the protocol. 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 DSMB or designee within 24 hours.

Medication Error

Medication Error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm, while the study drug is in the control of the healthcare professional, or in certain cases, the patient. Such incident may be due to health-care 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.

Accidental/Occupational Exposure

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

11.5.2.3 Death

Death is an outcome of an event. 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.

11.5.3 Responsibilities of the Investigator

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

- Monitor and record all AEs
- Determine seriousness, severity, and relationship to IP and/or study procedure and/or underlying disease
- Determination of the onset and end date of each event
- Report SAEs to the DSMB, IRB, FDA (Investigator-Initiated IND) and Sarepta within the timelines outlined in Section 11.5.1.
- Report follow-up information on SAEs within the timelines outlined in Section 11.5.
- Ensure source documentation for all AEs are accurate and complete
- Ensure that the study is conducted as defined in this document

11.5.4 Responsibilities of Sarepta

Notification of SUSARs to Sarepta's FDA INDs and NDAs, as applicable, all ex-US regulatory authorities and Investigators in ongoing studies of casimersen, eteplirsen, and golodirsen

12 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

12.1 Recording of Data

Clinical data for this study will be captured in an electronic format. Electronic data capture (EDC) will be built by the Nationwide Children's Hospital Research Information. The Investigator, or personnel delegated by the Investigator, will perform primary data collection/perform assessments based on the protocol design and captured in source documentation. All required study information must be recorded on the appropriate CRF screens/forms using the CRF Completion Guidelines for the study. A CRF must be completed for each subject that is enrolled. The study monitor will conduct 100% source data verification to ensure maximum data integrity. All data must be carefully entered in a timely fashion to permit meaningful interpretation and study oversight.

12.2 Quality Assurance

The CRFs will be reviewed at regular intervals by a clinical monitor per the agreed upon Monitoring Plan against the source documentation for identification and clarification of any discrepancies. Automated and manual quality checks will be in place to identify discrepancies, such as missing data, protocol deviations, out-of-range data, other data inconsistencies and compliance. Requests for data clarification or correction will be documented as electronic queries within the CRF and for the Investigator or study coordinator to resolve. All changes to the CRFs will be tracked in an electronic audit trail. Site Study Files will be reviewed for compliance throughout the study.

Audits may be carried out by the IIS Supporter's representatives, and inspections may be performed by IRBs or regulatory authorities before, during, or after the study. The Investigator will allow and assist the IIS Supporter's representatives and any regulatory agency to have direct access to all study records, CRFs, subject medical records and other source documentation, IP dispensing records and IP storage area, study facilities, and any other source documentation.

The Investigator must make study files and data accessible to the study monitor, to other authorized representatives of the IIS Supporter, and to the appropriate regulatory authority inspectors such as the United States Food and Drug Administration (US FDA).

12.3 Retention of Study Documents

At study completion, all CRF data will be copied onto a compact disc (CD) and provided to the Investigator for retention in the Study Files. The supporting Site Study Files must be retained by the Investigator for a period of 3 years after the investigation is discontinued and regulatory authorities are notified.

However, these documents must be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the IIS Supporter. No study documents will be destroyed or moved to a new location without prior written approval from the IIS Supporter. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study are to be transferred to an agreed-upon designee.

Subject records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records must be retrieved and made available for review at the time of an audit or regulatory authority inspection.

12.4 Essential Study Documents

Essential study documents are among the critical documents required before study enrollment is to occur. Essential documents, as well as supplemental information such as the Investigator's Brochure or package insert for each product (as applicable), final protocol, as specified in the Clinical Operations Manual and/or Regulatory Binder, must be kept on-site in a designated study site file.

The study site files will also contain, including but not limited to, subject accountability records, drug accountability (receipt/dispensing) records, Study Sponsor/Investigator correspondence, IRB correspondence, deviations, biological sample records, and SAE and Investigational New Drug (IND) safety reports/Safety Alert Letters/SUSARs.

13 STUDY REPORTS

13.1 Final Study Report

The final study report will include data through the final study visit and the safety follow-up phone call approximately 28 days after the last infusion of study drug.

13.2 Annual Study Report

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, the Principal Investigator will submit information set forth as follows:

(a) Clinical Trial Information. This will be a brief summary of the status of the trial in progress or completed during the previous year. The summary will include the following information for the trial: (1) the title and purpose of the trial; (2) clinical site; (3) the Principal Investigator; (4) clinical protocol identifiers, NCH IRB 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 trial; the number entered into the trial to date; the number whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons; (7) the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed, and (8) if the trial 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 serious adverse events submitted during the past year; (3) a summary of serious adverse events 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 trials, and information about bioavailability.

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

13.3 Data and Safety Monitoring Plan

13.3.1 The Data Safety Monitoring Plan

A Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to review participant safety and study progress for the "48-Week, Open Label, Study to Evaluate the Efficacy and Safety of Casimersen, Eteplirsen and Golodirsen in Subjects with Duchenne Muscular Dystrophy carrying eligible DMD duplications " study.

The activities and composition of this committee will be detailed in the DSMB Charter, which will be ratified during the initial DSMB meeting, which will occur prior to the commencement of dosing of the patients.

13.3.1.1 DSMB Membership

The DSMB membership consists of 3-4 persons completely independent of the investigator who have no financial, scientific, or other conflicts of interest with the trial. Current or past collaborators of Dr. Flanigan must note any significant conflict of interest before their eligibility to serve on the DSMB is approved.

The DSMB will include experts in or representatives of the fields of:

- Pediatric Neurology and Neuromuscular Diseases
- Muscular Dystrophy Clinical Care
- Clinical Research and Clinical Trials
- Pulmonology
- Complex Care

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 NIH Grant Policy Statement and 45 CFR Part 94. 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.

14.1.2 DSMB Responsibilities

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 trial, including periodic assessments of data quality and timelines, participant recruitment, accrual and retention, participant risk versus benefit, trial 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 trials;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Review safety data to determine whether to recommend dose escalation;
- Ensure the confidentiality of the trial data and the results of monitoring; and
- Assist by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

An additional responsibility of the non-voting Sarepta member is to provide additional or relevant safety information occurring in other Sarepta clinical trials using these three products that is relevant and pertinent to the safety of the participants in this NCH clinical trial.

13.4 Safety Reporting and Meetings

Reports describing the status of the study will be prepared by the Principal Investigator's staff and sent to the DSMB before every meeting, every 6 months beginning with the first infusion, or at the DSMB's request.

A meeting (either by teleconference or webcast) with the DSMB will be scheduled prior to study initiation and 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 (i.e., dose level, visit number, adverse event information);
- A timeline outlining the study progress relative to visit number for each participant, as well as time points for each SAE. A total for Adverse Events (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 summary of TEAEs by Sytem Organ Class, Preferred Term, and Maximum Severity
- A listing of deaths
- A summary of clinically significant laboratory test results

14 STATISTICAL CONSIDERATIONS

Analysis for both efficacy and safety will be occur for each subject.

14.1 General Considerations

This section describes the rules, conventions, statistical analysis, and presentation of data for this study.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Percentages of subjects with AEs or laboratory abnormalities will be based on non-missing values.

All data collected in this study will be presented using summary tables and subject data listings. Summary statistics for raw and change from Baseline data of continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Endpoints will be assessed primarily using simple descriptive statistics and/or inferential statistics. Baseline will generally be defined as the last available value before dosing.

14.2 Determination of Sample Size

The sample size for this study was based on the availability of subjects with these unusual mutations for this open label study, and not on power estimates of effect size.

14.3 Analysis Sets:

Three analysis sets will be considered:

Efficacy Analysis Set: All patients who are enrolled in this study and receive at least 1 dose of study treatment, and at least one post-baseline measurements.

Safety Analysis Set: All patients who are enrolled in the study and receive at least 1 dose of study treatment.

14.3.1 Efficacy Analyses

Change from Baseline in the dystrophin protein levels by Western blot and dystrophin intensity levels determined by immunofluorescence will be based on a 1-sample permutation t-test.

14.3.1.1 Analyses of the Primary Efficacy Endpoint

The population for the primary endpoint analysis will be all patients who receive at least one dose of any type of study drug, and who has both Baseline and Week 48 dystrophin expression quantified by Western blot in muscle biopsy tissue. The change from Baseline at Week 48 in dystrophin level (as percent normal) by Western blot will be analyzed by 1-sample permutation test, assuming the treatment effects are similar for the three types of study drug. Note that the 1-sample permutation test is an exact test and the smallest two-sided p value with sample size of 5 and 6 are 0.0625 and 0.03125, respectively. Hence the sample size needs to be at least 6 for rejecting the null hypothesis of no treatment effect.

Sensitivity analysis may be performed to assess the impact of assay results outside of the limits of quantification on the conclusion of treatment effects, using different imputation methods. For the calculation of average assay value, if there are assay results outside of the limits of quantification, different imputation methods will be used. Values less than the lower limit of quantification (LLOQ) will

be imputed using one of 3 methods: as 0, as 0.24 (level immediately below the LLOQ), and as the actual measured value, even if those values are below the LLOQ. Values greater than the upper limit of quantification (ULOQ) will be imputed using one of 2 methods: as 4.01 (level immediately above the ULOQ), and as the actual measured value, even if those values are above the ULOQ. If there are both values less than LLOQ and values greater than ULOQ, then there will be 6 imputation methods. Of them, the primary analysis will be based on the actual measured value for values less than LLOQ and based on the actual measured value for values greater than ULOQ. Analyses based on other imputation methods will be considered sensitivity analyses.

Imputation method for values of dystrophin expression determined by Western blot outside of the limits

Imputation type	Treat value<=LLOQ as	Treat value>=ULOQ as	Analysis type
1	As measured	As measured	Main analysis
2	0	As measured	Sensitivity analysis
3	0.24	As measured	Sensitivity analysis
4	As measured	4.01	Sensitivity analysis
5	0	4.01	Sensitivity analysis
6	0.24	4.01	Sensitivity analysis

Descriptive statistics on primary efficacy endpoint will be provided for different treatment groups.

14.3.1.2 Analyses of the Secondary Efficacy Endpoints

The change from Baseline Week 48 in the expression of dystrophin as measured by immunofluorescent signal intensity and percent dystrophin positive fibers (PDPF) in muscle tissue sections will be analyzed similarly, in all patients who receive at least one dose of any type of study drug, and who has both measurements at both Baseline and Week 48. Descriptive statistics on primary efficacy endpoint will be provided for different treatment groups.

A 10 percent increase in dystrophin positive fibers defined as fibers with 30 percent of the circumference positive for dystrophin will be used as the threshold for continuation of study drug and pursuit of insurance authorization to transition the subjects out of the Clinical TransitionProgram/SareptAssist.

14.3.1.3 Analyses of Additional Efficacy Endpoints

Listing and descriptive summary statistics may be provided for additional efficacy endpoints.

14.3.2 Safety Analysis

All subjects who are enrolled in the study and receive at least 1 dose of study treatment (casimersen, eteplirsen, or golodirsen) will be included in the safety analysis set.

The safety and tolerability of casimersen, eteplirsen, and golodirsen will be assessed through a review and evaluation of:

- Treatment emergent adverse events (TEAEs) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group.
- Non-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of subjects reporting AEs will be grouped by SOC and PT.

Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in the frequency tables. If a subject experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to study treatment will be used to summarize AEs by relationship and severity.

Descriptive statistics for ECG, ECHO, vital signs, and safety laboratory parameters will be generated. Summary statistics for each parameter at specific time points, as well as the change from Baseline to that time point, will also be displayed. All safety data will be presented in the data listings. Safety analyses will be descriptive in nature. All safety data will be presented in the data listings.

14.3.2.1 Physical Examination, Vital Signs, Weight, and Height

Vital signs, weight, and height will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Frequency tables of predefined change abnormal in vital sign values will be generated.

Results from physical examinations will be presented in subject data listings.

14.3.2.2 Clinical Laboratory Tests

Clinical chemistry, hematology, coagulation, and urinalysis will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics for each continuous, and frequency tables for each discrete parameter. Frequency tables of predefined abnormal changes of select laboratory parameter values will be generated.

14.3.2.3 Electrocardiograms

The actual value and change from Baseline to each visit will be presented by treatment group and visit, summarizing the actual values and change from Baseline to each visit for each parameter using descriptive statistics. Shift and frequency tables of predefined abnormal change of select ECG parameter values will be generated.

14.3.2.4 Echocardiograms

The actual value and change from Baseline to each visit will be summarized by treatment group for each ECHO for EF.

14.3.2.5 Overdoses

Overdoses will be presented in data listings as defined in Section 11.5.2.2.

14.3.2.6 Prior and Concomitant Medications and Physiotherapeutic Interventions

All prior and concomitant medications, as well as physiotherapeutic interventions, will be presented in data listings.

14.3.2.7 Additional Analysis

Additional analyses may be conducted by data listings and descriptive summary.

14.4 Statistics

14.4.1 Disposition, Demographics, and Baseline Characteristics

The number and percentage of subjects completing or prematurely discontinuing the study will be summarized. Reasons for premature discontinuation will also be summarized.

Demographic characteristics including age (years), race, ethnicity, and Baseline characteristics including height (cm), weight (kg), and body mass index (kg/m2) will be summarized. Demographic data and Baseline characteristics will be presented in data listings.

14.4.2 Medical History

Medical history will be presented in data listings.

14.4.3 Concomitant Medications and Therapies

Concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be reviewed and recorded at each visit from the time the parent(s)/guardian(s) sign(s) the informed consent and the subject signs the assent form (if applicable). Information on any physiotherapeutic intervention must be collected in detail for this study.

14.4.4 Dosing and Compliance

The cumulative exposure to study treatment, including the total volume of drug administered (mL), total number of infusions received, and the cumulative amount of drug received, will be summarized by treatment group. Dosing information will be provided in a data listing.

14.4.5 Protocol Deviations

A listing of protocol deviations will be provided. This deviation listing will be based on review of study data prior to locking the database and will include the nature of the deviation (e.g., inclusion/exclusion, prohibited therapies).

14.4.6 Other Statistical Issues

Additional analyses may be conducted.

15 GENERAL INFORMATION

15.1 SPECIAL REQUIREMENTS AND PROCEDURES

15.1.1 Compliance with Ethical and Regulatory Guidelines

This study will comply with the requirements that are enunciated in the European Clinical Trial Directive 2001/20/EC and/or in the US Code of Federal Regulations (CFR).

15.1.2 Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56 and/or the European Clinical Trial Directive 2001/20/EC. Before enrollment of subjects into the study, the protocol and informed assent (for subjects, if applicable) and informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB and regulatory authority. Amendments to the protocol will be subjected to the same IRB and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB and DSMB of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals and regulatory authorities' approvals must be sent to the DSMB, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB and the regulatory authority must be retained in the study regulatory files.

15.1.3 Informed Consent/Assent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent from each subject's parent(s) or legal guardian(s) and written assent from each subject, if applicable, must be obtained before any study-specific screening or Baseline period evaluations are performed. One copy of the signed informed consent/assent documents will be given to the subject; the Investigator will retain the original copies of these documents.

The informed consent/assent documents, as prepared by the Study Sponsor or designee, must be reviewed and approved by the IRB and regulatory authorities, as applicable, before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in the 21 CFR 50.25.

15.1.4 Compliance with the Protocol

All processes and procedures defined in this protocol must be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed by the Investigator as crucial for the safety and wellbeing of that subject may be instituted for that subject only and documented as deviations. The Investigator will contact the DSMB as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB; however, the IRB and DSMB must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made.

15.1.5 Confidentiality

15.1.5.1 Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the DSMB, the DSMB's designee, or the study monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB, the subject's parent(s) or legal guardian(s) or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards and/or European standards.

15.1.5.2 Subject Confidentiality

The anonymity of participating subjects will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Subjects may be referenced by their initials and an assigned subject identification number on the CRFs and other data collected by the Study Sponsor. The Investigator must maintain all documents related to the study that identify the subject (e.g. the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB, or the study monitor.

15.2 General Information

The Investigator should be familiar with and refer, as needed, to Safety Alert Letters, the Clinical Study Operations Manual, Laboratory Manual, and all other study-specific information that is provided during the study initiation visit or by the study monitor.

15.3 Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. Sharing of the study data must follow the stipulations in the agreement with the IIS Supporter or other Third Parties.

15.4 Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the IP, theInvestigator, clinical site pharmacist or pharmacy designee should contact the DSMB or designated contract research organization (CRO).

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