CLINICAL STUDY PROTOCOL

DRUG:	Casimersen (Casimersen Injection) and Golodirsen (Golodirsen Injection)
STUDY NUMBER:	4045-302
STUDY TITLE:	Long-term, Open-label Extension Study for Patients with Duchenne Muscular Dystrophy Enrolled in Clinical Trials Evaluating Casimersen or Golodirsen
IND Number	CCI (casimersen) CCI (golodirsen)
EUDRACT Number:	2017-004625-32
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000
CURRENT VERSION DATE:	Amendment 4, Version 5, 03 March 2020
REPLACES VERSION DATE:	Amendment 3, Version 4, 22 October 2019


PPD

SIGNATURE PAGE FOR SPONSOR

Protocol Title:	Long-term, Open-label Extension Study for Patients with Duchenne Muscular Dystrophy Enrolled in Clinical Trials Evaluating Casimersen or Golodirsen
Study No:	4045-302 (Amendment 4, Version 5)
Current Version Date:	03 March 2020

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational products (IPs).
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice as described the European Clinical Trial Directive 2001/20/EC.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the IPs.

Signature: PPD

Email: PPD

Title: PPD

Company: Sarepta Therapeutics Inc

PPD

PPD
PPD

Date

Sarepta Therapeutics, Inc.
215 First Street
Cambridge, MA 02142 USA

INVESTIGATOR'S AGREEMENT

I have read the Study Protocol 4045-302 Amendment 4, Version 5 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

NAME OF COMPANY Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** Casimersen Injection and Golodirsen Injection **NAME OF ACTIVE INGREDIENT** casimersen and golodirsen

TITLE: Long-term, Open-label Extension Study for Patients with Duchenne Muscular Dystrophy Enrolled in Clinical Trials Evaluating Casimersen or Golodirsen

Study Number: 4045-302

Phase of Study: Phase 3

INVESTIGATOR STUDY SITES: This multinational study will be conducted at approximately [redacted] sites worldwide.

OBJECTIVES:

Primary objective

- To evaluate the safety and tolerability of long-term treatment with 30 mg/kg of casimersen or golodirsen.

[redacted]

- [redacted]
- [redacted]
- [redacted]

METHODOLOGY:

Patients with Duchenne muscular dystrophy (DMD) who are amenable to treatment by skipping exons 45 or 53 and who have been participating in a clinical trial evaluating casimersen (SRP-4045) or golodirsen (SRP-4053) will be eligible to transfer into this long-term extension (LTE) study. Patients can enroll in the LTE only after completing the original study, per protocol. Every effort will be made to ensure that the patient will not experience any interruption in dosing of casimersen or golodirsen during the transition from the original study to the LTE.

Patients will continue to receive 30 mg/kg of either casimersen or golodirsen once-weekly by intravenous (IV) infusion, depending upon their genotype, starting at Week 1 of this study. [redacted]

[redacted]

DURATION OF STUDY:

Screening period: 1 week

Treatment period: Up to 144 weeks

NUMBER OF PATIENTS:

NAME OF COMPANY Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** Casimersen Injection and Golodirsen Injection **NAME OF ACTIVE INGREDIENT** casimersen and golodirsen

The number of patients will be based on the number of patients enrolled in qualifying studies (ie, studies evaluating casimersen or golodirsen in patients with DMD amenable to skipping either Exon 45 or Exon 53, respectively).

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

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

I 1. Completed a clinical trial evaluating casimersen or golodirsen, per protocol.

I 2. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose of study drug. The sexual partner must also use a medically acceptable form of contraceptive (eg, female oral contraceptives) during this time frame.

I 3. Is able to understand and comply with all the study requirements and, if under 18 years of age, has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.

I 4. Is willing and legally able to provide written informed assent and/or consent, or, if not legally able to provide written informed assent and/or consent, has (a) parent(s) or legal guardian(s) who is (are) willing and legally able to provide written informed assent and/or consent for the patient to participate in the study.

I 5. Is between 7 and 23 years of age, inclusive, at enrollment.

Exclusion Criteria:

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

E 1. Any medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results.

E 2. Any patient who, in the Investigator's opinion, seems unable/unwilling to comply with the study procedures.

E 3. Treatment with any investigational therapies at the time of consent or within 6 months prior to dosing, if there was an unexpected gap in treatment.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Casimersen (SRP-4045) or golodirsen (SRP-4053) (each at 30 mg/kg) will be administered according to the patient's genotype as an IV infusion over approximately 35 minutes CCI [redacted] to 60 minutes CCI [redacted].

In the event it becomes necessary, or at the discretion of the patient or parent(s)/guardian(s), in consultation with the Investigator and consulting surgeon and following adequately informed and voluntary patient or parent/guardian permission and patient/child assent, a totally implantable central venous access device (ie, port) may be used, contingent upon any required approval by local and/or country-specific regulatory body(ies). The use of alternative methods of central venous access, such as a percutaneously inserted or tunneled central venous catheter, are permitted as long as the patient has a documented contraindication in the opinion of the consulting surgeon for the placement of a totally implantable central venous access device.

REFERENCE TREATMENT: None

NAME OF COMPANY Sarepta Therapeutics, Inc. 215 First Street Cambridge, MA 02142 USA Phone: +1-617-274-4000	**NAME OF FINISHED PRODUCT** Casimersen Injection and Golodirsen Injection **NAME OF ACTIVE INGREDIENT** casimersen and golodirsen
CRITERIA FOR EVALUATION: Primary Endpoint: • Patient incidence of serious adverse events (SAEs)	
CCI [redacted]	

CCI

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be classified as treatment-emergent (TEAE) and nontreatment-emergent (nonTEAE). A TEAE is defined as an AE that emerges during treatment, having been absent pre-treatment, or worsens relative to the pretreatment state. A treatment-related TEAE will be defined as a TEAE that the Investigator considers definitely related or possibly/probably related to the study treatment.

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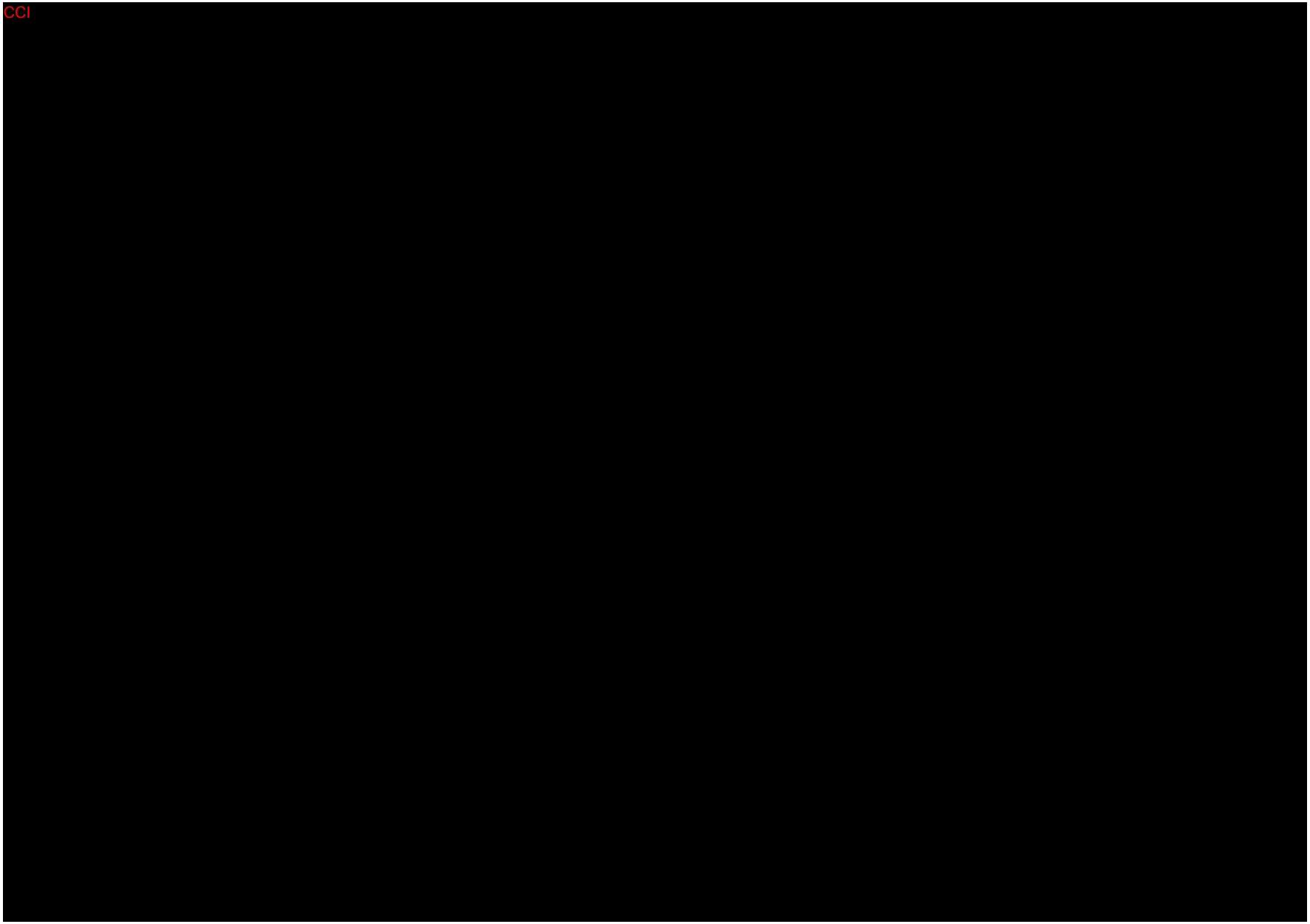
CCI [redacted]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3. TABLE OF CONTENTS

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CCI	CCI
10 MWRT	10-meter walk run test
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CK	Creatine kinase
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CWU	Continuous wheelchair use
DMC	Data monitoring committee
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HEENT	Head, ears, eyes, nose, throat
ICH	International Council for Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ISF	Investigator site files

Abbreviation	Definition
IV	Intravenous, intravenously
CCI	CCI
CCI	CCI
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
CCI	CCI
MRI	Magnetic resonance imagining
mRNA	Messenger ribonucleic acid
CCI	CCI
CCI	CCI
PK	Pharmacokinetic
PT	Preferred term
CCI	CCI
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UACR	Urinary albumin to creatinine ratio
UPCR	Urinary protein to creatinine ratio
ULN	Upper limits of normal

5. INTRODUCTION

5.1. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare, serious, life-threatening, X-linked recessive degenerative neuromuscular disease caused by mutations in the *DMD* gene. These mutations disrupt the reading frame of the dystrophin messenger ribonucleic acid (mRNA) preventing the translation of functional dystrophin protein. Dystrophin is a critical structural protein that protects muscle from repeated strain-induced injury. In the absence of dystrophin, the stress of repeated muscle contraction causes cellular degeneration, regeneration, and inflammation, and, over time, myonecrosis.

The progression of DMD follows a highly predictable course. Significant motor deficits may be present during the first year of life, but a diagnosis is usually made between the ages of 3 to 5 years, when toddlers begin to show functional symptoms (eg, waddling gait, toe walking, and difficulty climbing stairs). Over time, ambulation becomes increasingly abnormal, and by 8 years of age, most patients lose the ability to rise from the floor and climb stairs, and often fall while walking. By 10 to 14 years of age, most lose the ability to walk. Upper limb, cardiac, and diaphragmatic muscles progressively weaken during adolescence. Historically, patients died from respiratory or cardiac failure in their late teens or early 20s (Eagle 2002; Brooke 1989). The use of ventilation support and steroids may increase life span by several years; however, DMD still has a mortality rate of 100% (Kohler 2009).

Existing interventions for DMD patients with mutations amenable to exon skipping are largely supportive in nature and include bracing, muscle-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and assisted ventilation. Current pharmacologic treatments, such as glucocorticoids, focus on alleviation of symptoms, but do not address the underlying cause of the disease. Corticosteroids may prolong ambulation, delay the onset of scoliosis, and improve performance on some measures of clinical function (Biggar 2006; Pradhan 2006; Beenakker 2005). However, their benefits are only temporary, and their use is often limited by numerous side effects, including growth inhibition, effects on pubertal changes, weight gain, behavioral changes, osteoporosis, Cushingoid facies and habitus, and cataracts (Biggar 2006; Manzur 2004).

5.2. Casimersen and Golodirsen

Ribonucleic acid (RNA) therapeutics are compounds composed of heterocyclic nucleobases (adenine, cytosine, guanine, and uracil, or analogues) linked together on an oligomer backbone that supports hybridization via Watson-Crick base pairing with specific complementary RNA targets. A relatively new use of oligonucleotide-based therapeutics is to target a pre-mRNA in the nucleus of a cell to influence the splicing process that creates a mature mRNA. Referred to as “exon skipping,” this approach allows determination of which exons will be incorporated into the mature mRNA to be translated into the protein product.

Casimersen (SRP-4045) and golodirsen (SRP-4053) are phosphorodiamidate morpholino oligomers that are chemically, structurally, and biologically distinct from other synthetic antisense RNA therapeutics. Phosphorodiamidate morpholino oligomers differ from natural nucleic acids and other oligonucleotide therapeutic platforms by having the attachment of

nucleobases to a 6-membered morpholine ring as opposed to the 5-membered ribose ring found in RNA and deoxyribonucleic acid (DNA). Moreover, the morpholine rings are linked through neutrally charged phosphorodiamidate moieties as opposed to negatively charged phosphodiester linkages in RNA and DNA. These differences were designed to increase stability and address safety issues seen with some earlier oligonucleotide backbone chemistries.

Casimersen and golodirsen were developed specifically for patients with DMD who are amenable to skipping Exon 45 or Exon 53, respectively. Approximately 8% of all DMD patients are amenable to skipping Exon 45 or Exon 53 (Aartsma-Rus 2009). Each of these drugs will hybridize with a specific sequence of pre-mRNA transcripts of the *DMD* gene so that Exon 53 or Exon 45 (ie, the targeted exon), is excluded or skipped, restoring the mRNA open reading frame. This exon skipping restores the reading frame and results in the production of an internally shortened, functional dystrophin protein.

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[redacted]

5.2.2. Clinical Experience with Casimersen and Golodirsen

Casimersen:

- Study 4045-101 was a Phase 1, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetic (PK) study of SRP-4045 in ambulatory patients with Duchenne muscular dystrophy amenable to Exon 45 skipping. The study was conducted as a double-blind, placebo-controlled, dose-titration portion followed by an open-label extension.

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[redacted]

- Study 4045-301 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 Exon 53, respectively.

Golodirsen:

- Study 4053-101 was a Phase 1/2, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and PK study evaluating golodirsen in patients with advanced-stage DMD who are amenable to Exon 53-skipping. The study was 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.

CCI [redacted]

- Study 4045-301 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 Exon 53, respectively.

Further details are provided in the Investigator's Brochure of each study drug.

5.3. Rationale for the Current Study

Clinical studies evaluating casimersen and golodirsen may conclude prior to these products being commercially available. In December 2019, golodirsen (VYONDYS 53®) received accelerated approval from the Food and Drug Administration (FDA) for the treatment of DMD in patients who have a confirmed mutation in the *DMD* gene that is amenable to exon 53 skipping. As there are no other nonsteroidal treatment options for DMD patients who are amenable to Exon 45 or Exon 53 skipping, removing active treatment from the patients enrolled in these studies is not ethical. In addition, there is a need to understand the effects of long-term treatment with casimersen and golodirsen. An extension study will allow the continued treatment of the patients with either casimersen or golodirsen (depending on their genotype) and the long-term assessment of efficacy and safety endpoints.

5.4. Benefit and Risk Assessment

Although no clinical study can guarantee an improvement in efficacy outcome measures to any of the patients, the continued long-term treatment with casimersen and golodirsen are expected to attenuate the decline in physical functioning that typically occurs with DMD. Analysis of muscle biopsies collected at Baseline and Week 48 during Study 4053-101 indicated that all 25 patients had evidence of Exon 53 skipping. In addition, golodirsen significantly increased mean dystrophin levels (10.7-fold increase from Baseline) and the dystrophin was localized to the sarcolemma (required for proper functioning) (Muntoni 2017).

Both casimersen and golodirsen have been studied in DMD patients at weekly doses of 30 mg/kg IV, the same dose to be used in the present study.

As of data cut-off date of 21 July 2019, [redacted] clinical studies with SRP-4045 have been initiated. Three of these studies (Study 4045-101, Study 4045-301 [ESSENCE], and Study 4045-302) enrolled patients with mutations of the *DMD* gene amenable to exon 45 skipping, and CCI [redacted]

In Study 4045-101, the double-blind, placebo-controlled, dose-titration period has been completed. During this period, 12 patients were randomized and treated with once-weekly IV infusions of placebo (n=4) or casimersen (n=8) in escalating doses (4 mg/kg for 2 weeks, 10 mg/kg for 2 weeks, 20 mg/kg for 2 weeks, and 30 mg/kg until rollover was allowed into the open-label extension period). All 12 patients entered the open-label period of the study and continue to receive 30 mg/kg IV casimersen. As of 02 February 2018 in Study 4045-301, CCI patients amenable to Exon 45 skipping have received 30 mg/kg IV casimersen or placebo. CCI

Golodirsen is being evaluated in [redacted] studies: Studies 4053-101, CCI, and 4045-301. As of data cut-off date of 09 September 2019, in the golodirsen clinical development program, CCI and Study 4053-101 in patients with DMD) have been completed, and 2 studies are ongoing (Study 4045-301 and Study 4045-302 in patients with DMD). As of 02 February 2018 in Study 4045-301, CCI patients amenable to Exon 53 skipping have received 30 mg/kg IV golodirsen or placebo. CCI

The safety and efficacy assessments scheduled during this long-term extension (LTE) study will have either no increase or a minimal increase in risk to the patients, beyond that associated with DMD.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of casimersen and golodirsen may be found in their respective Investigator's Brochures.

6. STUDY OBJECTIVES

6.1. Primary Objective

- To evaluate the safety and tolerability of long-term treatment with 30 mg/kg casimersen or golodirsen

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

Study 4045-302 is a multicenter, open-label study evaluating the long-term safety and efficacy of 30 mg/kg casimersen or golodirsen in patients with DMD amenable to skipping Exon 45 or Exon 53, respectively.

Patients with DMD who are amenable to skipping Exon 45 or Exon 53 and who have been participating in a clinical trial evaluating casimersen or golodirsen will be eligible to transfer into this LTE study. Patients can enroll in the LTE only after completing the original study, per protocol. Every effort will be made to ensure that the patient will not experience any interruption in dosing of casimersen or golodirsen during the transition from the original study to the LTE.

Patients will continue to receive 30 mg/kg of either casimersen or golodirsen once weekly by IV infusion, depending upon their genotype, once weekly by IV infusion starting at Week 1 of this study. CCI

CCI

CCI

7.3. Study Endpoints

7.3.1. Primary Endpoint

- Patient incidence of serious adverse events (SAEs)

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7.4. Discussion of Study Design

This study is designed as an open-label extension study. The dosing and assessment endpoints are predicated by the original studies.

7.5. Data Monitoring Committee

An independent DMC will be formed to assist in the periodic monitoring of safety, data quality, and integrity of study conduct. The DMC will meet approximately every 6 months throughout the study. At each DMC meeting, the DMC will review the cumulative safety data and make 1 of the following recommendations: study may proceed as planned, resume study with major/minor modifications (to be specified), temporarily suspend enrollment and/or dosing pending further DMC evaluation, or permanently discontinue the study.

Any decision to interrupt, restart, or discontinue the study will be made by the Sponsor in consultation with the DMC and other parties, as appropriate.

A DMC charter will be prepared to formalize the process for the meetings and data reviews. The outcome of any DMC meeting will be communicated to the Investigators by the Sponsor or designee. The relevant regulatory authorities will be promptly notified of study suspension or discontinuation related to safety concerns. Any suspension or discontinuation of the study for any reason will be promptly reported to the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Patients

The number of patients enrolled in the LTE study will be predicated on the number of patients completing the original studies.

8.2. Patient Inclusion Criteria

A patient must meet all of the following criteria to be eligible to participate in this study.

I 1. Completed a clinical trial evaluating casimersen or golodirsen, per protocol.

I 2. If sexually active, agrees to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose. The sexual partner must also use a medically acceptable form of contraceptive (eg, female oral contraceptives) during this time frame.

I 3. Is able to understand and comply with all the study requirements and, if under 18 years of age, has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with all the study requirements.

I 4. Is willing and legally able to provide written informed assent and/or consent, or, if not legally able to provide written informed assent and/or consent, has (a) parent(s) or legal guardian(s) who is (are) willing and legally able to provide written informed assent and/or consent for the patient to participate in the study.

I 5. Is between 7 and 23 years of age, inclusive, at enrollment.

8.3. Subject Exclusion Criteria

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

E 1. Any medical condition that could, in the Investigator's opinion, adversely affect the safety of the patient, make it unlikely that the course of treatment would be completed, or impair the assessment of study results.

E 2. Any patient who, in the Investigator's opinion, seems unable/unwilling to comply with the study procedures.

E 3. Treatment with any investigational therapies at the time of consent or within 6 months prior to dosing if there was an unexpected gap in treatment.

8.4. Completion of a Patient's Participation in the Study

Patients will be considered to have completed their participation in the LTE study after they have completed the last study visit or have withdrawn from the study early.

8.5. Completion of the Trial

The trial will be considered complete when the last patient completes the last study visit.

8.6. Patient Withdrawal Criteria

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

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

The Investigator or study staff will document the reason(s) for treatment discontinuation.

Any patient who discontinues study treatment in order to transition to commercial therapy will be encouraged to complete an Early Termination visit (to complete the assessments scheduled for the End of Study visit).

Patients who discontinue from the study or treatment will not be replaced.

8.7. Trial Discontinuation

If the Sponsor, the Investigator, the Medical Monitor, the study monitor, IRB/IEC, or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that a study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the Investigator, the IRB/IEC, and the Medical Monitor.

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 patients enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities
- Failure of the Investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements consistent with the European Clinical Trial Directive 2001/20/EC

- The investigational product is commercially approved and accessible to patients in their individual country

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Casimersen (Casimersen Injection) and golodirsen (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 Injection and Golodirsen Injection are supplied as sterile, clear, colorless, isotonic, phosphate-buffered saline (PBS) solutions in single-use, 2 mL glass vials each containing 2 mL of casimersen or golodirsen at a concentration of 50 mg/mL. The solutions are clear to slightly opalescent and colorless liquids that may contain white to off-white particles.

The study drug (either casimersen or golodirsen) will be administered according to the patient's genotype as an IV infusion over approximately 35 minutes CCI to 60 minutes CCI.

9.1.1. Packaging and Labeling

The label text for the study drug will, at a minimum, include the following information: product name/identifier, cautionary statement, lot number (or alternative code), storage conditions, and the name of the Sponsor pursuant to regional requirements.

Please refer to the study-specific Pharmacy Manual for information on packaging, labeling, and preparation instructions.

9.1.2. Storage

The study drug should be kept in a temperature-controlled, light-protected area and keeping the vials in the foam inserts is a sufficient form of light protection.

Vials of study drug must be stored in a secured, limited access area with appropriate temperature recording, controls, and monitoring.

Chemical in-use stability has been demonstrated for up to 4 hours at room temperature and for up to 24 hours at 2°C to 8°C. From a microbiological point of view, the diluted drug product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Further details for storage can be found in the study-specific Pharmacy Manual.

9.2. Treatment Administered

Eligible patients will receive a weekly IV infusion of casimersen or golodirsen. The study drug should be prepared for dosing by following the steps detailed in the study-specific Pharmacy Manual.

Patients will continue to receive 30 mg/kg casimersen or golodirsen once weekly; the same dose as they had been receiving in the original study.

The administered dose of study drug will be calculated based on the patient's weight. Doses will be calculated based on the patient's most recent scheduled weight measured (as defined in Section 2) prior to the current visit.

In the event it becomes necessary, or at the discretion of the patient or parent(s)/legal guardian(s), in consultation with the Investigator and consulting surgeon and following adequately informed and voluntary patient or parent/legal guardian permission and patient/child assent, a totally implantable central venous access device (ie, port) may be used, contingent upon any required approval by local and/or country-specific regulatory body(ies). The use of alternative methods of central venous access, such as a percutaneously inserted or tunneled central venous catheter, are permitted as long as the patient has a documented contraindication in the opinion of the consulting surgeon for the placement of a totally implantable central venous access device.

If study treatment is administered into an existing IV line, the line must be flushed with normal saline (0.9% sodium chloride) before and after administration of study treatment. No other medications may be administered concomitantly during the study treatment infusion.

All treated patients will be monitored for CCI for the collection of vital signs following the end of each infusion of study drug (either casimersen or golodirsen).

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

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9.2.1. Dose Interruption, Modification, Reduction, or Delay

There is no provision for dose alteration in this study.

If a patient experiences any situation where the dose is interrupted, delayed or otherwise modified, the Investigator will consult with the Medical Monitor to determine whether the patient may resume treatment. If dosing is interrupted for any other AEs based on the clinical judgment of the Investigator, the Investigator will also consult with the Medical Monitor to determine whether the patient may resume treatment.

CCI

9.3. Randomization and Blinding

This is an open-label study. No randomization or blinding will be performed.

9.4. Prior and Concomitant Medications

No other medications may be administered concomitantly during the infusion of the study drug.

Patients are not permitted to receive any investigational therapeutic drug other than casimersen or golodirsen. There are no further restrictions for use of concomitant medications during this study.

If the Investigator is unsure of the impact of a concomitant medication on study assessments and outcomes, then he/she should contact the Medical Monitor.

9.5. Treatment Compliance

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

10. STUDY ASSESSMENTS

10.1. Study Schedule of Events

The schedule outlining the study assessments and times of assessments is shown in Section 2. Written informed consent from the parent(s)/legal guardian(s) and assent from the patient (if applicable) to participate in this study must be obtained prior to beginning any of the procedures for this study.

CCI

10.3. Baseline Assessments

Written informed consent/assent from the patient and, if the patient is younger than 18 years of age, the parent(s)/legal guardian(s) to participate in this study must be obtained prior to beginning any of the procedures for this study.

CCI

10.4. Safety Assessments

10.4.1. Adverse Events

The collection of AEs is detailed in Section 11.

10.4.2. Clinical Laboratory Evaluations

The following routine clinical laboratory tests will be performed at the time points specified in Section 2. Samples will be collected before administration of study drug and processed according to the Laboratory Manual provided for the study and analyzed by an accredited central laboratory selected by the Sponsor. All laboratory tests may be performed locally if required.

Chemistry:	Sodium, chloride, potassium, calcium, glucose, albumin, uric acid, total bilirubin, alkaline phosphatase (ALP), amylase, alanine aminotransferase, AST, GGT, GLDH, lactate dehydrogenase, C-reactive protein, and creatine kinase (CK)
Hematology:	Red blood cells, total white blood cells, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells
Coagulation Screen:	Prothrombin time, international normalized ratio, and activated partial thromboplastin time (aPTT)
Routine renal monitoring:	• Quantitative urine analysis: total protein to creatinine ratio (UPCR), urine albumin-to-creatinine ratio (UACR), CCI [redacted] and urinalysis (pH, specific gravity, protein, glucose, ketones, cytology, and hemoglobin) • Renal function blood tests: creatinine, blood urea nitrogen, and cystatin C • Urine dipstick testing

Persistent, unexplained abnormalities on routine renal blood test monitoring may result in additional renal function test such as 24-hour urine testing for protein.

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 or not clinically significant.

10.4.2.1. Clinical Significance

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 patient with additional assessments until:

- Values have reached normal range and/or Baseline levels; or

- In the judgment of the Investigator together with the Sponsor's Medical Monitor, abnormal values assessed to be not related to the administration of study treatment or other protocol-specific procedures, and additional assessments are not medically indicated. In the judgement of the Investigator, an unexplained laboratory abnormality that could potentially lead to a poor outcome should result in interruption of treatment.

10.4.3. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be obtained at the time points specified in Table 1. ECGs will be performed at a consistent time of day throughout the study and before any invasive procedures (eg, blood sampling or study drug infusion). ECGs will be performed only after the patient is in the supine position, resting, and quiet for a CCI. The ECG will be manually reviewed and interpreted by medically qualified personnel using a central vendor according to prespecified criteria. The Investigator will review the results of the centrally read ECG report and determine if the findings are clinically significant.

The definition of clinical significance is provided in Section 10.4.2.1.

10.4.4. Physical Examination

Physical examinations, full and brief, will be conducted at the time points specified in Section 2. Physical examinations will be performed by the Investigator or qualified study staff. Full physical examinations will include examination of general appearance; head, ears, eyes, nose, throat (HEENT); heart; chest; abdomen; skin; lymph nodes; extremities; musculoskeletal; and neurological systems. Brief physical examinations will include examination of general appearance, HEENT, heart, lungs, abdomen, and skin.

10.4.5. Vital Signs, Weight, and Height

Vital signs (blood pressure, heart rate, respiration, and temperature [oral, tympanic, or axillary]), height, and weight will be measured at the time points specified in Section 2.

On days when study drug is infused, vital signs will be collected CCI prior to infusion, CCI, and CCI after the end of the infusion. All assessments will be performed after patients have remained inactive for 5 minutes. Pulse 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 patient's weight varies by more than CCI from the prior visit, the patient is to be reweighed to confirm the result, and an explanation of the change must be documented.

For patients who are ambulatory, the height is to be measured from a standing position and CCI length will be measured and converted to height. For nonambulatory patients, the length of the CCI will be measured as a surrogate measure for height.

CCI measurements will be recorded for all patients at each CCI visit. Height will be measured at the time points specified in Section 2. Height is to be measured with shoes off. If

CCI [redacted]

10.4.6. Safety Monitoring, Additional Investigations, and Stopping Rules

10.4.6.1. Safety Monitoring for Liver Chemistry Tests

Liver chemistry tests need to be monitored as specified in the Schedule of Events (Section 2).

Initial abnormal liver chemistry test result(s) needs to be confirmed if:

- GGT or GLDH or AST or ALT measurement is CCI × upper limit of normal (ULN) (or [redacted] × Baseline value if the Baseline value was > ULN) at any time during the study.

Patients with confirmed liver chemistry test results (as above) need to have their liver chemistry tests (GGT, GLDH, ALT, AST, ALP, international normalized ratio [INR], and total bilirubin) retested CCI [redacted]. Frequency of retesting can decrease to CCI [redacted] or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.

Additional Investigations:

Patients with confirmed abnormal liver chemistry test results (as above) are recommended to have the following evaluations performed:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (CT) or magnetic resonance imaging (MRI scans; may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.

10.4.6.1.1. Stopping Rules for Liver Chemistry Test Results

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with SRP-4045 or SRP-4053 will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

- GGT or GLDH CCI × ULN, which is confirmed
- GGT or GLDH CCI × ULN, which is confirmed and persists for CCI weeks

- GGT or GLDH [redacted] × ULN, which is confirmed **and** total bilirubin [redacted] × ULN or INR [redacted]
- GGT or GLDH [redacted] × ULN which is confirmed, and the new appearance (ie, onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [redacted] assessed by the Investigator to be potentially related to hepatic inflammation.

10.4.6.2. Safety Monitoring for Renal Function

Renal function tests need to be monitored as specified in the Schedule of Events (Section 2).

Patients with the following test results need to undergo repeat testing for confirmation of abnormal test results:

- Protein [redacted] (dipstick)
- UPCR [redacted] mg/g or [redacted]
- UACR [redacted] mg/g or [redacted]
- Serum creatinine [redacted] mg/dL above baseline or [redacted] above Baseline
- Serum creatinine [redacted] × ULN
- Estimated glomerular filtration rate (eGFR) [redacted]
- Red blood cells (RBCs) [redacted]/hpf
- Elevated cystatin C [redacted]
- Elevated [redacted]

Additional Investigations:

A 24-hour urine collection needs to be undertaken to quantify any proteinuria and GFR changes indicated by confirmed results as above. Additional evaluations including nephrology consultation, renal ultrasound/CT/MRI, renal biopsy, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

10.4.6.2.1. Stopping Rules for Renal Function Test Results

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with SRP-4045 or SRP-4053 will be stopped permanently:

- Quantitative total urine protein measurement of [redacted] 24 hours
- Measured GFR (creatinine clearance) [redacted] mL/min/1.73 m^2
- [redacted]
- [redacted]
- Persistent microscopic hematuria [redacted]/hpf for [redacted] consecutive weeks

10.4.6.3. Safety Monitoring for Hypersensitivity

Patients will be monitored for occurrence of allergic reactions primarily via monitoring AEs as specified in the Schedule of Events (Section 2). Patients will be instructed to promptly report any signs or symptoms of fever or constitutional symptoms that may arise during the study and the Investigator needs to closely evaluate all potential causes, including concomitant illness.

Additional Investigations:

Patients who experience significant or persistent constitutional symptoms need to be discussed with the Sponsor Medical Monitor to determine whether additional monitoring or laboratory tests are required. Additional evaluations including immunology consultation, tests for allergic reactions (absolute eosinophils, serum/plasma tryptase), may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

10.4.6.3.1. Stopping Rules for Hypersensitivity Adverse Events

In the event of a confirmed hypersensitivity AE meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with SRP-4045 or SRP-4053 will have their treatment permanently discontinued.

- Anaphylaxis, anaphylactoid reaction, or angioedema
- Any serious allergic reaction

10.4.6.4. Safety Monitoring for CCI Results

CCI needs be monitored at the time points specified the Schedule of Events (Section 2).

Patients who have a confirmed occurrence of CCI /mm^3 need to have the following evaluations performed::

- Complete blood count with reticulocytes
- Peripheral blood smear
- Coagulation panel (preferred term [PT]/INR, aPTT)
- High-sensitivity C-reactive protein

Additional Investigations:

Additional CCI evaluations for confirmed, unexplained significant CCI reductions, including hematology consultation, fibrinogen, fibrinogen split products/D-dimer, von Willebrand factor, total immunoglobulins, complement levels, viral serologies, auto-antibody screen, antiplatelet antibodies and anti-PF4 assay, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

10.4.6.4.1. Stopping Rules for CCI Test Results

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with SRP-4045 or SRP-4053 will be stopped permanently:

- CCI

10.4.6.5. Safety Monitoring for CCI

CCI must be monitored by urine dipstick and AEs as specified in the Schedule of Events (Section 2).

Patients who have confirmed [redacted] dipstick urinalysis need to be evaluated for urine microscopy and the following AEs:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additional Investigations:

In case of any of the AEs above, subjects need to have evaluations of [redacted], CK, renal function (eg, serum cystatin C) and serum chemistry [redacted] until values reach usual/pre-event levels or stabilize.

In addition, Investigators should obtain a more detailed history of symptoms, preceding activity and hydration status, concomitant drug use, and recent or concurrent infections. Additional evaluations, including rheumatology/immunology consultations and anti-muscle antibodies, may be performed at the discretion of the Investigator in consultation with the Sponsor Medical Monitor.

10.4.6.5.1. Stopping Rules for [redacted]

Stopping rules are not applicable for [redacted]

[redacted]

CCI

[redacted]

10.4.7. 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 patient or parent(s)/legal guardian(s) sign(s) the informed consent and the patient signs the assent form (if applicable). See Section 9.4 for details on permitted concomitant medications.

Information on any physiotherapeutic intervention must be collected in detail for this study. It is important to note any assistive ventilation therapies/devices that the patient is using.

10.4.8. Immunogenicity Assessment

Blood serum samples will be collected prior to infusion at the time points specified in Section 2 to determine the development of immunogenicity over the course of the study.

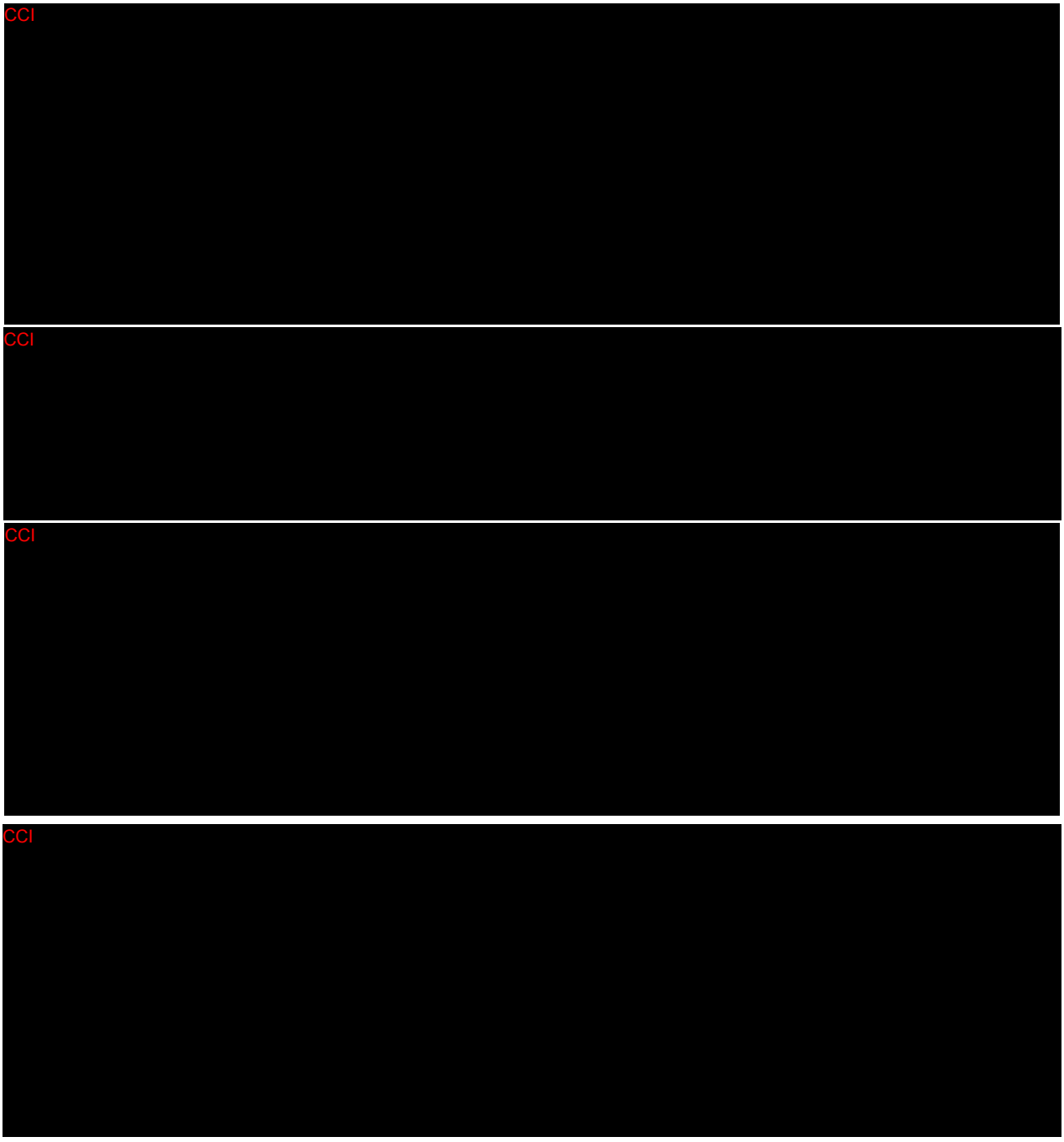
Anti-casimersen, anti-golodirsen, and anti-dystrophin antibodies will be measured using an immunosorbent assay. CCI

[redacted]

Any samples stored for future research will be coded with no other patient identifiers and would only be available to site staff, monitors, and auditors (where applicable) when reviewing relevant patient history at the designated site.

CCI

[redacted]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11. ADVERSE EVENTS

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 patient safety, and the Investigator will use his/her clinical judgment and expertise to determine the appropriate course of action.

All AEs from the time of informed consent/assent through the last follow-up visit will be recorded in each enrolled patient's case report form (CRF). For patients who prematurely discontinue from the study (see Section 8.6), AEs will continue to be recorded until 28 days after the last study treatment infusion. For patients who are found to be ineligible for the study during the Screening period and are not enrolled (ie, Screening failures), only SAEs (Section 11.2.2) will be reported (Section 11.7.1).

If, at any time after the patient has completed participation in the study (see Section 8.4), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the IPs (Section 11.4.1) or is possibly/probably or definitely related to a study procedure (Section 11.4.2), then the event and any known details must be reported promptly to the Sponsor.

11.2. Definition of Adverse Events

11.2.1. Adverse Event

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 whether or not considered related to the IP.

Adverse events include:

- Symptoms described by the patient 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

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

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, ie, does not include an AE that had it occurred in a more severe form, might have caused death.

- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected due to protocol procedures, based on Investigator judgment, will be considered prolonged hospitalizations.
- **Persistent or significant disability/incapacity**: An AE that results in persistent or significant disability or disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IPs.
- **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 patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.2.3. Adverse Events of Special Interest

Any AE (serious or nonserious) that is of scientific and medical interest specific to study treatment, for which ongoing and rapid communication by the Investigator to the sponsor is appropriate.

The adverse events of special interest (AESIs) for this study are listed below. All AESIs should be reported as AEs to the sponsor within 24 hours of awareness irrespective of AE seriousness including the events below that are based on lab abnormalities.

11.3. Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator should be recorded as an AE. A clinically significant abnormality is an abnormality confirmed by repeat testing, that is changed sufficiently from Screening/Baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis should be recorded as the AE term, rather than the laboratory abnormality. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

11.4. Classification of Adverse Events

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

11.4.1. 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.

11.4.2. 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.

11.4.3. 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.

11.4.4. 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 patient's usual activities.
Moderate:	The event interferes with the patient's usual activities.
Severe:	The event prevents the patient from undertaking their usual activities and requires therapeutic intervention or cessation of the study treatment.

11.5. Outcome

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

11.6. 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. Categories for action taken regarding study treatment will include none, drug interrupted, drug withdrawn, and not applicable.

11.6.1. 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 golodirsen.

11.6.1.1. Suspected Unexpected Serious Adverse Reactions

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

11.7. Recording Adverse Events

All AEs from the time of informed consent/assent through the last Follow-up visit will be recorded in each enrolled patient's CRF. 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 IPs or study procedure or underlying disease; and any action taken will be recorded. Resolution occurs when the patient 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 patient'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.

11.7.1. Reporting Serious Adverse Events and AESIs

It is the responsibility of the Investigator that reporting is done adequately. In order to meet reporting timelines, the study site is obligated to report any SAE(s) to the Sponsor or designee immediately and no later than 24 hours after receiving information of an event that meets at least one of the criteria for seriousness as defined in Section 11.2.2 or for AESIs as defined in Section 11.2.3.

Sarepta Therapeutics, Inc., Pharmacovigilance Department
Email: PPD
US Fax: PPD
EU Fax: PPD

11.8. Special Situations

11.8.1. 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 or golodirsen.

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

11.8.2. Overdose

Currently, there is no basis for determining a clinically meaningful definition of overdose for casimersen or golodirsen. Therefore, as a preliminary criterion, any dose CCI above the assigned dose level will be considered an overdose.

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

11.8.3. 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.

11.9. 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 IPs and/or study procedure and/or underlying disease
- Determination of the onset and end date of each event
- Provide initial report on all SAEs within 24 hours of first knowledge to the Sponsor or designee
- Provide follow-up information on SAEs in a timely and proactive manner
- Respond to queries regarding AEs and SAEs in a timely manner
- Ensure source documentation for all AEs are accurate and complete
- Ensure that the study is conducted as defined in this document

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

11.10. Responsibilities of the Sponsor

The responsibilities of the study Sponsor (Sarepta Therapeutics, Inc.) include, but are not limited to the following:

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

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 will be provided by a contract research organization. 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 Help Text. A CRF must be completed for each patient 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 from the Sponsor or a representative of the Sponsor 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. Investigator Site Files (ISF) will be reviewed for compliance throughout the study.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by IRBs/IECs or regulatory authorities before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all study records, CRFs, patient medical records and other source documentation, IPs dispensing records and IPs 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 Sponsor, and to the appropriate regulatory authority inspectors.

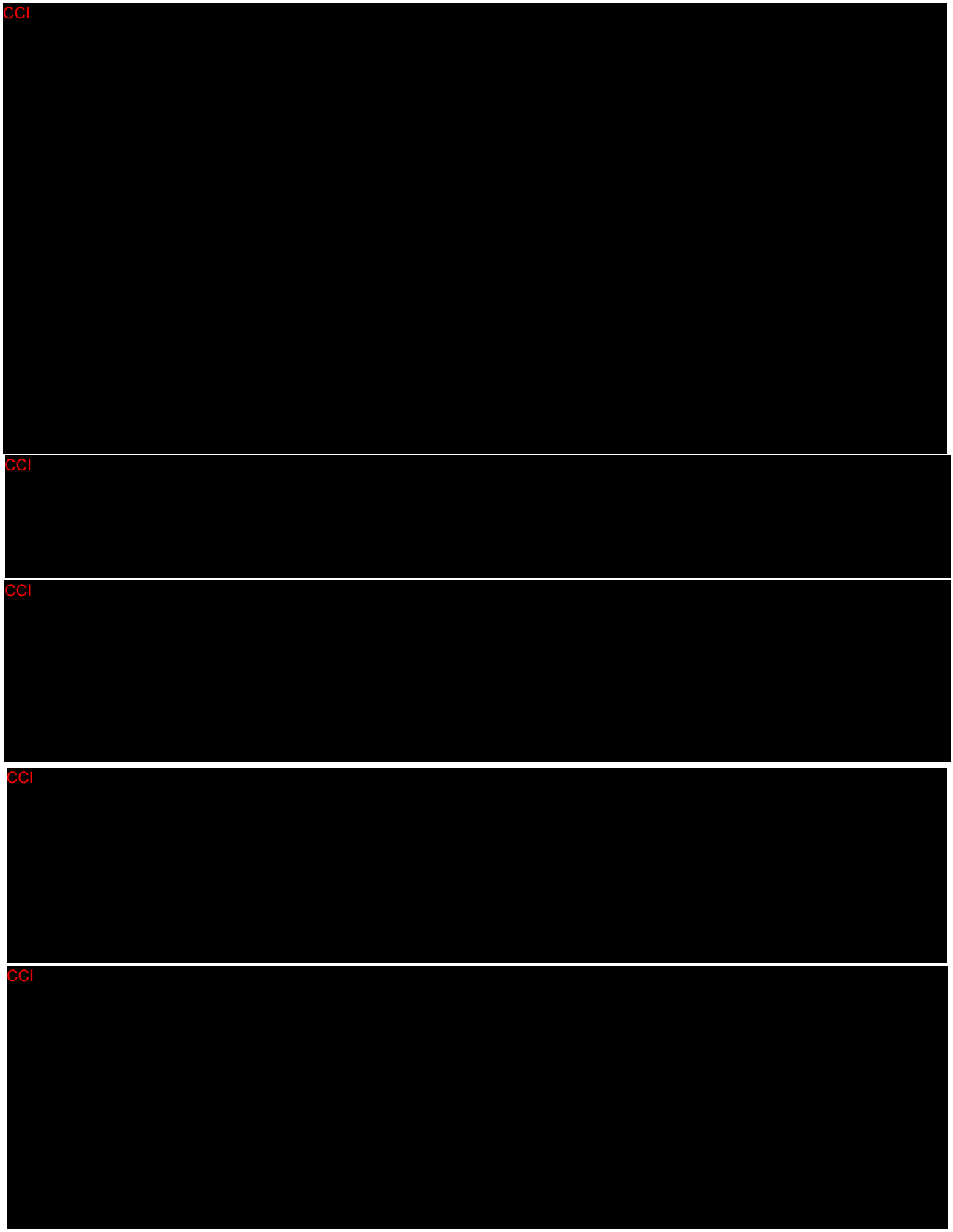
12.3. Retention of Study Documents

At study completion, all CRF data for an individual site will be copied onto a compact disc and provided to the Investigator for retention in the ISF. 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 Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. 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.

Patient 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 [redacted] years.

If offsite archiving is used, all records must be retrieved and made available for review at the time of an audit or regulatory authority inspection.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CCI [redacted]

13.4.5.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be classified as treatment-emergent and nontreatment-emergent (nonTEAE). A TEAE is defined as an AE that emerges during treatment, having been absent pre-treatment, or worsens relative to the pretreatment state. A treatment-related TEAE will be defined as a TEAE that the Investigator considers definitely related or possibly/probably related to the study treatment.

CCI [redacted]

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14. ETHICS AND OTHER SPECIAL REQUIREMENTS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice. This study will comply with the requirements that are enunciated in the European Clinical Trial Directive 2001/20/EC and in the United States Code of Federal Regulations (21 CFR 56).

14.1. Institutional and Ethics Review

Before enrollment of patients into the study, the protocol and informed consent, assent, and parental informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the study drug during the study. The IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority must be retained within the study regulatory files.

14.2. Written Informed Consent

Written informed consent and assent, if applicable, from each patient and/or parent/legal guardian must be obtained before any study-specific evaluations are performed. A copy of the signed informed consent and assent, if applicable, form will be given to the patient and/or parent/legal guardian; the Investigator will retain the original copies of these documents.

The informed consent/assent documents, as prepared by the Sponsor or designee, must be reviewed and approved by the IRB/IEC 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 21 CFR 50.25 and ICH GCP E6 (R2) and local requirements, as applicable.

14.3. 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 patient and that are deemed by the Investigator as crucial for the safety and well-being of that patient may be instituted for that patient only and documented as deviations. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB/IEC; however, the IRB/IEC and Medical Monitor must be notified in writing as soon as possible in accordance with the IRB/IEC policies after the departure has been made.

14.4. Confidentiality

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the study monitor, with the exception of

information that is required by law or regulations to be disclosed to the IRB/IEC, the patient, the patient'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.

Patients will be referenced by an assigned patient identification number on the CRFs and other data collected by the Sponsor. The Investigator must maintain all documents related to the study that identify the patient (eg, the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB/IEC, the study monitor, or the Sponsor or its representatives.

15. STUDY DOCUMENTATION AND GENERAL INFORMATION

15.1. 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, Pharmacy Manual, final protocol, and/or ISF, must be kept onsite in a designated study site file.

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

15.2. General Information

The Investigator should be familiar with and refer, as needed, to the current Investigator's Brochure along with subsequent Safety Alert Letters, Pharmacy Manual, Laboratory Manual, and all other study-specific information that is provided during the study initiation visit or throughout the duration of the study.

15.3. Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics, Inc. At the conclusion of this clinical study, a clinical study report will be prepared. In addition, a manuscript may be prepared for publication in a reputable scientific journal under the direction of the Sponsor. The Sponsor will publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by the Sponsor, as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov and the EudraCT public website. After completion of the study, results will be disseminated through these public websites.

15.4. Publication Policy

All unpublished information given to the Investigator by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor. The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations.

The publications committee established by the Sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the Clinical Trial Agreement.

15.5. Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the IPs, the Investigator, clinical site pharmacist or pharmacy designee should contact the Sponsor or designated contract research organization.

16. LIST OF REFERENCES

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