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ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

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PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443
Study Phase	Phase 3
Indication	Spinal Muscular Atrophy (SMA)
Treatment Group	12 mg nusinersen (also known as BIIB058 and ISIS 396443) **Note**: For the purposes of this protocol, when referring to "study drug," nusinersen will be used in place of ISIS 396443. When referring to the Protocol Title or previous ("index") studies, ISIS 396443 will be used. The term "study treatment" refers to administration of nusinersen or the sham procedure during the blinded portion of the study.
Objectives	Primary Objective To evaluate the long-term safety and tolerability of nusinersen administered by intrathecal (IT) injection to subjects with SMA who previously participated in investigational studies of ISIS 396443 Secondary Objective To examine the long-term efficacy of nusinersen administered by IT injection to subjects with SMA who previously participated in investigational studies of ISIS 396443 [redacted]
Number of Subjects	Up to 292 subjects who previously participated in investigational studies ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, or 232SM202 may be eligible to enroll in this study.
Important Study Design Update	**Change in Dosing Schedule Note**: From the Protocol Version 2.0, regardless of their original dosing visit schedule (i.e., 6-month dosing schedule), all subjects will begin receiving maintenance doses of nusinersen every 4 months upon entering the modified maintenance dosing period of the study; this updated maintenance dosing schedule will henceforth be referred to as the Modified Maintenance Dosing Regimen (MMDR) dosing period. **Unblinding of Index Studies ISIS 396443-CS3B and ISIS 396443-CS4:** Index studies ISIS 396443-CS3B and ISIS 396443-CS4 have

	been unblinded, and treatment assignments for subjects in the applicable groups (Groups 1A, 2A, 1B, and 2B) were released. Therefore, there was no longer any reason to continue the blinded loading dose period in a blinded fashion. For subjects in Group 1A and Group 2A who were receiving active drug (i.e., nusinersen) within the blinding loading dose period, visits continued to occur as scheduled, with all predose and postdose assessments performed. For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period, all visits and predose assessments were continued per the protocol; however, the sham procedure and all postdose procedures were not performed for those applicable visits.
Study Design	This is an open-label extension study in subjects with SMA who previously participated in investigational studies of ISIS 396443. The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of nusinersen (12 mg) administered as IT injections by lumbar puncture (LP) over a period of 5 years from MMDR Day 1 (End-of-Study [EOS] Evaluation Visit to occur at approximately MMDR Day 1800 [±14 days]), or as determined by the Sponsor (via early termination or amendment to extend). For the purposes of this protocol, investigational studies of ISIS 396443, henceforth referred to as index studies, include studies ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, and 232SM202. This study will consist of Screening, Treatment, and Post-Treatment Follow-Up Periods and an EOS Evaluation Visit. After informed consent/assent is obtained, subjects will undergo a screening evaluation up to 21 days prior to the first dose administration, during which their eligibility for the study will be determined. Subjects who meet the eligibility criteria will be enrolled in the study. Subjects who entered the study after completing the double-blind studies ISIS 396443-CS3B and ISIS 396443-CS4 (i.e., subjects in Groups 1A, 1B, 2A, and 2B) completed a blinded loading dose period and then transitioned to an open-label MMDR period. Subjects who were already enrolled in ISIS 396443-CS11 (SHINE) and had already participated in the blinded loading dose period continued their blinded loading dose/sham schedule through the last scheduled dose in that loading dose period and then transitioned to the open-label MMDR dosing schedule at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). The schedule for other MMDR visits should be based on MMDR Day 1.

	During the blinded loading dose period, subjects who previously received the sham procedure during the index study received blinded injections of nusinersen in order to achieve the full loading regimen of study treatment, and subjects who previously received nusinersen during the index study received a combination of nusinersen injections and sham procedures. This design was necessary to protect the full blind of the treatment assignment in the ongoing index studies. Subjects who entered the study after completing open-label studies ISIS 396443-CS12 and ISIS 396443-CS3A (i.e., subjects in Groups 3 and 4) will enter directly into the open-label MMDR period at MMDR Day 1. Subjects who were already enrolled in ISIS 396443-CS11 and were already receiving maintenance doses according to the original maintenance schedule transitioned to MMDR Day 1 at their next study visit (regardless of how many maintenance doses already received in the original schedule), which was scheduled <u>as close as possible</u> to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). Subjects entering the study after completing open-label study 232SM202 (i.e., subjects in Group 5) will enter directly into the open-label MMDR period at MMDR Day 1. The schedule for other MMDR visits should be based on MMDR Day 1. MMDR Days will be calculated by adding 120 days (±14 days) to the date of the last dosing visit and will begin at MMDR Day 1 (for all subjects entering the MMDR dosing schedule). The MMDR dosing schedule will consist of MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 (±14 days) until the EOS Evaluation/Early Termination (ET) Visit. The EOS Evaluation Visit will occur 4 months after the last open-label maintenance dose of nusinersen on approximately MMDR Day 1800 (±14 days). <u>Dosing for ISIS 396443-CS3B</u> • <u>Group 1A</u>: Subjects who entered the study after receiving sham procedures in the double-blind study ISIS 396443-CS3B received 4 loading doses of nusinersen administered by IT injection on Days 1, 15, 29, and 64 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1. • <u>Group 1B</u>: Subjects who entered the study after receiving nusinersen in the double-blind study ISIS 396443-CS3B received 3 sham procedures on Days 1, 15, and 64 and 1 loading dose of nusinersen administered by IT injection on Day 29 (±1 day) followed by maintenance doses of nusinersen approximately every

	4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1. Dosing for ISIS 396443-CS4 • Group 2A: Subjects who entered the study after receiving sham procedures in the double-blind study ISIS 396443-CS4 received 3 loading doses of nusinersen administered by IT injection on Days 1, 29, and 85 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1. • Group 2B: Subjects who entered the study after receiving nusinersen in the double-blind study ISIS 396443-CS4 received 2 loading doses of nusinersen administered by IT injection on Days 1 and 85 and 1 sham procedure on Day 29 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1. Dosing for ISIS 396443-CS12 • Group 3: Subjects who entered the study after receiving nusinersen in the open-label study ISIS 396443-CS12 received maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who received open-label maintenance doses of nusinersen in ISIS 396443-CS11 were transitioned to the MMDR dosing period at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). Dosing for ISIS 396443-CS3A • Group 4: Subjects who entered the study after receiving nusinersen in the open-label study ISIS 396443-CS3A received maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who received open-label maintenance doses of nusinersen in ISIS 396443-CS11 were transitioned to the MMDR dosing period at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). Dosing for 232SM202

	• Group 5: Subjects entering the study after receiving nusinersen during the open-label phase of Study 232SM202 (i.e., Part 2) will receive maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. All subjects will undergo predose evaluations according to the schedule of procedures and will remain at the study center for at least 1 hour after the study drug dosing/sham procedure for safety monitoring; the subjects can be discharged at the discretion of the Site Investigator and in compliance with the institutional requirements once they adequately recover from the dosing procedure. [redacted] Safety monitoring by telephone contact will occur to monitor the subjects' condition 1 to 14 days postdose and every other month (±14 days) thereafter throughout the duration of the study, except for the months during which a study visit occurs. Subjects who discontinue treatment will complete an early termination visit 4 months (+14 days) after administration of the last dose of nusinersen, unless consent is withdrawn. Subjects who discontinue from the study early will not be replaced.
Study Population and Main Criteria for Inclusion/Exclusion	Inclusion Criteria: Subjects must meet all of the following criteria at Screening to be eligible: 1. Signed informed consent of parent or guardian and signed informed assent of subject, if indicated per subject's age and institutional guidelines. 2. Completion of the index study in accordance with the study protocol or as a result of Sponsor decision (e.g., early termination of the index study) within the preceding 16 weeks. 3. Ability to complete all study procedures, measurements, and visits, and parent/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator. 4. Subjects who, in the opinion of the Investigator, have reached reproductive maturity, must satisfy one of the following: • Females must have a negative pregnancy test at Screening and must agree to employ adequate contraceptive measures for the duration of the study. Acceptable contraception methods are restricted to abstinence*, barrier contraceptives,

	intrauterine contraceptive devices, or licensed hormonal products. • Males must be abstinent* for the duration of the study or must be using an acceptable contraceptive method (i.e., use a condom together with spermicidal foam/gel/film/cream/suppository). *Abstinence is only acceptable as true abstinence (i.e., when this is representative of the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., abstinence for the duration of the study) and withdrawal are not acceptable methods of contraception. <u>Exclusion Criteria</u>: Subjects meeting any of the following criteria are not eligible for the study: 1. Have any new condition or worsening of existing condition, which in the opinion of the Investigator would make the subject unsuitable for enrollment or could interfere with the subject participating in or completing the study. 2. Clinically significant abnormalities in hematology or blood chemistry parameters or electrocardiogram (ECG), as assessed by the Site Investigator, at the Screening Visit that would render the subject unsuitable for participation in the study. 3. The subject's parent or legal guardian is unable to understand the nature, scope, and possible consequences of the study, or does not agree to comply with the protocol's schedule of procedures. 4. The subject's parent or legal guardian is not willing or able to meet guidelines in the consensus statement for standard of care in SMA or provide nutritional and respiratory support throughout the study. NOTE: Routine vaccinations and respiratory syncytial virus (RSV) prophylaxis are recommended per consensus guidelines on standard of care but are not required for study enrollment. Subjects who are not current on vaccinations or who are not receiving RSV prophylaxis, but otherwise meet study inclusion criteria, will be considered eligible for study enrollment. 5. Treatment with another investigational agent, biological agent, or device within 1 month of Screening or 5 half-lives of study agent, whichever is longer.
Study Treatment and Administration	Nusinersen (2.4 mg/mL) will be administered as an IT LP injection. All subjects will receive the full 12-mg dose of the study drug (5 mL).

	During the blinded loading dose period, the study treatment dosing or sham procedures were performed in a dedicated room and administered by dedicated study personnel who were unblinded to the treatment assignment; this was not any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors), and the key study personnel or the parents were not present during the procedure to ensure blinding. The sham procedure consisted of a small needle prick on the lower back at the location where the LP injection was normally made. The needle broke the skin, but no LP injection or needle insertion occurred. The site of the needle prick was covered in the same manner as that of the LP injection, thus simulating the appearance of an LP injection. If anesthesia or sedation was used for the LP procedure in nusinersen-treated subjects at an individual study center, in order to maintain the blind, minimal sedation (i.e., a low dose of an anxiolytic) was used for the sham procedure, following institutional procedures. Subjects who received the sham procedure were kept in the procedure room for the same amount of time as that for subjects who were administered study treatment, thus simulating the time period of a study treatment administration procedure. As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, there was no longer any reason to continue the blinded loading dose period in a blinded fashion. For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period since the time of unblinding, the sham procedure and all postdose procedures described above were not performed for those applicable visits. During these visits, study drug was not administered, and these visits were considered safety visits.
Criteria for Evaluation of Study Objectives For All Groups/Subjects	<u>Safety and Tolerability</u> • Adverse events (AEs) and serious adverse events • Vital signs and weight • Neurological examinations • Clinical laboratory tests (serum chemistry, hematology, urinalysis, and urine total protein) • Coagulation parameters (activated partial thromboplastin time and international normalized ratio) • ECGs • Use of concomitant medications <u>Efficacy</u>

	• Achievement of motor milestones (World Health Organization motor milestones and/or Section 2 of Hammersmith Infant Neurological Examination) • Time to death or permanent ventilation (tracheostomy **or** ≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event) • Percentage of subjects not requiring permanent ventilation • Change from baseline in applicable motor function assessments: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease, Hammersmith Functional Motor Scale – Expanded, Revised Upper Limb Module, 6-Minute Walk Test, and contracture assessment • Change from baseline in compound muscle action potential (CMAP) • Growth parameters • Proportion of CMAP responders • Number of motor milestones achieved per subject • Proportion of subjects who achieved standing alone • Proportion of subjects who achieved walking with assistance • Number of serious respiratory events • Number and length of hospitalizations • Change from baseline in Cobb-Angle on X-ray of the thoracolumbar spine • Changes in quality of life assessments: Pediatric Quality of Life Inventory, and/or Assessment of Caregiver Experience with Neuromuscular Disease • Disease-related hospitalizations and AEs • Survival rate [redacted]

	[redacted]
Safety Monitoring	Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor, with data cuts at regular intervals.
Statistical Considerations	The sample size is based solely on the number of subjects enrolled in ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, and 232SM202 studies who may be eligible for participation in this study.
Sponsor	Biogen

STUDY GLOSSARY

Abbreviation /Acronym	Definition
6MWT	6-Minute Walk Test
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
[redacted]	[redacted]
BiPAP	bilevel positive airway pressure
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
CMAP	compound muscle action potential
CNS	central nervous system
CPAP	continuous positive airway pressure
CRF	case report form
CSF	cerebrospinal fluid
[redacted]	[redacted]
DHA	Directions for Handling and Administration
[redacted]	[redacted]
ECG	electrocardiogram
EOS	End-of-Study
ET	Early Termination
FL	full-length
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

INR	international normalized ratio
IRB	Institutional Review Board
IT	intrathecal
ITT	Intent-to-Treat
IxRS	Interactive Voice/Web Response System
LP	lumbar puncture
MedDRA™	Medical Dictionary for Regulatory Activities
MMDR	Modified Maintenance Dosing Regimen
[redacted]	[redacted]
[redacted]	[redacted]id
NCS	not clinically significant
PedsQL™	Pediatric Quality of Life Inventory
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RSV	respiratory syncytial virus
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
snRNA	small nuclear ribonucleic acid
SUSAR	suspected unexpected serious adverse reaction
US	United States
[redacted]	[redacted]
[redacted]	[redacted]
WHO	World Health Organization

1. OBJECTIVES

The objective of this open-label extension study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated 12-mg doses of ISIS 396443 (also known as BIIB058 and nusinersen) administered as intrathecal (IT) injections by lumbar puncture (LP) in subjects with spinal muscular atrophy (SMA) who previously participated in investigational studies of ISIS 396443.

Note: For the purposes of this protocol, when referring to "study drug," nusinersen will be used in place of ISIS 396443. When referring to the Protocol Title or previous ("index") studies, ISIS 396443 will be used. The term "study treatment" refers to administration of nusinersen or the sham procedure during the blinded portion of the study.

1.1. Primary Objective

To evaluate the long-term safety and tolerability of nusinersen administered by IT injection to subjects with SMA who previously participated in investigational studies of ISIS 396443

1.2. Secondary Objective

To examine the long-term efficacy of nusinersen administered by IT injection to subjects with SMA who previously participated in investigational studies of ISIS 396443

[redacted]

2. BACKGROUND AND RATIONALE

2.1. Spinal Muscular Atrophy

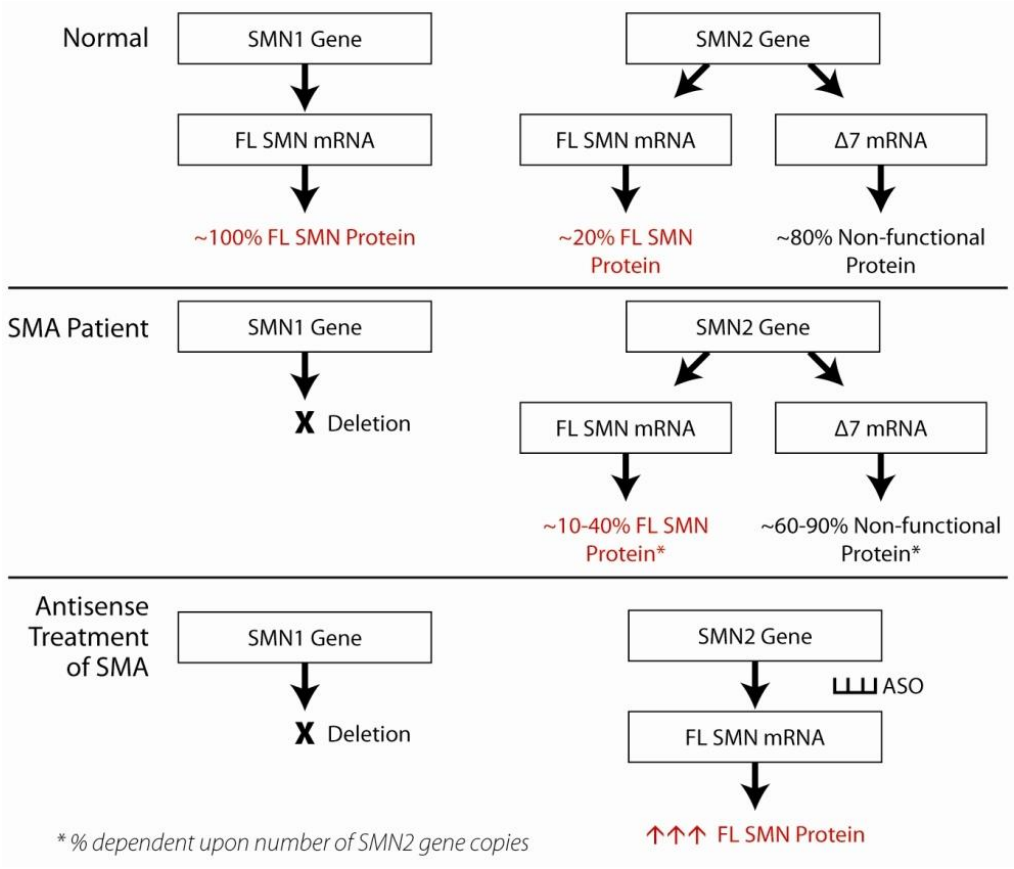
SMA is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. Despite being a rare disease, prior to the availability of therapeutic treatment options, SMA was one of the most common genetic causes of death in infants, with a reported birth prevalence ranging from 8.5 to 10.3 per 100,000 live births [Arkblad 2009; Jedrzejowska 2010; Prior 2010; Sugarman 2012; Tassie 2013]. The natural history of SMA includes 4 major recognized phenotypes that are dependent on age of onset and achieved motor abilities. The most severe form, Type 1 SMA (equivalent to infantile-onset SMA), has a disease onset within the first few months of life; these children are never able to sit or walk and usually die from respiratory failure by 2 years of age. Later-onset SMA can generally be divided into Type 2 and Type 3 SMA. Patients with Type 2 SMA are able to sit but never walk unaided, with symptoms presenting between 6 and 18 months of age. Patients with Type 3 SMA are able to sit and walk but may become severely and increasingly disabled. Patients with adult-onset SMA (Type 4) have an age of onset over 18 years and have normal life expectancies.

In 95% of patients with SMA, a deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q11-q13 is found; with the remaining 5% attributable to small mutations in the same gene [Helmken 2003; Lefebvre 1995]. *SMN1* lies in the telomeric portion of an inverted duplication of a region of chromosome 5. The centromeric half of the duplication contains a homologous gene named survival motor neuron 2 (*SMN2*) that differs from *SMN1* by 5 nucleotides. The open reading frames for both genes encode for proteins with identical amino acid sequences. Survival motor neuron (*SMN*) gene transcripts, similar to most mammalian transcripts, undergo alternative splicing in which certain exons are either included or excluded from the mature protein coding transcripts [Keren 2010]. In particular, exon 7 of the *SMN1* gene is alternatively spliced with 90% to 95% of the mature messenger ribonucleic acid (mRNA) transcripts derived from the *SMN1* gene containing exon 7, and 5% to 10% of transcripts missing exon 7. The transcripts missing exon 7 (often referred to as Δ7) produce a truncated protein that is defective and unstable [Cho and Dreyfuss 2010]. One of the 5 nucleotide differences between *SMN1* and *SMN2*, a C to T substitution occurs in exon 7 of the *SMN2* gene resulting in an alternative splicing pattern that favors skipping of exon 7. The result is that as much as 90% of the transcripts produced from *SMN2* are missing exon 7. The remainder, SMN2 transcripts containing exon 7, produces a full-length (FL) protein product identical to the SMN1 protein because the C to T substitution is silent. Humans have a variable copy number of the *SMN2* gene (0 to 8 copies) [Wirth 2006]. The number of *SMN2* copies and the resulting amount of FL-SMN protein expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlates with SMA disease severity, and thus, *SMN2* is a key modifier of disease phenotype [Coovert 1997; Feldkötter 2002; Lefebvre 1997; Prior 2004].

2.2. Therapeutic Rationale

Since the number of *SMN2* gene copies and the resulting amount of SMN protein is correlated with disease onset and severity, a therapeutic approach predicted to benefit patients with SMA is to increase the levels of FL-SMN2 pre-mRNA by restoring the splicing pattern that gives rise to FL-SMN2 mRNA. Increasing inclusion of exon 7 in the SMN2 transcript will increase FL-SMN protein levels and SMN protein activity. A therapeutic strategy for promoting exon 7 inclusion is through the use of antisense oligonucleotides (ASOs) [see Figure 1].

Figure 1: ASO Therapeutic Approach for Treatment of SMA



ASO = antisense oligonucleotide; FL = full-length; mRNA = messenger ribonucleic acid; SMA = spinal muscular atrophy; SMN = survival motor neuron; SMN1 = survival motor neuron 1; SMN2 = survival motor neuron 2.

The known potential risks associated with nusinersen are detailed in the Guidance to Investigator section of the Investigator's Brochure.

2.3. Nusinersen

2.3.1. Mechanism of Action

Nusinersen is a fully modified, 2′-*O*-2-methoxyethyl (MOE) chimeric ASO drug designed to bind to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript. The region of the pre-mRNA targeted by nusinersen is normally occupied by heterogeneous nuclear ribonucleoproteins (hnRNP) A1/2 proteins, masking the U1 small nuclear ribonucleic acid (snRNA) binding site at the 5′-exon-intron junction of exon 7, and is referred to as ISS-N1. U1 snRNA base pairs to the sequences that define the 5′-splice site, which is thought to be one of the first steps that initiate splicing of an intron. Nusinersen displaces the hnRNP A1/2 proteins from the pre-mRNA binding site, allowing U1 snRNA to bind to the exon-intron junction and promote assembly of the spliceosomal complex, thus promoting inclusion of exon 7 into the mRNA, which results in production of FL-SMN protein.

2.3.2. Chemistry

Chemically, nusinersen is a synthetic oligomer of 18 nucleotides (i.e., an 18-mer) that are connected sequentially by phosphorothioate linkages. Each of the 17 internucleotide linkages is a 3′-*O* to 5′-*O* phosphorothioate diester. The 18 sugar residues are uniformly modified with 2′-*O*-(2-MOE). These MOE-modified nucleotides confer (1) increased affinity to the target mRNA [McKay 1999], (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) [Geary 2003], and (3) amelioration of some of the high-dose toxicities associated with ASO containing only the phosphorothioate linkages [Henry 2000].

The sequence of nusinersen is written as follows:

5′-^{Me}U^{Me}CA^{Me}C^{Me}U^{Me}U^{Me}U^{Me}CA^{Me}UAA^{Me}UG^{Me}C^{Me}UGG- 3′

where A and G are 2′-*O*-(2-methoxyethyl)nucleosides, ^{Me}C is 5-methyl-2′-*O*-(2-methoxyethyl) cytidine, and ^{Me}U designates 5-methyl-2′-*O*-(2-methoxyethyl)uridine.

2.3.3. Nonclinical Experience

Nusinersen was identified after an extensive screen of greater than 500 2′-MOE oligonucleotides in in vitro splicing assays, reporter gene assays, and fibroblast cells from patients with SMA [Hua 2007; Hua 2008]. Data have shown that nusinersen promotes a concentration-dependent increase in FL transcripts (including exon 7) in patients' fibroblast cells, achieving greater than 90% FL-SMN2 transcripts and forming nuclear structures, called gems, known to contain SMN protein. In a mild mouse model of SMA, nusinersen promoted inclusion of exon 7 in the SMN2 transgene in a variety of peripheral tissues when dosed systemically [Hua 2007] and in central nervous system (CNS) tissue, including spinal cord, when injected into the lateral ventricle. Nusinersen produced greater than 90% exon 7 inclusion in the transgenic mice and increased SMN protein production in motor neurons, resulting in the appearance of gems in motor neurons. These studies were extended to a more severe mouse model of SMA (SMA Δ7) [Le 2005], where the delivery of drug through the CNS produced a dose-dependent effect on SMN2 exon 7 inclusion, SMN protein production, and survival. These mice treated with nusinersen demonstrated improved weight gain; improved muscle morphology, muscle strength, and motor coordination; and improved morphology of the motor neuron junctions [Passini 2011]. Further, nusinersen was shown to distribute widely in the CNS following IT administration in monkey [Passini 2011].

The PK and toxicity of nusinersen were assessed 1) following single IT lumbar bolus injections (1 to 7 mg) in adult monkeys, 2) following 14 weeks (with a 4-week interim sacrifice) of repeated IT lumbar bolus injections (0.3 to 3 mg weekly or every other week) in juvenile monkeys, and 3) following 53 weeks of repeated IT lumbar bolus injections in juvenile monkeys. In addition, a dedicated PK study in adult monkeys was performed to assess the half-life of nusinersen in CSF, tissues, and plasma.

Main findings from these studies are as follows:

- Dose-dependent concentrations of nusinersen were measured in spinal cord, brain, CSF, liver, and plasma of adult and juvenile monkeys and in kidney of juvenile monkeys.
- Tissue concentrations of nusinersen were measurable in all spinal cord and brain sections examined indicating broad distribution associated with single and repeated IT slow bolus administration.
- Highest tissue concentrations of nusinersen in monkey were generally observed in lumbar spinal cord, consistent with the IT route of administration.
- Systemic tissue (liver and kidney) concentrations were measurable but low, relative to parenteral administration.
- Neurological changes, assessed through evaluation of general sensory and motor functions, cerebral reflexes, and spinal reflexes, were limited to acute transient lower spinal reflex deficits in a few monkeys at the highest dose levels evaluated, 2 to 8 hours following dose administration. These effects were not observed in most monkeys within 48 hours postdose. The clinical signs were directly associated with administration of large amounts of drug to the lumbar spinal cord at the higher doses examined in these studies and were not cumulative with continued dosing through 14 or 53 weeks.
- No adverse treatment-related histologic changes were observed in the CNS. There was no evidence of neuronal cell death or degeneration in the brain or spinal cord through 4 weeks of treatment.
- Histologic changes observed in the CNS after 14 weeks of treatment included slight to minimal vacuolation in a focal region of the inferior hippocampus (1 mg/dose × 10 doses and 3 mg/dose × 15 doses) and was associated with very rare neuronal or glial cell necrosis at the 3 mg/dose only.
- Histologic changes observed in the CNS after 53 weeks of treatment included slight to mild vacuolation in a focal region of the inferior hippocampus (1 and 4 mg/dose × 13 doses) and was associated with non-neuronal cell necrosis (graded slight, 1 of 5 males at the 1 mg/dose × 13 doses and 3 of 5 males at the 4 mg/dose × 13 doses). None of these changes were deemed to be adverse as there were no sustained decrements in neurological function or learning ability, and the necrotic changes observed were slight, limited to a single sex, and did not affect neurons.
- Pro-inflammatory effects were limited in adult monkeys receiving single doses of nusinersen to very slight mononuclear cell infiltrates in the meninges of the brain and were similar in nature to those commonly observed in control animals from other IT studies. Pro-inflammatory effects in juvenile monkeys receiving 4 weeks of treatment were limited to observations in a single animal and included scattered, slight microglial foci and slight perivascular infiltrates in the brain and spinal cord. Pro-inflammatory effects in juvenile monkeys receiving 14 weeks of treatment were limited to observations of perivascular macrophages in the central canal of the spinal cord in a single female in the high-dose group and an increase of infiltrates in the

cerebral meninges in the mid- and high-doses groups (1 mg/dose × 10 doses and 3 mg/dose × 15 doses). None of these findings were deemed to be adverse and were reversible following the cessation of treatment. No local or systemic pro-inflammatory effects were observed following 53 weeks of treatment.

- Nusinersen did not produce any changes in clinical pathology parameters, complement activation or indications of systemic toxicity.
- No evidence of genotoxicity was observed in the Ames bacterial mutagenicity and in vitro chromosomal aberrations in Chinese hamster ovary cells.

Detailed results from these nonclinical studies conducted with nusinersen can be found in the nusinersen Investigator's Brochure.

2.3.4. Clinical Experience

Detailed information concerning the clinical studies conducted with nusinersen can be found in the current version of the Investigator's Brochure. A summary is included below.

Nusinersen has been evaluated in a completed open-label, single-ascending-dose, Phase 1 study designed to assess the safety, tolerability, and PK of nusinersen in subjects with SMA (ISIS 396443-CS1). A single dose of nusinersen was administered by IT injection to patients with SMA 2 to 14 years of age. Four dose levels (1, 3, 6, and 9 mg) were evaluated sequentially. Each dose level was studied in a cohort of 6 or 10 subjects, where all subjects received nusinersen.

Nusinersen was evaluated in 7 additional completed studies, ISIS 396443-CS2, ISIS 396443-CS10, ISIS 396443-CS12, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS3A, and 232SM202, and is being evaluated in 4 additional ongoing studies, 232SM201, 232SM203, 232SM302, and 232SM404:

- Study ISIS 396443-CS2 (completed) was an open-label, multiple-ascending-dose study designed to assess the safety, tolerability, and PK of nusinersen in patients with later-onset SMA. Multiple doses of nusinersen, ranging from 3 to 12 mg, were administered by IT injection to patients with SMA 2 to 15 years of age at screening.
- Study ISIS 396443-CS10 (completed) was an open-label, single-dose, redosing study for patients with SMA who previously participated in Cohorts 2, 3, and 4 of Study ISIS 396443-CS1.
- Study ISIS 396443-CS12 (completed) was an open-label, multiple-dose study to assess the safety and tolerability of a 12-mg dose level of nusinersen administered by IT injection in patients with SMA who previously participated in Study ISIS 396443-CS2 or Study ISIS 396443-CS10.
- Study ISIS 396443-CS3B (completed) was a randomized, double-blind, sham-procedure controlled study designed to assess clinical efficacy, safety, and PK of nusinersen in patients with infantile-onset SMA. A 12-mg dose equivalent scaled by CSF volume is being evaluated in infants with symptomatic SMA less than or equal to 7 months of age at screening.

- Study ISIS 396443-CS4 (completed) was a randomized, double-blind, sham-procedure controlled study designed to assess clinical efficacy, safety, and PK of nusinersen in patients with later-onset SMA 2 to 12 years of age at screening.
- Study ISIS 396443-CS3A (completed) was an open-label, multiple-dose study designed to assess the safety, tolerability, and PK of nusinersen in patients with infantile-onset SMA. Multiple doses of nusinersen were administered by IT injection to infants with symptomatic SMA who were less than or equal to 7 months of age at screening. Two dose levels (6-mg and 12-mg dose equivalent scaled by CSF volume) were being evaluated sequentially.
- Study 232SM201 (ongoing) is an open-label study to assess the efficacy, safety, tolerability, and PK of multiple doses of nusinersen delivered by IT injection to subjects with genetically diagnosed and presymptomatic SMA.
- Study 232SM202 (completed) was a randomized, double-blind, sham-procedure controlled study to assess safety and tolerability and to explore efficacy of nusinersen administered by IT injection in subjects with SMA who were not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.
- Study 232SM203 (ongoing) is a 3-part dose-escalating and randomized control study to assess safety, efficacy, and PK of higher dose regimen of nusinersen in subjects with SMA. Part A is open-label with a 28-mg loading dose, Part B is double-blind with a 50-mg loading dose, and Part C is open-label with a 50-mg loading dose.
- Study 232SM302 (ongoing) is a long-term extension study; blinding only for subjects with SMA from Study 232SM203 Part B for the first dose in Study 232SM302 to assess the safety, efficacy, and PK of higher dose regimen of nusinersen.
- Study 232SM404 (ongoing) is an open-label, single-arm study in patients who previously received onasemnogene abeparvovec to assess the efficacy, safety, and PK of nusinersen.

The primary support for the safety and efficacy of nusinersen in the treatment of SMA derives from pre-planned interim analyses of Study ISIS 396443-CS3B, the sham-controlled study in subjects with infantile-onset SMA, and final analyses of Study ISIS 396443-CS4, the sham-controlled study in subjects with later-onset SMA. Subjects receiving nusinersen in these 2 studies achieved statistically significant improvements in motor function compared to subjects in the control arms.

Nusinersen has a favorable safety profile. Uncontrolled studies in presymptomatic infants (Study 232SM201), subjects with infantile-onset SMA (Study ISIS 396443-CS3A), and subjects with later-onset SMA (longitudinal analysis of studies ISIS 396443-CS2 and ISIS 396443-CS12) are highly supportive of the results of the pivotal efficacy studies (Studies ISIS 396443-CS3B and ISIS 396443-CS4) and provide evidence of the long-term benefit of treatment with nusinersen.

2.4. Rationale for Dose and Schedule of Administration

The proposed study will test the clinical efficacy, safety, tolerability, and PK of multiple doses of nusinersen administered by IT injection to subjects with SMA who previously participated in investigational studies of ISIS 396443. A single dose level of 12 mg of nusinersen will continue to be evaluated in this long-term extension study.

The nusinersen dose level and dose interval were selected based on nonclinical toxicology and PK observations from studies in monkey utilizing single- and repeat-dosing IT administration, consideration of the target tissue concentration anticipated for drug pharmacology, severity of SMA phenotype, and safety data in the completed and ongoing clinical studies of ISIS 396443 to date. Based on the pharmacology and PK results in SMA transgenic mice, it was estimated that the target tissue concentration to produce 50% to 90% SMN2 exon 7 inclusion is between 2 and 10 µg/g spinal cord tissue. Nonclinical studies in juvenile monkeys receiving IT doses of nusinersen showed a resulting gradient of distribution of nusinersen along the spinal cord, with mean lumbar spinal cord concentrations ranging from 1.6- to 2.3-fold and 2.0- to 3.5-fold higher than thoracic and cervical spinal cord levels, respectively. The dose level selected for this multiple-dose clinical study (12 mg nusinersen) is predicted to achieve levels at the high end of this range (approximately 10 µg/g lumbar and 3 µg/g cervical spinal cord tissue concentrations), following the first dose.

The loading dose interval was selected as the dose interval based on the nonclinical PK and pharmacology data to achieve and maintain nusinersen spinal cord tissue levels that are predicted to be within the upper end of the pharmacologically active range by Day 64 in subjects with the more severe infantile-onset SMA phenotype (predicted to be approximately 30 µg/g lumbar and 10 µg/g cervical spinal cord tissue concentrations) and by Day 85 in subjects with the less severe later-onset SMA phenotype (predicted to be approximately 24 µg/g lumbar and 8 µg/g cervical spinal cord tissue concentrations), while at the same time considering subject safety and convenience for repeated LP IT injections.

The maintenance dose intervals were selected based on nonclinical PK and pharmacology data and clinical PK data from subjects in ongoing and completed clinical studies with the goal of maintaining the spinal cord tissue levels of nusinersen at a steady-state level within the estimated pharmacologically active range. The elimination half-life of nusinersen from human CSF is approximately 135 to 177 days and was estimated based on a limited number of postdose levels. Although CNS tissue half-life cannot be measured in humans, the median terminal elimination half-life was measured in the CNS tissue of adult monkeys and found to be 116 days, approximately 4 months. Because the site of action of nusinersen is within the CNS tissues, these findings support maintenance doses administered every 4 months.

The maintenance dosing regimen of 12 mg every 4 months was implemented in a sham-controlled study in infantile-onset SMA (Study ISIS 396443-CS3B [ENDEAR]), an open-label study in presymptomatic SMA (Study 232SM201 [NURTURE]), an open-label study in infantile-onset SMA (Study ISIS 396443-CS3A), and a sham-controlled study in both infantile-onset and later-onset SMA (Study 232SM202 [EMBRACE]). For subjects in a sham-controlled study in later-onset SMA (Study ISIS 396443-CS4 [CHERISH]) and an open-label study in later-onset SMA (Study ISIS 396443-CS12) who are eligible to enroll in this open-label extension study (Study ISIS 396443-CS11), the maintenance dose schedule is shortened from every 6 months to every 4 months. The change is further supported by available data on the exposure-response relationship as well as efficacy and safety data from the clinical studies. Data from the population PK analyses suggest that higher CSF exposure leads to improvements in compound muscle action potential (CMAP), a measure of motor neuron health; Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND), a measure of motor strength; and motor milestones in symptomatic infants with infantile-onset SMA treated with nusinersen. While the clinical endpoints differ between populations, the relationship between increased CSF trough concentration or overall exposure and improved

functional outcomes is also anticipated in older subjects receiving more frequent maintenance doses. Because the majority of adverse events (AEs) in the clinical studies have been more likely related to the natural history of the disease rather than to nusinersen, any additional safety concerns associated with the Modified Maintenance Dosing Regimen (MMDR) are expected to be mostly limited to procedure-related AEs, such as post-lumbar puncture syndrome and back pain.

Additional details on dosing and expected CSF and tissue concentrations are summarized in the Investigator's Brochure.

3. EXPERIMENTAL PLAN

3.1. Study Design

This is an open-label extension study in subjects with SMA who previously participated in investigational studies of ISIS 396443. For the purposes of this protocol, investigational studies of ISIS 396443, henceforth referred to as "index" studies, include studies ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, and 232SM202.

3.1.1. Important Study Design Update

Change in Dosing Schedule Note: From the Protocol Version 2.0, regardless of their original dosing visit schedule (i.e., 6-month dosing schedule), all subjects will begin receiving maintenance doses of nusinersen every 4 months upon entering the MMDR period of the study. This updated maintenance dosing schedule will henceforth be referred to as the MMDR dosing period.

3.2. Number of Study Centers

This study will be conducted at up to 50 sites in up to 15 countries worldwide.

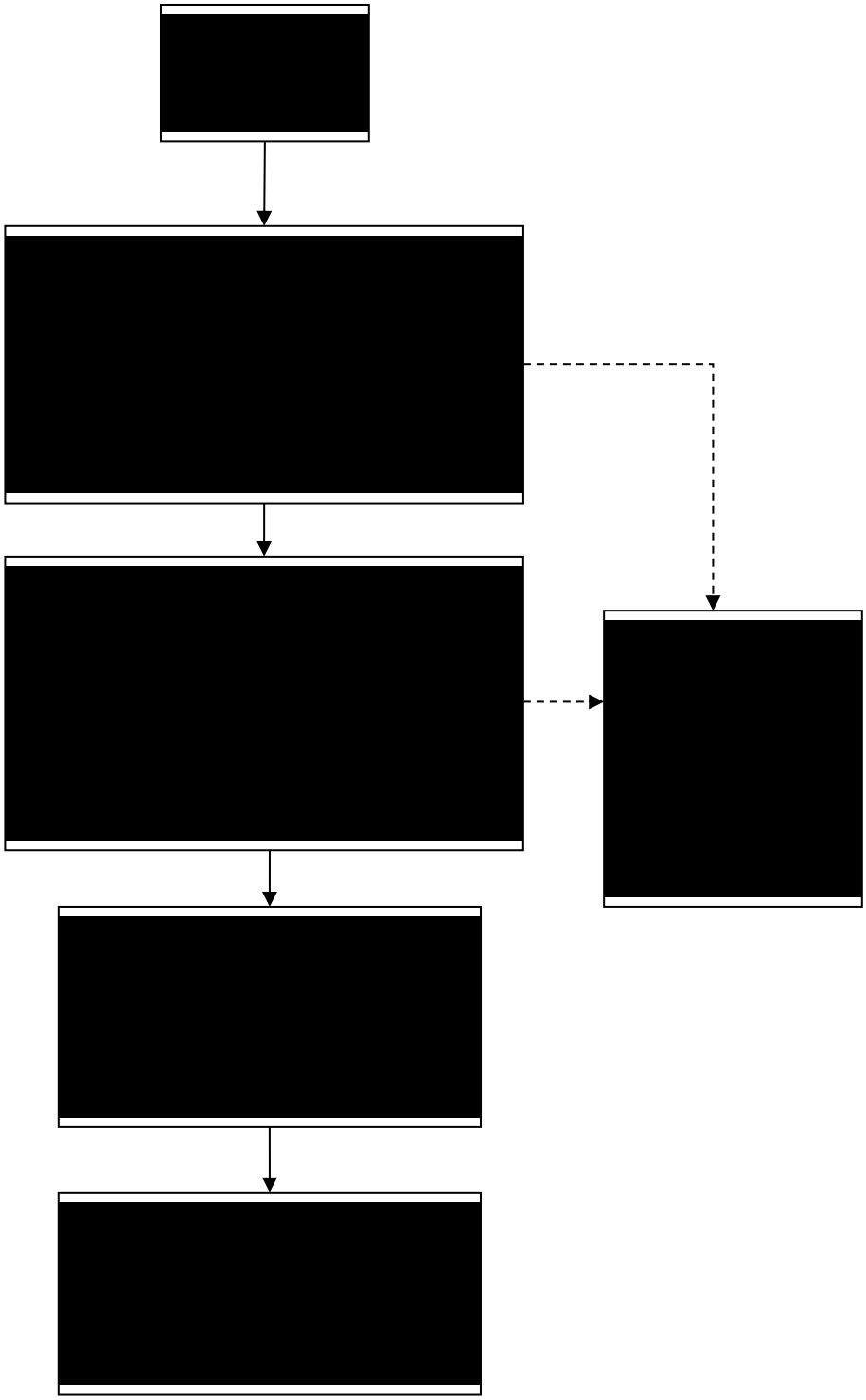
3.3. Number of Subjects

Up to 292 subjects who previously participated in investigational studies ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, or 232SM202 may be eligible to enroll in this study.

3.4. Overall Study Duration and Follow-Up

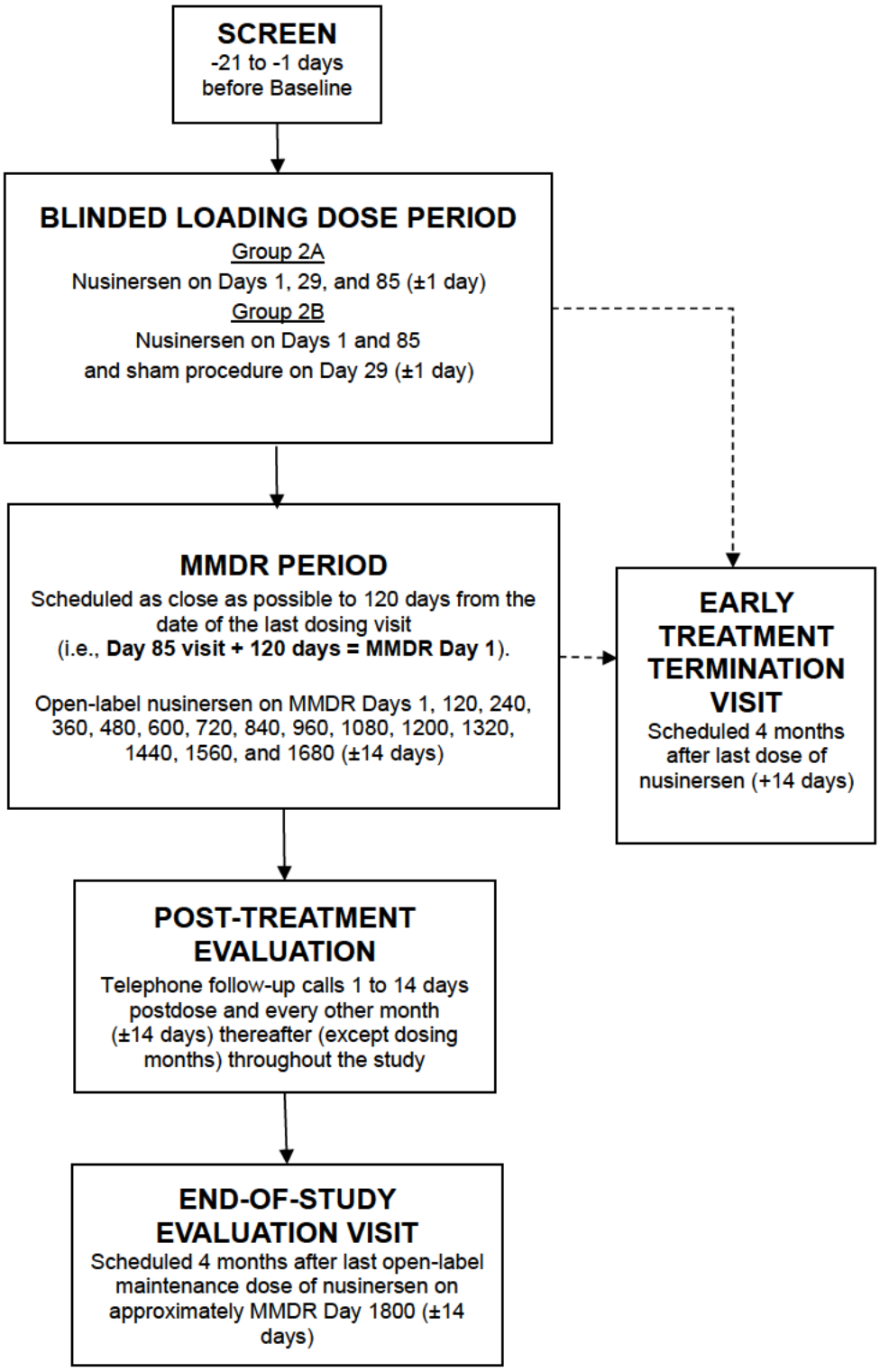
This study will consist of Screening, Treatment, and Post-Treatment Follow-Up Periods, and an End-of-Study (EOS) Evaluation Visit. The total duration of participation in the study is 5 years from MMDR Day 1 (EOS Evaluation Visit to occur at approximately MMDR Day 1800 [±14 days]). A study schematic for Groups 1A and 1B, Groups 2A and 2B, and Groups 3, 4, and 5 is provided in Figure 2, Figure 3, and Figure 4, respectively. The Sponsor acknowledges that any references to Groups 3, 4, and 5 do not apply to participating clinical study sites that do not have subjects from these groups. Please refer to the Schedule of Procedures in Appendix A.

Figure 2: Study Design and Treatment Schema: Groups 1A and 1B



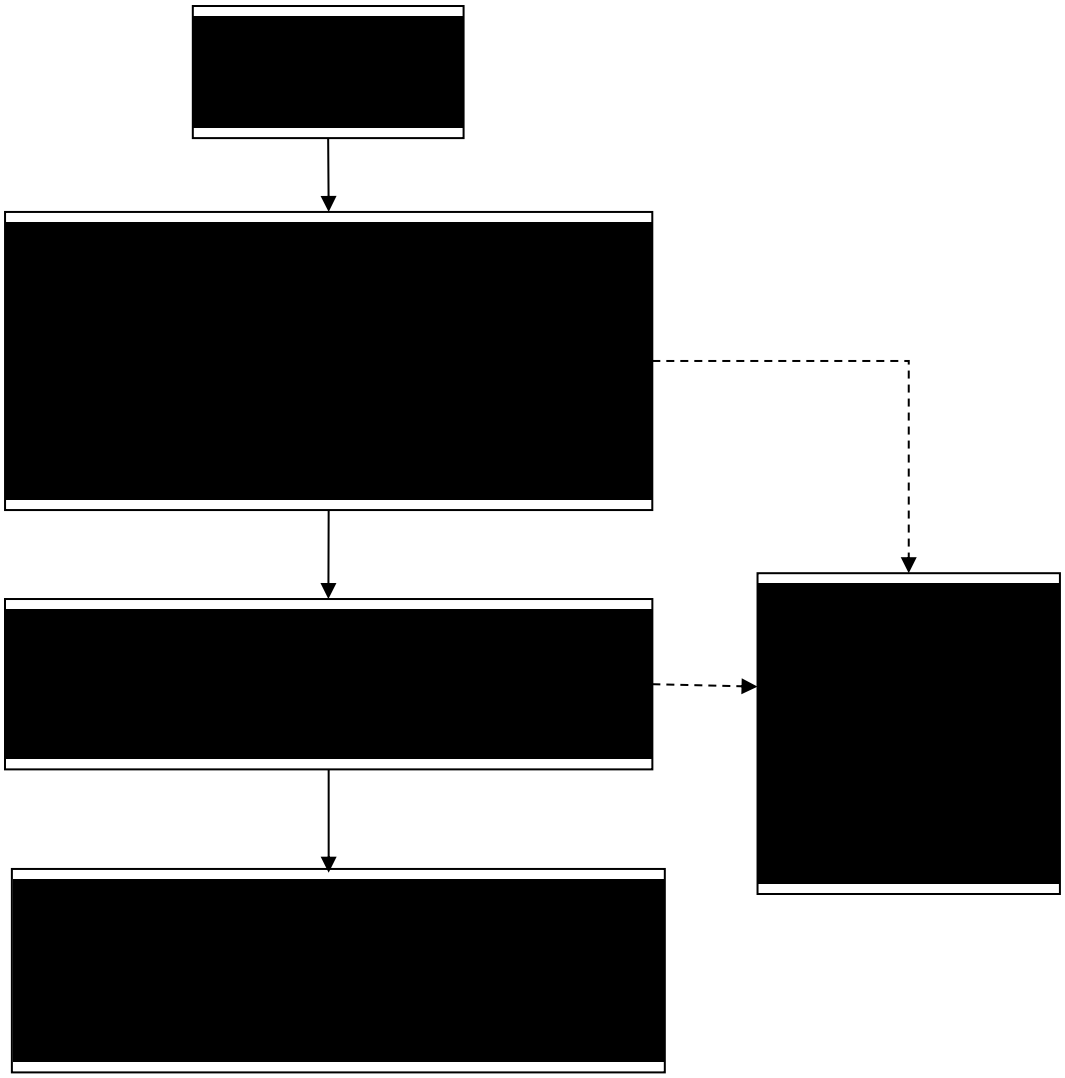
MMDR = Modified Maintenance Dosing Regimen.

Figure 3: Study Design and Treatment Schema: Groups 2A and 2B



MMDR = Modified Maintenance Dosing Regimen.

Figure 4: Study Design and Treatment Schema: Groups 3, 4, and 5



MMDR = Modified Maintenance Dosing Regimen.

3.4.1. Screening

After informed consent/assent is obtained, subjects will undergo a screening up to 21 days prior to first dose administration, during which their eligibility for the study will be determined. Subjects who meet the eligibility criteria will be enrolled into the study.

3.4.2. Treatment

Subjects who entered the study after completing the double-blind studies ISIS 396443-CS3B and ISIS 396443-CS4 (i.e., subjects in Groups 1A, 1B, 2A, and 2B) completed a blinded loading dose period and then transitioned to the open-label MMDR period. Subjects who were already enrolled in ISIS 396443-CS11 (SHINE) and had already participated in the blinded loading dose period continued their blinded loading dose/sham schedule through the last scheduled dose in that loading dose period and then transitioned to the open-label MMDR dosing schedule at their next study visit, which was scheduled as close as possible to 120 days from the date of the last

dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). The schedule for other MMDR dosing visits should be based on MMDR Day 1.

During the blinded loading dose period, subjects who previously received the sham procedure during the index study received blinded injections of nusinersen in order to achieve the full loading regimen of study treatment, and subjects who previously received nusinersen during the index study received a combination of nusinersen injections and sham procedures. This design was necessary to protect the full blind of the treatment assignment in the ongoing index studies.

Subjects who entered the study after completing open-label studies ISIS 396443-CS12 and ISIS 396443-CS3A (i.e., subjects in Groups 3 and 4) will enter directly into the open-label MMDR period at MMDR Day 1. Subjects who were already enrolled in ISIS 396443-CS11 and were already receiving maintenance doses according to the original maintenance schedule transitioned to MMDR Day 1 at their next study visit (regardless of how many maintenance doses already received in the original schedule), which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). Subjects entering the study after completing open-label Study 232SM202 (i.e., subjects in Group 5) will enter directly into the open-label MMDR period at MMDR Day 1. The schedule for other MMDR dosing visits should be based on MMDR Day 1.

The MMDR dosing schedule will consist of MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 (±14 days) until the EOS Evaluation/Early Termination (ET) Visit. The EOS Evaluation Visit will occur 4 months after the last open-label maintenance dose of nusinersen on approximately MMDR Day 1800 (±14 days).

Dosing for ISIS 396443-CS3B

- Group 1A: Subjects who entered the study after receiving sham procedures in the double-blind study ISIS 396443-CS3B received 4 loading doses of nusinersen administered by IT injection on Days 1, 15, 29, and 64 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1.
- Group 1B: Subjects who entered the study after receiving nusinersen in the double-blind study ISIS 396443-CS3B received 3 sham procedures on Days 1, 15, and 64 and 1 loading dose of nusinersen administered by IT injection on Day 29 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1.

Dosing for ISIS 396443-CS4

- Group 2A: Subjects who entered the study after receiving sham procedures in the double-blind study ISIS 396443-CS4 received 3 loading doses of nusinersen administered by IT injection on Days 1, 29, and 85 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1.

- Group 2B: Subjects who entered the study after receiving nusinersen in the double-blind study ISIS 396443-CS4 received 2 loading doses of nusinersen administered by IT injection on Days 1 and 85 and 1 sham procedure on Day 29 (±1 day) followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who participated in the loading dose treatment cycle in ISIS 396443-CS11 completed the cycle and then transitioned to MMDR Day 1.

Dosing for ISIS 396443-CS12

- Group 3: Subjects who entered the study after receiving nusinersen in the open-label study ISIS 396443-CS12 received maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who received open-label maintenance doses of nusinersen in ISIS 396443-CS11 were transitioned to the MMDR dosing period at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1).

Dosing for ISIS 396443-CS3A

- Group 4: Subjects who entered the study after receiving nusinersen in the open-label study ISIS 396443-CS3A received maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule. Subjects who received open-label maintenance doses of nusinersen in ISIS 396443-CS11 were transitioned to the MMDR dosing period at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1).

Dosing for 232SM202

- Group 5: Subjects who entered the study after receiving nusinersen during the open-label phase of Study 232SM202 (i.e., Part 2) received maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule.

All subjects will undergo predose evaluations according to the schedule of procedures and will remain at the study center for at least 1 hour after the study drug dosing/sham procedure for safety monitoring; the subjects can be discharged at the discretion of the Site Investigator and in compliance with the institutional requirements once they adequately recover from the dosing procedure.

[redacted]

Safety monitoring by telephone contact will occur to monitor the subjects' condition 1 to 14 days postdose and every other month (±14 days) thereafter throughout the duration of the study, except for the months during which a study visit occurs.

Subjects who discontinue treatment will complete an early termination visit 4 months (+14 days) after administration of the last dose of nusinersen, unless consent is withdrawn.

Subjects who discontinue from the study early will not be replaced.

3.4.3. Post-Treatment Follow-Up

After completion of the study treatment and open-label MMDR period, subjects will enter the Post-Treatment Follow-Up Period. This period will consist of telephone contact with the subject (1 to 14 days postdose and every other month [±14 days]) thereafter throughout the duration of the study (except for the months during which a study visit occurs) and an EOS Evaluation Visit.

3.5. End of Study

The end of study is defined as the last study visit for the last study subject and will occur 4 months after the last open-label maintenance dose of nusinersen on approximately MMDR Day 1800 (±14 days) or as determined by the Sponsor (via early termination).

3.6. Safety Monitoring

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor, with data cuts at regular intervals.

4. SUBJECT ENROLLMENT

4.1. Screening

Before subjects may be screened for the study, the Sponsor will require a copy of the study center's written Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol, informed consent form (ICF), informed assent form (if applicable), and all other subject information and/or recruitment material.

Before a subject's participation in the study, the Investigator will be responsible for obtaining written informed consent from the parent(s) or legal guardian(s) and, in cases where institutional guidelines or the subject's age dictate, informed assent from the subject. Consent/assent must be signed before any study procedures, including screening procedures, are performed. If all eligibility criteria are met and the subject is enrolled into the study, the extension study subject identification number will be maintained from, or linked to, the index study subject identification number. This will be outlined in the ISIS 396443-CS11 data management documentation.

4.2. Randomization

No randomization of subjects will be utilized for this extension study.

4.3. Replacement of Subjects

Subjects will not be replaced.

4.4. Unblinding of Treatment Assignment

During the blinded loading dose period of this study, subjects received either blinded injections of nusinersen (Groups 1A and 2A) or a combination of nusinersen and sham procedures (Groups 1B and 2B) in order to allow subjects who previously participated in a sham procedure group of the index studies to obtain a loading regimen of nusinersen while maintaining the blind of the treatment assignment in the index study. Following that, during the open-label

maintenance period of the study, all study subjects received nusinersen in an unblinded manner using a maintenance dosing regimen of once every 4 months.

Index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, and treatment assignments for subjects in the applicable groups (Groups 1A, 2A, 1B, and 2B) were released. Therefore, there was no longer any reason to continue the blinded loading dose period in a blinded fashion. Procedures for subjects still attending visits within the blinding loading dose period at the time of unblinding were revised as follows:

- For subjects in Group 1A and Group 2A who were receiving active drug (i.e., nusinersen) within the blinding loading dose period, visits occurred as scheduled, with all predose and postdose assessments performed.
- For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period, all visits and predose assessments were continued per the protocol; however, the sham procedure and all postdose procedures were not performed for those applicable visits. The required assessments for sham visits performed after the time of unblinding are described in Section 8.2.

During the blinded loading dose period, all suspected unexpected serious adverse reactions (SUSARs) were unblinded by the Sponsor's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting. As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, SUSARs will be submitted to regulatory agencies and Investigators in an unblinded fashion (Section 9.2).

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

Subjects must meet all of the following criteria at Screening to be eligible:

1. Signed informed consent of parent or guardian and signed informed assent of subject, if indicated per subject's age and institutional guidelines.
2. Completion of the index study in accordance with the study protocol or as a result of Sponsor decision (e.g., early termination of the index study) within the preceding 16 weeks.
3. Ability to complete all study procedures, measurements, and visits, and parent/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.
4. Subjects who, in the opinion of the Investigator, have reached reproductive maturity, must satisfy one of the following:
   - Females must have a negative pregnancy test at Screening and must agree to employ adequate contraceptive measures for the duration of the study. Acceptable contraception methods are restricted to abstinence*, barrier contraceptives, intrauterine contraceptive devices, or licensed hormonal products.

- Males must be abstinent* for the duration of the study or must be using an acceptable contraceptive method (i.e., use a condom together with spermicidal foam/gel/film/cream/suppository).

*Abstinence is only acceptable as true abstinence (i.e., when this is representative of the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., abstinence for the duration of the study) and withdrawal are not acceptable methods of contraception.

5.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Have any new condition or worsening of existing condition, which in the opinion of the Investigator would make the subject unsuitable for enrollment or could interfere with the subject participating in or completing the study.
2. Clinically significant abnormalities in hematology or blood chemistry parameters or electrocardiogram (ECG), as assessed by the Site Investigator, at the Screening Visit that would render the subject unsuitable for participation in the study.
3. The subject's parent or legal guardian is unable to understand the nature, scope, and possible consequences of the study, or does not agree to comply with the protocol's schedule of procedures.
4. The subject's parent or legal guardian is not willing or able to meet guidelines in the consensus statement for standard of care in SMA [Wang 2007] or provide nutritional and respiratory support throughout the study. NOTE: Routine vaccinations and respiratory syncytial virus (RSV) prophylaxis are recommended per consensus guidelines on standard of care [Wang 2007] but are not required for study enrollment. Subjects who are not current on vaccinations or who are not receiving RSV prophylaxis, but otherwise meet study inclusion criteria, will be considered eligible for study enrollment.
5. Treatment with another investigational agent, biological agent, or device within 1 month of Screening or 5 half-lives of study agent, whichever is longer.

6. STUDY PROCEDURES

Please note: The following assessments are listed according to their assessment timing for each visit throughout the study as outlined in the Schedule of Procedures (Appendix A). Please review each assessment for specific details and refer to the Schedule of Procedures in Appendix A for clarification.

If any additional clarification is required, please contact the Study Medical Monitor.

6.1. Study Assessments for Injection Days Only

[redacted]

[redacted]

6.2. Study Assessments for Screening Only

Assessments to be performed at Screening only include informed consent/assent, inclusion/exclusion criteria, and medical history.

6.3. Study Assessments for Every Study Visit and the End-of-Study Evaluation Visit

6.3.1. Ventilator Use Diary Recording

For all subjects, ventilator support/use will be assessed throughout the study, regardless of ventilation status. This information will be obtained from the caregivers during onsite study visits and every-other-month telephone contacts. This assessment will document whether respiratory support is being used (or not), what type of respiratory support is being used (noninvasive [i.e., bilevel positive airway pressure (BiPAP)/continuous positive airway pressure (CPAP)] or permanent ventilation), the number of hours per day, and the number of days the support is being used.

Ventilator use should also be recorded within a ventilator use diary if the subject's daily ventilator support increases to ≥16 hours/day. The ventilator use diary should be dispensed during onsite study visits as needed. Once ventilator use increases to ≥16 hours/day, ventilator use should continue to be recorded within the diary for a minimum of 30 days. If ventilator use decreases to <16 hours/day and subsequently increases to ≥16 hours/day, the 30-day period for collecting the data should be restarted. Investigators may instruct caregivers to continue recording in the ventilator use diary for an additional 30 or more days, based on clinical judgment. The purpose of the ventilator use diary is to determine whether a subject has reached the permanent ventilation endpoint. Thus, once a subject has met the permanent ventilation endpoint, the ventilator use diary should be discontinued, as it is no longer needed. Once a subject has met the permanent ventilation endpoint, ventilation support/use should continue to be obtained at study visits and every-other-month telephone contacts, as described.

Please note: Predose ventilator use assessments should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.2. Dysphagia Assessment

Dysphagia assessment may be performed at home up to 7 days prior to the dosing visit using the Parent Assessment of Swallowing Ability Weekly Version. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

Assessment will be performed for all subjects including those on tube feeding; however, tube-fed subjects only need to be assessed with Questions 1 to 5 of the survey.

6.3.3. Urine/Serum Pregnancy Tests

Urine pregnancy tests will be performed and evaluated predose (within 7 days of dosing) at every onsite visit for female subjects of childbearing potential (defined as any female who has experienced menarche). If positive, the results will be confirmed locally by serum pregnancy test.

Please note: Predose pregnancy tests should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.4. Weight

Weight will be collected predose (within 7 days of dosing) for all subjects at every onsite visit throughout the study.

Please note: Predose weight assessments should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.5. Growth Parameters

Growth parameters of body length or height (for all subjects), head circumference (for subjects up to 36 months of age), chest circumference (for subjects up to 36 months of age), and arm circumference (for subjects up to 36 months of age) will be measured predose (within 7 days of dosing) by the Investigator (or designee) at every onsite visit throughout the study. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

In subjects with scoliosis and contractures, the Investigator (or designee) may measure arm span or ulnar length in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. The investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist.

Additional parameters of weight-for-age, weight-for-length, and head-to-chest circumference ratio will be calculated by the Sponsor during the analysis as described in the Statistical Analysis Plan (see Section 10.1.2).

Please note: Growth parameters should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.6. Physical Examinations

Physical examinations will be performed predose (within 7 days of dosing) for all subjects at every onsite visit throughout the study. Any abnormal findings observed during physical examinations will be captured as AEs and reported according to Section 9.

If the consent for videotaping of the physical examination is provided, then videotaping should be performed.

Please note: Predose physical examinations should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.7. Vital Signs

Vital signs include resting blood pressure, pulse, pulse oximetry, respiratory rate, and temperature. Vital signs will be taken predose **and** approximately 1 hour postdose at every onsite visit throughout the study.

Please note: Vital signs should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.3.8. Neurological Examinations

Focused neurological examinations will be performed within 7 days of dosing **and** approximately 1 hour postdose at every onsite visit throughout the study. **Please note**: If sedation was used, please allow sufficient recovery time for the subject to be fully engaged in the examination because change from baseline in neurological examinations outcome is a primary study endpoint. It is important that the data collected truly reflect the subject's neurological performance.

Sections 1 and 3 of the HINE will be conducted on all subjects ≤24 months of age. This standard examination (developed by [Dubowitz and Dubowitz 1981]) is a quantitative scorable method for assessing the neurological development of infants between 2 and 24 months of age. The examination includes assessment of cranial nerve functions, posture, movements, tone, and reflexes.

For all subjects >24 months of age, focused neurological examinations, which include assessments of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes, will be conducted.

Please note: Neurological examinations should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

6.4. Study Assessments for Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 4 Months Thereafter (Every Modified Maintenance Dosing Regimen Visit), and the End-of-Study Evaluation/Early Termination Visit

6.4.1. Clinical Safety Laboratory Evaluations

Laboratory measurements of serum chemistry, hematology, urinalysis, and urine total protein will be collected at Screening and predose at MMDR Day 1 (not required to repeat on MMDR Day 1 if visit is within 7 days of Screening), predose (within 7 days of dosing) every 4 months thereafter (i.e., MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 [±14 days]), and at the EOS Evaluation/ET Visit. The laboratory analytes to be measured are shown in Appendix B.

Please note: Predose clinical safety laboratory evaluations should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation. Quantitative urine total protein assessment should be prioritized if there is not enough urine sample for all tests.

6.4.2. Coagulation Parameters

Coagulation parameters (activated partial thromboplastin time [aPTT] and international normalized ratio [INR]) will be collected at MMDR Day 1, every 4 months thereafter (i.e., MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 [±14 days]), and at the EOS Evaluation/ET Visit.

Coagulation testing will continue to be conducted at each visit or up to 7 days prior to dosing, and results should be reviewed prior to dosing. In situations where predose verification of coagulation laboratory results is not feasible or optimal (e.g., prolonged sedation of the subject would be required to allow adequate time for laboratory processing), the Investigator may exercise discretionary clinical judgment and proceed with the LP procedure, based on the subject's clinical and coagulation laboratory results history.

Please note: Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

[redacted]

6.5. Study Assessments for Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 8 Months Until Modified Maintenance Dosing Regimen Day 720 and Every 12 Months Thereafter, and the End-of-Study Evaluation/Early Termination Visit

6.5.1. Motor Milestones

For all subjects, motor milestones will be assessed using the World Health Organization (WHO) Motor Milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004] at Screening and/or predose at MMDR Day 1, every 8 months until MMDR Day 720 (inclusive) [i.e., predose at MMDR Days 240, 480, and 720], and every 12 months thereafter (i.e., predose at MMDR Days 1080 and 1440), and at the EOS Evaluation (MMDR Day 1800 [±14 days])/ET Visit. If the WHO motor milestones assessment has already been performed at MMDR Day 960 for a subject prior to approval of Protocol Version 5.0 at a site, the WHO motor milestones assessment will still need to be performed at MMDR Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

For subjects <2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the HINE.

Please note: The WHO motor milestone assessment should be performed even if the subject is not ambulatory.

If the consent for videotaping of the WHO and/or HINE motor milestone assessments is provided, then videotaping should be performed.

6.5.2. Motor Function Assessments

Motor function assessments include all assessments listed in Section 6.5.2.1, Section 6.5.2.2, Section 6.5.2.3, Section 6.5.2.4, and Section 6.5.2.5. Motor function assessments will be performed at Screening and/or predose at MMDR Day 1, every 8 months until MMDR Day 720 (inclusive) [i.e., predose at MMDR Days 240, 480, and 720], and every 12 months thereafter (i.e., predose at MMDR Days 1080 and 1440), and at the EOS Evaluation (MMDR Day 1800 [±14 days])/ET Visit. If motor function assessments have already been performed at Day 960 for a subject prior to approval of Protocol Version 5.0 at a site, motor function assessments

(i.e., CHOP INTEND, HFMSE, Revised Upper Limb Module [RULM], 6-Minute Walk Test [6MWT], and contracture assessment) will still need to be assessed at Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit.

The assessments that are performed at a given visit will depend on the subject's age at that visit and current motor abilities. For the purposes of this protocol, ambulatory will be defined as any subject who has achieved independent walking as defined by the WHO Motor Milestones criteria (Test Item #6 – Walking Alone).

If the consent for videotaping of all motor function assessments is provided, then videotaping should be performed.

6.5.2.1. Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease

CHOP INTEND will be assessed in subjects with infantile-onset SMA until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

The CHOP INTEND test was specifically designed to evaluate the motor skills of infants with significant motor weakness, including infants with SMA [Glanzman 2010]. The CHOP INTEND test captures neck, trunk, and proximal and distal limb strength in 14 elicited and 2 observational items. The CHOP INTEND has been established as a safe and reliable infant motor measure in infantile-onset SMA and has been validated [Glanzman 2011].

6.5.2.2. Hammersmith Functional Motor Scale – Expanded

All subjects ≥2 years of age will be evaluated using the HFMSE for the duration of the study. Subjects who are ≥2 years of age but have not yet achieved the maximum score of 64 with CHOP INTEND will be assessed with both until a CHOP INTEND maximum score of 64 is achieved. The HFMSE should be performed after the CHOP INTEND with an approximately 15-minute rest period in between to allow the subject to be fully engaged with both assessments. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

Note: Any subjects currently being assessed with both the CHOP INTEND and HFMSE under a previous version of this protocol will continue to have both assessments performed under the current Version 6.0 of this protocol (even if they are <2 years of age) until they achieve a CHOP INTEND maximum score of 64.

The HFMSE is a reliable and validated tool used to assess motor function in children with SMA. The scale was originally developed with 20 scored activities and was devised for use in children with Type 2 and Type 3 SMA with limited ambulation to give objective information on motor ability and clinical progression [Main 2003]. The expanded scale includes an additional module of 13 items developed to allow for evaluation of ambulatory patients with SMA [O'Hagen 2007]. The HFMSE has been shown to be highly correlated with other clinical assessments and has shown good test-retest reliability.

6.5.2.3. Revised Upper Limb Module

All nonambulatory subjects ≥30 months of age will be evaluated using RULM [Mazzone 2016]. The RULM will continue to be performed should subjects subsequently become ambulatory. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

The RULM is an outcome measure developed to assess upper limb functional abilities in patients with SMA, including young children, and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The RULM is quickly administered and has been evaluated in patients with SMA 2 to 52 years of age [Mazzone 2016].

The purpose of an upper limb scale for use in SMA is to assess change that occurs in motor performance of the upper limb over time. Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be impacted by muscle strength, contractures, and maturational development (puberty), and the RULM aims to incorporate performance of the shoulder, elbow, wrist, and hand.

6.5.2.4. Six-Minute Walk Test

The 6MWT should be attempted once a subject achieves independent ambulation and will continue to be assessed in subjects who are ambulatory. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

The 6MWT is an objective evaluation of functional exercise capability that measures the distance a person can walk quickly in 6 minutes. The 6MWT can be performed safely in ambulatory patients with SMA and correlates with standard SMA outcome measures including timed walking tests [Montes 2010]. In SMA, the 6MWT may be more sensitive to clinically meaningful changes in patients with Type 3 SMA because it is a direct measure of their functional mobility. The 6MWT has also been used as a primary outcome measure in several clinical studies in neuromuscular disease including Duchenne muscular dystrophy [McDonald 2010] and late-onset Pompe disease [van der Ploeg 2010].

6.5.2.5. Contracture Assessment

Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be affected by muscle strength, contractures, and maturational development (puberty). All subjects will be evaluated for contractures. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

6.6. Study Assessments to be Performed at Screening and/or Modified Maintenance Dosing Regimen Day 1, Annually, and at the End of Study Evaluation/Early Termination Visit

6.6.1. Electrocardiograms

ECGs will be performed for all subjects at Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

Please note: Predose ECGs should be repeated when the assessment falls outside the protocol-specified window due to a delay in dosing (Section 6.10).

After the ECG is completed, an initial local read of the ECG should occur before the ECG is sent for a central read (**all ECGs will be centrally read**). If the subject's initial ECG results show a QTc interval of ≥500 milliseconds, then the ECG should be repeated prior to the subject leaving the visit. If the second ECG QTc again reads ≥500 milliseconds, the Investigator should use best clinical judgment to address the condition.

Additional ECGs may be performed per the judgment of the Investigator, as deemed clinically necessary.

6.6.2. X-Ray of Spine

Subjects currently ≥2 years of age or upon turning 2 years of age (with the exception of subjects treated at German sites) will have an X-ray of the thoracolumbar spine on Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit. X-ray assessments performed as standard of care may be used for protocol-required assessments, if the image acquisition guidelines are met and the X-ray was obtained within 4 months prior to the scheduled visit.

The X-rays will be used to determine the severity of scoliosis by measuring the Cobb angle. The spine X-ray was performed in the index studies, and the image acquisition guidelines will remain consistent between the index study and the current extension study. The technical details for image acquisition will be outlined in a separate document provided to the sites.

6.6.3. Quality of Life Questionnaires

Quality of life questionnaires include all questionnaires listed below. Generally, quality of life questionnaires will be collected at Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit.

The questionnaires that are performed at a given visit will depend on the subject's age at that visit. If needed, the subject's caregiver may complete the applicable quality of life questionnaires at home up to 7 days prior to dosing visit. If a quality of life questionnaire is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing

visit(s) until completed; however, an assessment should not be performed more than once at any visit.

6.6.3.1. Pediatric Quality of Life Inventory (Generic Core Scales and Neuromuscular Module)

Subjects 2 to 25 years of age will be evaluated using the Pediatric Quality of Life Inventory (PedsQL™) Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module [Varni 1999]. This assessment has been validated by the American Spinal Muscular Atrophy Randomized Trials group [Iannaccone 2009]. The PedsQL Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. The PedsQL consists of brief, practical, generic core scales, as well as condition-specific modules for use in designated clinical populations. Pediatric self-report is measured in children, adolescents, and young adults 5 to 25 years of age, and parent proxy-report of child HRQOL is measured for children, adolescents, and young adults 2 to 25 years of age. The PedsQL 4.0 Generic Core Scales include assessment of physical functioning, emotional functioning, social functioning, and school functioning. The PedsQL 3.0 Neuromuscular Module was designed to measure HRQOL dimensions specific to children, adolescents, and young adults 2 to 25 years of age with neuromuscular disorders, including SMA.

6.6.3.2. Assessment of Caregiver Experience With Neuromuscular Disease

Parents of subjects will complete the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) questionnaire. This assessment instrument has been designed to quantify the caregiver impact experienced by parents of children affected with severe neuromuscular diseases, including children with SMA [Matsumoto 2011]. The ACEND includes domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance).

Please note: Subjects should not complete quality of life questionnaires intended for completion by a caregiver.

6.7. Study Assessments to be Performed at Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 16 Months Thereafter (Modified Maintenance Dosing Regimen Days 480, 960, and 1440), and the End-of-Study Evaluation/Early Termination Visit

6.7.1. Compound Muscle Action Potential

For all subjects, measurements of ulnar and peroneal CMAP will be conducted at Screening and/or MMDR Day 1, approximately every 16 months thereafter (i.e., MMDR Days 480, 960, and 1440), and at the EOS Evaluation/ET Visit. If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit. If CMAP measurements are not approved as a mandatory outcome measure by local authorities, they will be considered optional in the respective country.

CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles. CMAP is a well-validated method for tracking disease progression in neuromuscular disorders such as SMA [Lewelt 2010;

Swoboda 2005] and amyotrophic lateral sclerosis [Shefner 2011] and has been proposed as a potential biomarker of a therapeutic effect in SMA.

[redacted]

[redacted]

6.9. Study Assessments to be Performed Continuously Throughout the Study

6.9.1. Telephone Assessments

Follow-up safety monitoring telephone calls will occur 1 to 14 days postdose and every other month (±14 days) thereafter for the duration of the study, except for the months when in-clinic visits occur. During these calls, changes in concomitant medications, AEs, ventilator use/status,

and contraceptive methods that have occurred since the last phone call or study visit will be recorded.

6.10. Study Assessments to be Repeated Due to Delayed Dosing

If a dosing visit is delayed, the following predose procedures should be repeated at the delayed dosing visit:

- Vital signs (resting blood pressure, pulse, pulse oximetry, respiratory rate, and temperature)
- Weight
- Growth parameters
- Ventilator use
- Physical examination
- Neurological examination
    - Focused neurological examination for subjects >24 months of age
    - HINE Section 1 and 3 for subjects ≤24 months of age
- Safety laboratory evaluations:
    - Serum chemistry (central laboratory)
    - Hematology (central laboratory)
    - Urinalysis (central laboratory)
    - Urine total protein (local laboratory)
- Coagulation parameters (local laboratory)
- [redacted]
- Urine/serum pregnancy test
- ECG (predose at applicable visits: MMDR Days 1, 360, 720, 1080, and 1440)
- Concomitant medications assessment
- Ancillary procedure recording
- AE collection

All procedures should be performed predose (within 7 days of dosing). Vital signs and neurological examination should also be performed at approximately 1 hour postdose. The purpose of repeating these assessments is to ensure the safety of the subject prior to dosing and to collect important study information pertaining to each dose.

At the discretion of the Investigator, additional visit-specific assessments may be repeated as needed, as long as they are performed predose within 7 days of the rescheduled dosing visit.

7. STUDY DRUG

7.1. Study Drug Description

The nusinersen (study drug) characteristics are listed in Table 2.

The study drug is contained in a 6-mL clear glass vial. The study drug and its storage and preparation instructions will be provided by the Sponsor or designee. The study drug must be stored securely at 2°C to 8°C and protected from light.

Table 2: Study Drug Characteristics

Study Drug	**Nusinersen Drug Product**
Strength	2.4 mg/mL
Volume/vial	5.0 mL solution per vial
Route of administration	IT injection

IT = intrathecal.

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged study drug labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document receipt, dispensing and return, and/or destruction of study drug supplies provided by the Sponsor.

8. TREATMENT OF SUBJECTS

8.1. Study Drug Administration

Details regarding the LP dosing injection procedure are provided in the Dosing Administration Manual, also known as the Directions for Handling and Administration (DHA) guidelines.

The DHA guidelines supersede all other references (e.g., protocol).

Nusinersen will be administered as an IT LP injection. All subjects will receive the full 12-mg dose of nusinersen (5 mL).

During the blinded loading dose period, the study treatment dosing or sham procedures were performed in a dedicated room and administered by dedicated study personnel who were unblinded to the treatment assignment; this was not administered by any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors), and the key study site personnel or the parents were not present during the procedure to ensure blinding.

After the loading dose period has been completed (and/or after unblinding of index studies ISIS 396443-CS3B and ISIS 396443-CS4; see Section 4.4), subsequent doses of nusinersen will not involve a sham procedure and, with the agreement of the Sponsor, may be administered by the Principal Investigator or Subinvestigator.

Nusinersen will be administered as an IT slow bolus (1 to 3 minutes) LP injection. Nusinersen will be administered using a "spinal anesthesia" needle and syringe. A 22G to 25G spinal anesthesia needle is recommended, but a 21G may be used if indicated by subject size or clinical condition. The target site for needle insertion is the L3/L4 space but may be 1 segment above or 1 to 2 segments below this level, if needed. [redacted]

Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure, following institutional procedures. Subjects will be encouraged to lie flat for 1 hour following dosing, if possible.

8.2. Sham Procedure

During the blinded loading dose period of this study, subjects received blinded injections of either nusinersen or sham procedures, to allow subjects who previously participated in a sham procedure group of the index studies to obtain a loading dose regimen of nusinersen and maintain the blind on the regimen that was administered in the index study. Details of the sham procedure were provided in the Dosing Administration Manual (or DHA guidelines). The sham procedure was performed in a dedicated room and administered by dedicated study personnel who were unblinded to the treatment group; this was not administered by any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors), and the key study site personnel or the parents were not present during the sham procedure to ensure blinding.

The sham procedure consisted of a small needle prick on the lower back at the location where the LP injection was normally made. The needle broke the skin, but no LP injection or needle insertion occurred. The site of the needle prick was covered in the same manner as that of the LP injection, thus simulating the appearance of an LP injection. If anesthesia or sedation was used for the LP procedure in nusinersen-treated subjects at an individual study center, in order to maintain the blind, minimal sedation (i.e., a low dose of an anxiolytic) was used for the sham procedure, following institutional procedures. Subjects who received the sham procedure were kept in the procedure room for the same amount of time as that for subjects who were administered study treatment, thus simulating the time period of a study treatment administration procedure.

Study treatment and sham kits were packaged in a blinded fashion. [redacted]

As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, there was no longer any reason to continue the blinded loading dose period in a blinded fashion (see Section 4.4). For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period since the time of unblinding, the sham procedure and all postdose procedures described above were not performed for those applicable visits. The procedure at sham visits was recorded as "NOT DONE" in the eCRF, and the reason was specified as "subject is in Group 1B or Group 2B; visit occurred after treatment assignments were released by study Sponsor." During these visits, study drug was not administered, and these visits were considered safety visits. The visit was still registered in the Interactive Voice/Web Response System (also known as the IxRS system) to allow for all future visits to be recorded without issue; however, the dispensed study drug was

set aside, marked as "Not Used," recorded as such in the site and/or patient drug accountability log, and then returned for destruction. Safety assessments of predose vital signs and neurological examination were performed, and AEs, concomitant medications, general health, and ventilator use/status were reviewed.

8.3. Other Protocol-Required Drugs

There are no other protocol required drugs.

8.4. Other Protocol-Required Procedures

There are no other protocol-required treatment procedures.

8.5. Treatment Precautions

There are no protocol-required treatment precautions.

8.6. Safety Monitoring Rules

Please refer to the Guidance to Investigator section of the Investigator's Brochure.

8.7. Stopping Rules

There are no additional specific stopping rules for this study, but the Investigator should discuss significant concerns relating to individual subjects with the Medical Monitor and the Sponsor to ensure that it is appropriate for the subject to continue study treatment.

8.8. Adjustment of Dose and/or Treatment Schedule

No adjustment of dose is permitted. If dosing does not occur as per the schedule of activities, a protocol deviation should be logged. In the event of delayed or missed doses due to, for example, a concurrent illness or other circumstances (e.g., the coronavirus disease 2019 pandemic), the Investigator should refer to the DHA, which includes recommended dosing administration in the event of delayed or missed doses.

8.9. Discontinuation of Study Treatment

A subject must permanently discontinue study treatment for any of the following reasons:

- The subject or subject's parent/guardian withdraws consent.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.

The reason for discontinuation of study treatment must be recorded in the case report form (CRF) and source documentation.

Subjects who discontinue treatment will complete an early termination visit 4 months (+14 days) after administration of the last dose of nusinersen (Appendix A), unless consent is withdrawn (Section 8.10).

8.10. Withdrawal of Subjects From the Study

Subjects must be withdrawn from the study for any of the following reasons:

- The subject or the subject's parent/guardian withdraws consent.
- The subject or the subject's parent/guardian is unwilling or unable to comply with the protocol.

Other reasons for withdrawal of subjects from the study might include the following:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Initiation of commercial nusinersen treatment
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor

All efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal from the study. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any subject for whom consent to participate in the study is withdrawn will be removed from further treatment and study observation immediately upon the date of request. It should be encouraged that these subjects complete the early termination study procedures and observations at the time of withdrawal (Appendix A).

For subjects withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (Appendix A).

8.11. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.11.1. Concomitant Therapy

A concomitant therapy is any non-protocol-specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered between the beginning of Screening and the last telephone contact or study visit.

Subject's parents/guardians should consult with the Site Investigator or qualified designee prior to initiating any new medication, including non-prescription compounds or any other non-drug therapy.

8.11.1.1. Allowed Concomitant Therapy

Any concomitant medications, including SMA therapies, will be captured in the CRF.

Approved concomitant therapies may be used at the discretion of the Investigator. With implementation of Protocol Version 6.0, investigators with subjects newly seeking combination therapy with other SMA therapies should consult and obtain approval from the Medical Monitor.

This will be permitted for country-approved SMA therapies, if the total number of study subjects concurrently receiving nusinersen and other SMA therapies has not yet reached 20% of all enrolled subjects. This is consistent with the primary and secondary objectives of this study. Any subjects already receiving combination therapy with other SMA therapies at the time of Protocol Version 6.0 implementation may continue this combination therapy regardless of the 20% limit.

Throughout the study, the Site Investigators or designated licensed physicians may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care. In addition, a mild sedative (e.g., midazolam) and a local anesthetic (e.g., lidocaine) may be used for the LP procedure (per institutional guidance).

8.11.1.2. Disallowed Concomitant Therapy

As noted above in Section 8.11.1.1, with implementation of the Protocol Version 6.0, new subjects seeking combination therapy of nusinersen with other SMA therapies should consult the Medical Monitor. Any subjects already receiving investigational drug for any other condition should consult with the Medical Monitor.

8.11.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, myringotomy, and placement of tympanostomy tubes) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the beginning of Screening and last telephone contact or study visit.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical study.

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to the study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Complete an SAE form for each serious event and fax it as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of new information.
- Ensure that all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local ethics committees, as required by local law.

The Sponsor's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor (or designee) is responsible for reviewing with study site staff the definitions of AE and SAE as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor (or designee) is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

9.2. Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of SAEs including SUSARs per the International Council for Harmonisation (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines. SUSARs are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

During the blinded loading dose period, SUSARs were unblinded by appropriate Sponsor personnel for the purpose of regulatory reporting. The Sponsor submitted SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law and submitted SUSARs to Investigators in a blinded fashion.

As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, this unblinding is no longer needed. SUSARs will be submitted to regulatory agencies and Investigators in an unblinded fashion.

IRBs/IECs will be notified of any SAE according to applicable regulations.

9.3. Definitions

9.3.1. Adverse Event

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2. Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any AE caused by the study treatment.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event

An SAE is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death.
- Is life threatening (i.e., poses an immediate risk of death at the time of the event).
  - An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - **Please note**: Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent/assent) should be recorded as medical history and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis**, if possible.

9.4.1. Serious Adverse Events

In the interest of subject safety and to fulfill regulatory requirements, all SAEs (regardless of their relationship to study treatment) should be reported to the Sponsor within 24 hours of the study center's first knowledge of the event. The collection of SAEs will begin after the subject signs the ICF and will stop at the end of the subject's follow-up period, which is defined as the subject's last visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial SAE Form should be completed and a copy should be faxed to the Sponsor or designee; refer to the Study Reference Guide for complete contact information.

Detailed information should be actively sought and included on Follow-Up SAE Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the ICF and will stop at the end of the subject's follow-up period, which is defined as subject's last visit. The Investigator will monitor each subject closely and will record all observed or volunteered AEs on the AE CRF.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the AE CRF.

9.4.3.1. Relationship to the Study Treatment

The event's relationship to the study treatment is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of study treatment (e.g., confirmation by positive rechallenge test).
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study treatment administration.
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to study treatment administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, unlikely/remote will be grouped together with not related).
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and study treatment.

9.4.3.2. Severity

The event's severity is characterized by one of the following:

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities.
- **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities.
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities.

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3. Action Taken With Study Treatment

The action taken with study treatment due to the event is characterized by one of the following:

- **None:** No changes were made to study treatment administration and dose.
- **Permanently Discontinued:** Study treatment was discontinued and not restarted.
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose.

9.4.3.4. Treatment Given for the Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the AE CRF (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- **AE Persists:** Subject terminates from the study and the AE continues.
- **Recovered:** Subject recovered completely from the AE.
- **Became Serious:** The event became serious (the date when the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE).
- **Change in Severity (if applicable):** AE severity changed.

If the event is a SAE, then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing.
- **Persists (as non-serious AE):** Subject has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE CRF (the SAE resolution date should be entered as the date of onset of that AE).
- **Recovered:** Subject recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date).
- **Fatal:** Subject died (the date of death should be entered as the SAE resolution date).

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment (e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia). Whenever possible, the underlying diagnosis should be listed, in preference to abnormal laboratory values, as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Medical

Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory report.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the study center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the timing of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

9.5.3. Dosing Errors

All dosing errors (including but not limited to route of administration, wrong dose, etc.) must be reported as protocol deviations. A brief description should be provided in the deviation, including information about whether the subject was symptomatic or not. Dosing details should be captured on the Dosing CRF.

A dosing error will be considered an overdose when any of the following conditions are met:

- Any single dose given exceeds the dose level described in the protocol and DHA Guidelines.
- Dosing frequency exceeds 4 doses in a 60-day period.
- Study drug is administered less than 14 days from the previous dose.

Overdoses are not considered AEs and should not be recorded as an AE on the CRF unless an AE or an SAE occurs. All overdoses (regardless of whether or not they result in an AE) must be recorded on an overdose form and faxed to Biogen or designee within 24 hours of the site becoming aware of the overdose. If an overdose results in an SAE, both the SAE and overdose forms must be completed and faxed to Biogen or designee. Should an overdose occur, the Investigator or designee must contact the Medical Monitor within 24 hours; refer to the Study Reference Guide for complete contact information.

9.5.4. Contraception and Pregnancy

Female subjects of childbearing potential (defined as any female who has experienced menarche) must have a negative pregnancy test at every study visit as described in Section 6.3.3 and must either be abstinent or practice adequate contraception during the study.

Male subjects must remain abstinent during the study or must be using an acceptable contraceptive method.

For the purposes of the study, acceptable contraception methods are abstinence, barrier contraceptives, intrauterine contraceptive devices, licensed hormonal products, and the use of a condom together with spermicidal foam/gel/film/cream/suppository. Abstinence is only acceptable as true abstinence (i.e., when this is representative of the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., abstinence for the duration of the study) and withdrawal are not acceptable methods of contraception.

If a subject becomes pregnant or a pregnancy is suspected, or if a male subject makes or believes that he has made someone pregnant during the study, then the study site staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of (possible) pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and is reported within 24 hours of the study site staff becoming aware.

Payment for all aspects of obstetrical, child, or related care will be the subject's responsibility.

Female subjects: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The subject with a confirmed pregnancy will be immediately withdrawn from study drug treatment. However, the subject will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the subject in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the study center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male subjects: The progress of the pregnancy in a male subject's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by relevant guidelines (e.g., Health Insurance Portability and Accountability Act [HIPAA]) and privacy considerations.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the conduct of the study (including follow-up).

9.5.5. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's official study contact list for complete contact information.

10. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints, Subsets, and Covariates

10.1.1. Safety and Tolerability Endpoints

- AEs and SAEs
- Vital signs and weight
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology, urinalysis, and urine total protein)
- Coagulation parameters (aPTT and INR)
- ECGs
- Use of concomitant medications

10.1.2. Efficacy Endpoints

For all groups/subjects:

- Achievement of motor milestones (WHO motor milestones and/or Section 2 of HINE)
- Time to death or permanent ventilation (tracheostomy **or** ≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event). The definition of an acute reversible event is provided in the SHINE Ventilation Endpoint Guidance.
- Percentage of subjects not requiring permanent ventilation
- Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, RULM, 6MWT, and contracture assessment
- Change from baseline in CMAP
- Growth parameters
- Proportion of CMAP responders
- Number of motor milestones achieved per subject
- Proportion of subjects who achieved standing alone
- Proportion of subjects who achieved walking with assistance
- Number of serious respiratory events
- Number and length of hospitalizations
- Change from baseline in Cobb-Angle on X-ray of the thoracolumbar spine
- Changes in quality of life assessments: PedsQL, and/or ACEND
- Disease-related hospitalizations and AEs
- Survival rate

[redacted]

10.1.6. Future Scientific Research Assessments

In subjects who provide additional optional consent, [redacted] may be stored for future, unspecified, [redacted]. Subjects will sign a separate written ICF if they opt for samples (including samples collected during index studies) to be retained and used in this way.

The samples collected may be utilized to identify or verify putative, prognostic, and predictive markers associated with the disease as well as markers of therapeutic response to treatment and/or develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated [redacted] data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

10.2. Sample Size Considerations

The sample size is based solely on the number of subjects enrolled in the ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ISIS 396443-CS12, and 232SM202 studies who may be eligible for participation in this study.

10.3. Populations

Intent-to-Treat (ITT) Set: All subjects who are enrolled and received at least 1 dose of nusinersen.

Safety Set: All subjects who are enrolled and received at least 1 dose of nusinersen.

[redacted]

10.4. Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

The analyses will focus on the ISIS 396443-CS11 data. The baseline will be the last non-missing assessment prior to the first dose of study treatment in the ISIS 396443-CS11 study. If any integration of data with the index study is conducted, the following definitions of baseline will be used:

- For safety, baseline for subjects on active treatment in the index study will be the index study baseline. For subjects on sham in the index study, baseline for safety will be the last non-missing assessment prior to the first dose of study treatment in this study.
- For efficacy, 2 baselines are defined for each subject: index study baseline and the baseline in this study, which is defined as the end-of-treatment assessment in index studies or the last non-missing assessment before the first dose of study treatment in this study.

10.5. Interim Analysis

Interim analyses may be performed to provide content for regulatory submissions and to support nusinersen drug development planning and business activities.

10.6. Planned Methods of Analysis

Data collected on CRF, laboratory data transfers, as well as any outcomes derived from the data, will be provided in the subject data listings. Subject data listings will be presented for all subjects enrolled into the study.

Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables and counts and percentages for categorical variables will be used to summarize most data.

All efficacy endpoints will be assessed in the ITT Set. All safety assessments will be performed on the Safety Set. [redacted]

10.6.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics, as well as subject disposition, will be summarized using descriptive statistics. All subjects enrolled will be included in a summary of subject disposition.

10.6.2. Safety and Tolerability Analysis

Safety analyses will be conducted in the Safety Set. Treatment duration and amount of study treatment received will be summarized.

All treatment-emergent AEs and SAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system by system organ class, preferred term, relationship to study treatment, and severity. Narratives of deaths and SAEs, including early withdrawals from the study treatment and from the study due to AEs, will also be provided.

When applicable for Groups 2A, 2B, and 3, the incidence of AEs will be evaluated by treatment phase (original dosing schedule phase versus MMDR).

Laboratory tests, including chemistry panel and complete blood count with differential, will be summarized by study visit. These safety variables will also be presented over time after study treatment administration, as appropriate. Vital sign results will be presented similarly.

Physical and neurological examination findings and results from ECG will be listed for review. As appropriate, results will also be summarized descriptively. Concomitant medication usage for each subject will be listed for review.

The end date of study drug exposure will be set to be at 1 year following the last administration of study drug. This is based on considerations of the half-life of nusinersen in plasma and CSF. Treatment-emergent AEs will be presented to include events occurring within this time frame.

Additional details of the analyses to be conducted will be provided in the Statistical Analysis Plan.

10.6.3. Efficacy Analysis

For subjects <2 years of age who have not yet achieved independent walking, motor milestones will be assessed using Section 2 of the HINE, which is composed of 8 motor milestone categories as follows: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each motor milestone category, there are 3 to 5 levels that can be achieved. All 8 motor milestones will be tested during each assessment. A subject whose results after testing all appear in the first column (no grasp, no kicking, unable to maintain head upright, and so on) has not achieved any motor milestone. Motor milestone achievement is depicted by movement from the left side of Table 3 to the right side of the table, as denoted by the Milestone Progression arrow in the table [Haataja 1999].

Table 3: Hammersmith Infant Neurological Examination Section 2 - Motor Milestones

Motor Milestone Category	Milestone Level Progression (Age Expected in Heathy Infants)[a] →				
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb; immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) [3 months]	Touches leg (4 to 5 months)	Touches toes (5 to 6 months)
Head control	Unable to maintain upright (<3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolling to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sit with support at hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) [10 months]
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4 to 5 months)	Crawling flat on abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4 to 5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) [11 months]	Walking independently (15 months)	

[a] Values for healthy infants in [Haataja 1999].

The proportion of motor milestone responders is defined based on the 7 motor milestones categories, with the exclusion of voluntary grasp using the assessment at the later study visits, as follows:

1. Subject demonstrates at least a 2-point increase in the motor milestone category of ability to kick or achievement of the maximal score on that category (touching toes) or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
2. Among the 7 motor milestone categories with the exclusion of voluntary grasp, subject demonstrates improvement (defined in [1]) in more categories than worsening.
   Note: For the category of ability to kick, similar to the definition of improvement in (1) mentioned previously, worsening is defined as at least a 2-point decrease or decrease to

the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease.

Subjects who die or withdraw from the study will be counted as nonresponders and will be included in the denominator for the calculation of the proportion. As a result, mortality will be accounted for in the motor milestone analysis. For subjects on permanent ventilation, because motor milestone assessment continues, functional scores after permanent ventilation has been achieved will be used to assess improvement in motor milestones.

The median time to death or permanent ventilation, survival rates over time, and the percentage of subjects requiring permanent ventilation will be estimated using the Kaplan-Meier method.

Change from baseline in CHOP INTEND total score and HFMSE score for subjects as described in Section 6.5.2.1 and Section 6.5.2.2, respectively, proportion of subjects who achieved any new motor milestone, number of motor milestones achieved per subject, proportion of subjects who achieved standing alone milestone, proportion of subjects who achieved walking with assistance milestone, change from baseline in RULM, change from baseline in 6MWT distance, CMAP parameters, change from baseline in PedsQL, change from baseline in ACEND, and disease-related hospitalizations and AEs, [redacted]

The proportion of CMAP responders is defined as the proportion of subjects with peroneal CMAP amplitude increasing to or maintained at ≥1 mV, comparing to the baseline, based on assessment at the later study visits.

Additional details of the analyses to be conducted will be provided in the Statistical Analysis Plan.

[redacted]

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent/Assent

The written informed consent and assent documents should be prepared in the language(s) of the potential subject population, based on an English version provided by the Sponsor and should be easy to understand.

Before a subject's participation in the study, the Investigator is responsible for obtaining written informed consent from the parent or legal guardian and, in cases where institutional guidelines and the subject's age dictate, informed assent from the subject, after adequate explanation of the

aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study treatment are administered. Sufficient time must be given to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity may be collected and may be used during analysis of study results.

The acquisition of informed consent/assent and the parent/legal guardian's/subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent/assent form(s) should be signed and personally dated by the parent/legal guardian/subject and by the study person who conducted the informed consent/assent discussion. The original signed informed consent/assent form(s) should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent/assent form(s) should be provided to the parent or guardian.

11.2. Ethical Conduct of the Study

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki. The applicable regulations and guidelines of current Good Clinical Practice (GCP), ICH, as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3. Institutional Review Board/Institutional Ethics Committee/Research Ethics Board

A copy of the protocol, proposed ICF and optional genetics and future research ICFs, proposed informed assent form (if applicable), other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval by the Investigator. A copy of the IRB/IEC written approval must be received and approved by the Sponsor before recruitment of subjects into the study and shipment of study drug. The Investigator's Brochure must be submitted to the IRB/IEC for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent/assent documents. The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IRB/IEC of SAEs occurring at the study center and other AE reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. A progress report must be submitted to the ethics committee at required intervals and not less than annually. Copies of the Investigator's reports, all IRB/IEC submissions, and the IRB/IEC continuance of approval must be sent to the Sponsor. At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and the Sponsor (or designee).

11.4. Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the CRFs or other documents submitted to the Sponsor, subjects should be identified by unique, anonymous initials and a subject study number only. Documents that are not for submission to the Sponsor

(e.g., signed informed consent/assent forms) should be kept in strict confidence by the Investigator.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject's parent or guardian to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

11.4.1. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, the subjects' race, ethnicity, and full date of birth will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the efficacy, safety, and/or PK profile of the study treatment.

SMA is caused by the loss of SMN protein due to a homozygous deletion or mutation or a compound heterozygous mutation in the SMN1 gene on chromosome 5q11-q13. Thus, patients with SMA are completely dependent on the amount of SMN protein produced by the SMN2 gene. Genetic modifiers, such as the number of copies of the SMN2 gene, are known to impact the eventual phenotype of SMA. The incidence and prevalence of SMA and its subtypes have been reported to vary based on country. One hypothesis for these variances is a difference in the frequency of certain genetic mutations that may be associated with different racial and ethnic groups within each country. Therefore, the race/ethnicity of subjects will be collected as part of the medical history, where local regulations allow. The full date of birth is needed in order to precisely calculate the age at achievement of motor milestones and the weight-for-age percentiles.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The regulatory authority and IRB/IEC must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the study. The Investigator **must** send a copy of the approval letter from the IRB/IEC to the Sponsor.

12.2. Study Termination

The Sponsor reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the termination to the Sponsor.

12.3. Study Documentation and Storage

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated study duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and study center staff is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include the following:

- Subject files containing completed CRFs, informed consents/assents, and supporting copies of source documentation.
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IRB and the Sponsor.
- If drug supplies are maintained at the study center, proof of receipt, study drug product accountability record, return of study drug for destruction, and all drug-related correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor prior to doing so.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Research Associate/Monitor (Sponsor or designee) is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Research Associate/Monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of study center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to in order evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data, a clinical data management review will be performed on subject data received by the Sponsor. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or study center notifications will be sent to the study center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the study center notifications, and agrees with the content.

12.5. Language

CRFs must be completed in English. Whenever possible, the trade name rather than the generic name for concomitant medications should be recorded and, if possible, in English. Generic names are acceptable if the trade name is unknown. Combination medications should be recorded using their trade name in English, if possible.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. Subjects will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the ICF.

12.7. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor or Ionis with the subject before the subject makes a decision to participate in the study).

12.8. Registration of Study and Disclosure of Study Results

The Sponsor (or designee) will register the study and poststudy results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

12.9. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

12.10. Publications

Details are included in the clinical trial agreement for this study.

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES: GROUPS 1A/1B AND 2A/2B BLIND LOADING DOSE PERIOD AND ALL GROUPS MMDR SCHEDULE

Study Period	**Screen**	**Treatment Period[a]**									**EOS Evaluation**
Study Day	**Day -21 to Day -1**	**Groups 1A/1B Blind Loading Study Treatment/Sham Days 1, 15, 29, and 64 (±1 day)**			**Groups 2A/2B Blind Loading Study Treatment/Sham Days 1, 29, and 85 (±1 day)**			**All Groups MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 (±14 days)**			**EOS MMDR Day 1800 (±14 days)**
Refer to Section 6 (Study Procedures)	**Screen[b c]**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**EOS/ET[d]**
Study treatment: nusinersen LP injection			X			X			X		
[redacted]											
The following assessments will be collected at Screening ONLY											
Informed consent/assent	X										
Inclusion/exclusion criteria	X										
Medical history	X										
The following assessments will be collected at every study visit											
Assessment of ventilator support/use	X	X			X			X			X
Ventilator use diary dispensation	X	X			X			X			X
Dysphagia assessment[e]	X	X			X			X			X
Urine/serum pregnancy test[f]	X	X			X			X			X
Weight	X	X			X			X			X
Growth parameters[g]	X	X			X			X			X

Study Period	**Screen**	**Treatment Period[a]**									**EOS Evaluation**
Study Day	**Day -21 to Day -1**	**Groups 1A/1B Blind Loading Study Treatment/Sham Days 1, 15, 29, and 64 (±1 day)**			**Groups 2A/2B Blind Loading Study Treatment/Sham Days 1, 29, and 85 (±1 day)**			**All Groups MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 (±14 days)**			**EOS MMDR Day 1800 (±14 days)**
Refer to Section 6 (Study Procedures)	**Screen[b c]**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**EOS/ET[d]**
Physical examination	X	X			X			X			X
Vital signs	X	X		X	X		X	X		X	X
Focused neurological examination[h]	X	X		X	X		X	X		X	X
The following assessments will be collected at Screening and/or predose MMDR Day 1, every 4 months thereafter (every MMDR Visit), and at EOS Evaluation/ET Visit											
Clinical safety laboratory evaluations	X[i]							X			X
Coagulation parameters[j]								X			X
[redacted]											
The following assessments will be collected at Screening and/or MMDR Day 1, every 8 months until Day 720 (i.e., MMDR Days 240, 480, and 720) and every 12 months thereafter (i.e., MMDR Days 1080 and 1440), and at EOS Evaluation/ET Visit											
Motor milestones[l]	X							X			X
Motor function assessments[m]	X							X			X
The following assessments will be collected at Screening and/or MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at EOS Evaluation/ET Visit											
ECG	X							X			X

Study Period	Screen	Treatment Period[a]									EOS Evaluation
Study Day	**Day -21 to Day -1**	**Groups 1A/1B Blind Loading Study Treatment/Sham Days 1, 15, 29, and 64 (±1 day)**			**Groups 2A/2B Blind Loading Study Treatment/Sham Days 1, 29, and 85 (±1 day)**			**All Groups MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, and 1680 (±14 days)**			**EOS MMDR Day 1800 (±14 days)**
Refer to Section 6 (Study Procedures)	**Screen[b c]**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**Pre**	**Dose**	**Post**	**EOS/ET[d]**
X-ray of spine[n]	X							X			X
Quality of life questionnaires (PedsQL and ACEND)[o]	X							X			X
The following assessments will be collected at Screening and/or MMDR Day 1, approximately every 16 months thereafter (i.e., MMDR Days 480, 960, and 1440), and at EOS/ET Visit											
CMAP (ulnar and peroneal)[p]	X							X			X
The following assessments will be collected as noted below or in the footnotes											
[redacted]											
Concomitant medication usage recording	**Continuous**										
AE collection	**Continuous**										
Telephone contact	1 to 14 days postdose and every other month (±14 days) thereafter (except dosing months)										

6MWT = 6-Minute Walk Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; [redacted]; CHOP INTEND = Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; CMAP = compound muscle action potential; CSF = cerebrospinal fluid; [redacted]; ECG = electrocardiogram; EOS = End-of-Study; ET = Early Termination; HFMSE = Hammersmith Functional Motor Scale – Expanded; LP = lumbar puncture; MMDR = Modified Maintenance Dosing Regimen; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetic(s); [redacted];

[redacted]; RULM = Revised Upper Limb Module; SMA = spinal muscular atrophy; US = United States; [redacted]; WHO = World Health Organization.

Notes: For growth parameters, dysphagia assessment, motor milestones, motor function assessments, [redacted], ECGs, X-ray of the spine, and quality of life questionnaires, if an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit. For study visits with a large number of planned assessments, assessments can be completed over 1 to 2 days and assessments for primary and secondary outcomes (e.g., motor milestones/functional assessments) should be prioritized. Among the laboratory measurements, quantitative urine total protein should be prioritized if there is not enough urine sample for all tests.

[a] Refer to Section 6 of this protocol for specific instructions and/or clarifications regarding which assessments to perform and the timing of each. General visit windows are as indicated in this appendix, unless stated otherwise for specific assessments in Section 6. **If further clarifications are required, contact the Study Medical Monitor.**

[b] If assessments are marked for Screening Visit and the subject is already enrolled in ISIS 396443-CS11, that assessment (unless marked for every visit) will be collected at MMDR Day 1.

[c] If the Screening assessments completed at the index EOS Evaluation Visit have occurred within 4 months, only the following Screening assessments need to be repeated: informed consent/assent, inclusion/exclusion criteria, new medical history, ventilator use, urine pregnancy test, weight, vital signs, and clinical safety laboratory evaluations (only if there were clinically significant abnormalities at the index EOS Evaluation Visit).

[d] Subjects who discontinue treatment will complete an early termination visit 4 months (+14 days) after administration of the last dose of nusinersen, unless consent is withdrawn.

[e] Dysphagia assessment may be performed within 7 days prior to the dosing visit using the Parent Assessment of Swallowing Ability Weekly Version. Assessment will be performed for all subjects including those on tube feeding; however, tube-fed subjects only need to be assessed with Questions 1 to 5 of the survey.

[f] Urine pregnancy tests will be performed and evaluated predose (within 7 days) at every visit only on females of childbearing potential (defined as any female who has experienced menarche).

[g] In subjects with scoliosis and contractures, the Investigator (or designee) may measure arm span or ulnar length in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. The investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist.

[h] Neurological examinations are conducted within 7 days of dosing and approximately 1 hour after dosing. If sedation was used, please allow sufficient recovery time for the subject to be fully engaged in the examination because it is important that the data collected truly reflect the subject's neurological performance.

[i] Clinical safety laboratory evaluations are not required to be repeated on MMDR Day 1 if visit is within 7 days of Screening.

[j] Coagulation testing will continue to be conducted at each visit or up to 7 days prior to dosing and results must should be reviewed prior to dosing. In situations where predose verification of coagulation laboratory results is not feasible or optimal (e.g., prolonged sedation of the subject would be required to allow adequate time for lab processing), the Investigator may exercise discretionary clinical judgment and proceed with the LP procedure, based on the subject's clinical and coagulation laboratory results history.

[k] For subjects ≥12 years of age at US sites whose primary language is American English only. Assessment can be performed up to 7 days prior to the dosing visit.

[l] The WHO motor milestone assessment should be performed even if the subject is not ambulatory. If the WHO motor milestones assessment has already been performed at Day 960 for a subject prior to approval of Protocol Version 5.0 at a site, the WHO motor milestones assessment will still need to be performed at Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit.

[m] Motor function assessment includes CHOP INTEND, HFMSE, RULM, 6MWT, and contracture assessment. If motor function assessments have already been performed at Day 960 for a subject prior to approval of Protocol Version 5.0 at a site, motor function assessments (i.e., CHOP INTEND, HFMSE, RULM, 6MWT, and contracture assessment) will still need to be assessed at Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit.

[n] X-ray assessments performed as standard of care may be used for protocol-required assessments, if the image acquisition guidelines are met and the X-ray was obtained within 4 months prior to the scheduled visit.

[o] If needed, the subject's caregiver may complete the applicable quality of life questionnaires at home up to 7 days prior to the dosing visit. If a quality of life questionnaire is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

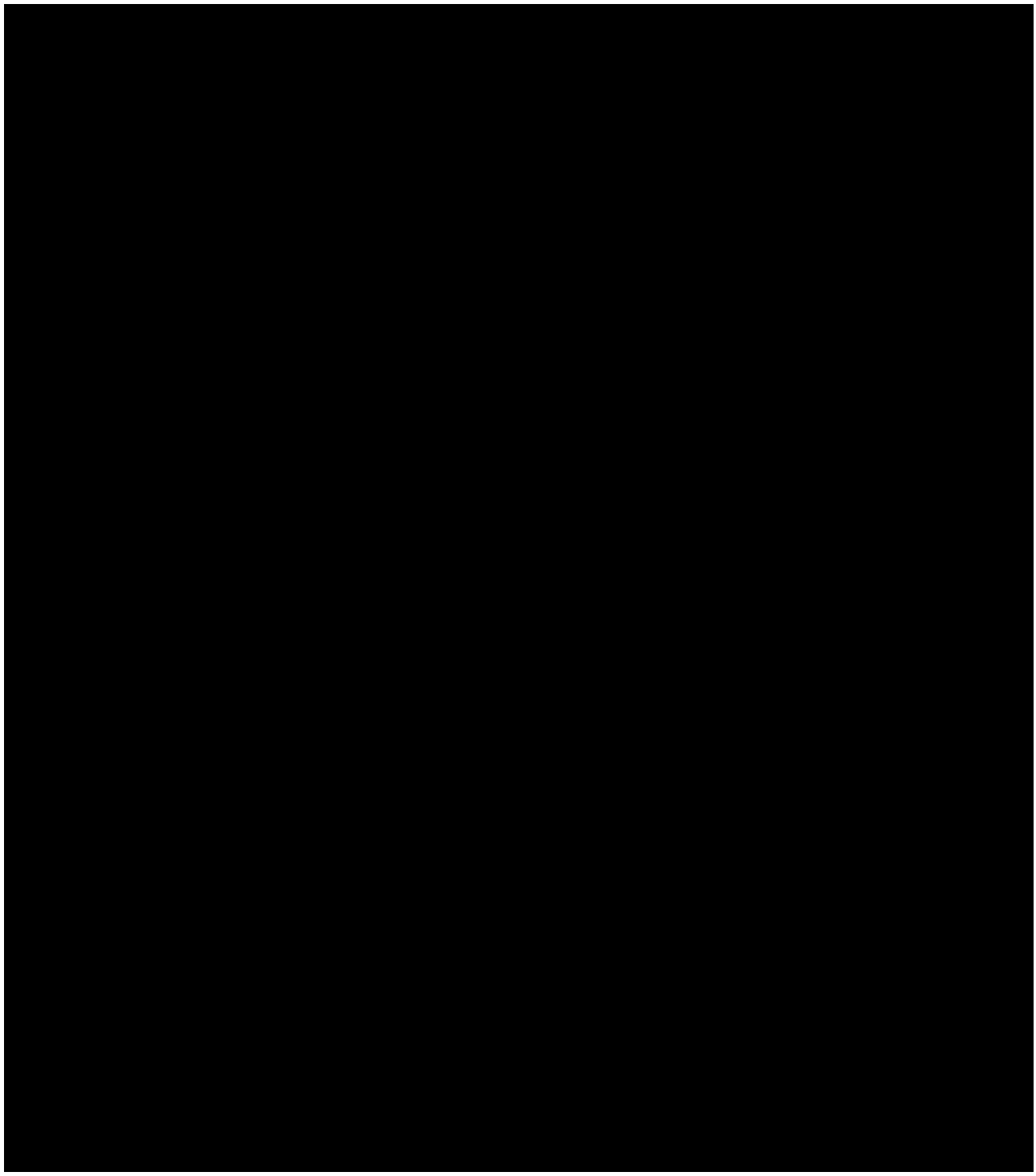
[p] If CMAP measurements are not approved as a mandatory outcome measure by local authorities, they will be considered optional in the respective country.

APPENDIX B. LABORATORY ANALYTES

Clinical Safety Assessments (minimum requirements)		**Other Assessments**
Blood Chemistry	Urinalysis	Pregnancy
Sodium	Specific gravity	Urine hCG
Potassium	pH	
Chloride	Protein	[redacted]
Total protein	Glucose	[redacted]
Albumin	Ketones	
Calcium	Bilirubin	[redacted]
Phosphorus	Blood	[redacted]
Bicarbonate	Red blood cells	
Glucose	White blood cells	[redacted]
BUN	Epithelial cells	[redacted]
Creatinine	Bacteria	[redacted]
Cystatin C	Casts	[redacted]
Total serum bilirubin (direct and indirect)	Crystals	[redacted]
Alkaline phosphatase	Hematology	[redacted]
AST (SGOT)	Red blood cells	[redacted]
ALT (SGPT)	Hemoglobin	[redacted]
CPK	Hematocrit	
CK MB	Platelets	The following are to be assessed by local laboratory only
CK BB	WBCs	Urine total protein
CK MM	WBC differential (% and absolute)	Coagulation (aPTT and INR)
GGT	• Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	

Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CK BB = creatine kinase isoenzyme predominantly expressed in the brain; CK MB = creatine kinase isoenzyme expressed in the myocardium; CK MM = creatine kinase isoenzyme expressed in skeletal muscle; CPK = creatinine phosphokinase; CSF = cerebrospinal fluid; [redacted]; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; PK = pharmacokinetic(s); [redacted]; SMA = spinal muscular atrophy; SMN = survival motor neuron; WBC = white blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Note: Quantitative urine total protein should be prioritized if there is not enough urine sample for all tests.



15. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol ISIS 396443-CS11 V6.0, "An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site Name (Print) Site Number

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AMENDMENT SUMMARY

Biogen Protocol ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Version 6.0

Date: 20 October 2021

EUDRA CT Number: 2015-001870-16

Version 6.0 of the protocol has been prepared for this amendment, which supersedes Version 5.0 dated 24 March 2020.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol ISIS 396443-CS11 is to limit the number of subjects who are receiving nusinersen concomitantly with other SMA therapies to 20% (n = 58) of the total population. The text describing the number of subjects who will be able to be concurrently treated with nusinersen and other SMA therapies has been added

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 8.11.1, Concomitant Therapy

Now reads:

8.11.1 Concomitant Therapy

A concomitant therapy is any non-protocol-specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered between the beginning of Screening and the last telephone contact or study visit.

Subject's parents/guardians should consult with the Site Investigator or qualified designee prior to initiating any new medication, including non-prescription compounds or any other non-drug therapy.

8.11.1.1 Allowed Concomitant Therapy

Any concomitant medications, including SMA therapies, will be captured in the CRF.

Approved concomitant therapies may be used at the discretion of the Investigator. With implementation of Protocol Version 6.0, investigators with subjects newly seeking combination therapy with other SMA therapies should consult and obtain approval from the Medical Monitor. This will be permitted for country-approved SMA therapies, if the total number of study subjects concurrently receiving nusinersen and other SMA therapies has not yet reached 20% of all enrolled subjects. This is consistent with the primary and secondary objectives of this study. Any subjects already receiving combination therapy with other SMA therapies at the time of Protocol Version 6.0 implementation may continue this combination therapy regardless of the 20% limit.

Throughout the study, the Site Investigators or designated licensed physicians may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care. ~~Subjects will be allowed to take concomitant Food and Drug Administration-approved and/or country-specific approved therapies and experimental therapies for SMA (at the Investigator's discretion).~~ In addition, a mild sedative (e.g., midazolam) and a local anesthetic (e.g., lidocaine) may be used for the LP procedure (per institutional guidance).

8.11.1.2 Disallowed Concomitant Therapy

~~None.~~**As noted above in Section 8.11.1.1, with implementation of the Protocol Version 6.0, new subjects seeking combination therapy of nusinersen with other SMA therapies should consult the Medical Monitor. Any subjects already receiving investigational drug for any other condition should consult with the Medical Monitor.**

Rationale: The primary objective of this study is to evaluate the long-term safety and tolerability of nusinersen administered by intrathecal (IT) injection to subjects with SMA who previously participated in investigational studies of ISIS 396443. The secondary objective is to examine the long-term efficacy of nusinersen administered by IT injection in these same subjects. Including a limit on the total number of subjects concurrently treated with nusinersen and other SMA therapies is consistent with evaluating the primary and secondary objectives of the study in subjects receiving only nusinersen. In addition, a limit on the total number of subjects concurrently treated with nusinersen and other SMA therapies will maintain the intent of the European Union post-authorization commitment to evaluate the long-term safety and efficacy of nusinersen.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Protocol Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Sections 6.3.2, Dysphagia Assessment

Change: Text was added to clarify that if an assessment was not performed at a visit, then the assessment should be collected at subsequent visit(s) until the assessment is completed (but should not be done twice at any visit).

Now reads:

…If an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

Rationale: To clarify that the investigator should continue to attempt to complete the missed assessment at subsequent visits until the assessment is completed.

This change affects Sections 6.3.5 (Growth Parameters), 6.4.5 ([redacted]), 6.5.1 (Motor Milestones), 6.5.2.1 (Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease), 6.5.2.2 (Hammersmith Functional Motor Scale – Expanded), 6.5.2.3 (Revised Upper Limb Module), 6.5.2.4 (Six-Minute Walk Test), 6.5.2.5 (Contracture Assessment), 6.6.1 (Electrocardiograms), 6.6.2 (X-Ray of Spine), 6.6.3 (Quality of Life Questionnaires), 6.7.1 (Compound Muscle Action Potential), 6.8.1 ([redacted]), and Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 6.3.2, Dysphagia Assessment

Change: Text was added to allow the dysphagia assessment to be done at home 7 days prior to dosing.

Now reads:

Dysphagia ~~will~~ **assessment may** be ~~assessed within~~**performed at home up to** 7 days prior to the dosing visit using the Parent Assessment of Swallowing Ability ~~w~~**W**eekly ~~survey~~**Version**.

Rationale: The change was made to allow for completion of the dysphagia assessment in alignment with other assessments that can be conducted at home.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 6.3.5, Growth Parameters

Change: Text was revised to allow for ulnar length measurement (rather than only arm span) in lieu of body length or height.

Now reads:

…

In subjects with scoliosis **and contractures**, the Investigator (or designee) may measure arm span **or ulnar length** in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. ~~If arm span cannot be measured due to contractures,~~ ~~t~~**T**he investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist.

Rationale: This change will allow the sites more flexibility to measure growth parameters by using only ulnar length in instances where other growth parameters are challenging to measure.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 6.3.8, Neurological Examinations

Change: Text was revised to change the window of completion of the neurological examination to within 7 days of dosing.

Now reads:

Focused neurological examinations will be performed ~~predose~~**within 7 days of dosing and** approximately 1 hour postdose at every onsite visit throughout the study. **Please note**: If sedation was used, please allow sufficient recovery time for the subject to be fully engaged in the examination because change from baseline in neurological examinations outcome is a primary study endpoint. It is important that the data collected truly reflect the subject's neurological performance.

Rationale: Clarification that the neurological examinations can be done along with other predose assessments.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 6.4.1, Clinical Safety Laboratory Evaluations

Change: Text was revised to provide details on prioritization of urinalysis tests in the event there is not enough sample for all tests.

Now reads:

…

For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation. **Quantitative urine total protein assessment should be prioritized if there is not enough urine sample for all tests.**

Rationale: Clarification regarding prioritization of urinalysis tests in the event there is not enough sample for all tests.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule) and new Appendix B (Laboratory Analytes).

Section 6.4.2, Coagulation Parameters

Change: Text was revised to provide additional clarity around the requirement that coagulation testing results must be reviewed prior to dosing.

Now reads:

…

~~The coagulation testing must be performed and reviewed predose (within 7 days of dosing).~~**Coagulation testing will continue to be conducted at each visit or up to 7 days prior to dosing, and results should be reviewed prior to dosing. In situations where predose verification of coagulation laboratory results is not feasible or optimal (e.g., prolonged sedation of the subject would be required to allow adequate time for laboratory processing), the Investigator may exercise discretionary clinical judgment and proceed with the LP procedure, based on the subject's clinical and coagulation laboratory results history.**

Rationale: While coagulation results should be reviewed prior to dosing, there may be situations where this is not feasible, and the Investigator may proceed with the lumbar puncture (LP) based on clinical judgment.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 6.6.3, Quality of Life Questionnaires

Change: Text was added to clarify that if a quality-of-life questionnaire was not performed at a visit, then the assessment should be collected at subsequent visit(s) until the assessment is completed (but should not be done twice at any visit).

Now reads:

…

The questionnaires that are performed at a given visit will depend on the subject's age at that visit. If needed, the subject's caregiver may complete the applicable quality-of-life questionnaires at home up to 7 days prior to dosing visit. If a quality-of-life questionnaire is not performed at a visit, ~~it~~**attempts** should be ~~collected~~**made to perform the assessment** at the ~~next scheduled~~**subsequent** dosing visit**(s) until completed; however, an assessment should not be performed more than once at any visit**.

Rationale: This text was revised to clarify that the investigator should continue to attempt to complete the missed assessment at subsequent visits.

This change also affects Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule).

Section 8.8, Adjustment of Dose and/or Treatment Schedule

Change: Text was revised to indicate that in the event of a delayed or missed dose, an adjustment in dosing schedule was allowed in the event of unique circumstances, including those related to the coronavirus disease 2019 pandemic, as indicated in the DHA.

Now reads:

No adjustment of dose ~~will be~~**is** permitted. **If dosing does not occur as per the schedule of activities, a protocol deviation should be logged.** In the event of **delayed or missed doses due to, for example,** a concurrent illness or ~~ongoing AE~~ ~~that would prevent the dosing procedure from being performed safely, an adjustment in the dosing schedule may be permitted but must be approved by~~ **other circumstances (e.g., the coronavirus disease 2019 pandemic)**, the ~~Medical Monitor. In this case,~~**Investigator should refer to the DHA, which includes recommended** dosing~~will be resumed as soon as possible.~~**administration in the event of delayed or missed doses.**

Rationale: Text was revised to broaden the circumstances in which delayed or missed doses may have occurred and to allow adjustment to the dose schedule as indicated in the DHA.

Section 8.9, Discontinuation of Study Treatment

Change: Text was revised to indicate that all subjects who discontinue study treatment will complete an early termination visit approximately 4 months after their last dose of nusinersen.

Now reads:

A subject must permanently discontinue study treatment for any of the following reasons:

- The subject or subject's parent/guardian withdraws consent.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.

The reason for discontinuation of study treatment must be recorded in the case report form (CRF) and source documentation.

Subjects who discontinue treatment ~~and do not agree to continue in the study should have~~**will complete** an ~~ET Visit performed (Appendix A).~~

~~Subjects who discontinue treatment but agree to continue in the study should have an ET~~**early termination** visit ~~performed (Appendix A). Subsequently, the first follow-up assessment will be planned approximately 4~~ months ~~(±~~**(**+14 days) after **administration of** the last ~~open-label maintenance~~ dose of nusinersen~~. Afterward, annual (±30 days) follow-up assessments will be performed (Appendix B). Telephone contact will occur every 4 months (±14 days), except for months when in-clinic visits occur. During these calls, changes in concomitant medications, ancillary procedures, AEs, and ventilator use/status will be recorded.~~

~~The following assessments will be conducted at these follow-up visits:~~

- ~~Assessment of ventilator support/use~~
- ~~Weight~~
- ~~Growth parameters~~
- ~~Physical examination~~
- ~~Vital signs~~
- ~~Focused neurological examination~~
- ~~Motor milestones~~
- ~~Motor function assessments, as appropriate per Investigator's discretion, including CHOP INTEND, HFMSE, RULM, and/or 6MWT (optional)~~

~~The following assessments will be collected on a continuous basis:~~

- ~~AEs and serious adverse events (SAEs) (see~~ **(Appendix A), unless consent is withdrawn (Section 8.10**~~10.6.2 for analysis of AEs~~).

- ~~Use of concomitant medications~~
- ~~Ancillary procedure recording~~

~~For subjects who discontinue from study treatment but agree to continue the study, the end date of study exposure will be set to be at 1 year following the last administration of study drug.~~

Rationale: These changes are consistent with the rationale of this study to assess long-term safety, efficacy, and tolerability of nusinersen. Additional follow-up beyond 4 months for collection of safety assessments in subjects who discontinued nusinersen is no longer required.

This change also affects Figure 2 (Study Design and Treatment Schema: Groups 1A and 1B), Figure 3 (Study Design and Treatment Schema: Groups 2A and 2B), Figure 4 (Study Design and Treatment Schema: Groups 3, 4, and 5), Section 3.4.2 (Treatment), Section 10.6.2 (Safety and Tolerability Analysis), and Appendix A (Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule). Appendix B (Schedule of Procedures for Subjects Who Discontinued Nusinersen but Agree to Remain in the Study) was deleted due to this change.

Section 11.4.1, Subject Data Protection

Change: Text was added to include language regarding the collection of a subject's race, ethnicity, and full date of birth.

Now reads:

Prior to any testing under this protocol, including screening tests and assessments, the subject's legally authorized representative(s) must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, the subjects' race, ethnicity, and full date of birth ~~may~~**will** be collected ~~for~~**(unless the collection is not permitted by applicable law or not approved by** the ~~purposes of~~**governing ethics committee). These** data **will be used in the** analysis~~.~~ **of the efficacy, safety, and/or PK profile of the study treatment.**

SMA is caused by the loss of SMN protein due to a homozygous deletion or mutation or a compound heterozygous mutation in the SMN1 gene on chromosome 5q11-q13. Thus, patients with SMA are completely dependent on the amount of SMN protein produced by the SMN2 gene. Genetic modifiers, such as the number of copies of the SMN2 gene, are known to impact the eventual phenotype of SMA. The incidence and prevalence of SMA and its subtypes have been reported to vary based on country. One hypothesis for these variances is a difference in the frequency of certain genetic mutations that may be associated with different racial and ethnic groups within each country. Therefore, the race/ethnicity of subjects will be collected as part of the medical history, where local regulations allow. The full date of birth is needed in order to ~~be able to~~precisely calculate the age at achievement of motor milestones and the weight--for--age percentiles.

Rationale: Race and ethnicity data can be collected, provided it is noted in the protocol; therefore, this text has been added to indicate that these parameters will be collected to be used in the analysis of the efficacy, safety and/or PK profile of nusinersen.

Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule

Change: Text was added to clarify that if a quality-of-life questionnaire was not performed at a visit, then the assessment should be collected at subsequent visit(s) until the assessment is completed (but should not be done twice at any visit). Text was also added to provide additional clarity on prioritization of assessments on visit days when a substantial number of assessments are planned.

Now reads:

Notes: For growth parameters, dysphagia assessment, motor milestones, motor function assessments, [redacted], [redacted], ECGs, X-ray of the spine, and quality of life questionnaires, if an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit. For study visits with a large number of planned assessments, assessments can be completed over 1 to 2 days and assessments for primary and secondary outcomes (e.g., motor milestones/functional assessments) should be prioritized. Among the laboratory measurements, quantitative urine total protein should be prioritized if there is not enough urine sample for all tests.

Rationale: To clarify that the investigator should continue to attempt to complete the missed assessment at subsequent visits. Clarification regarding prioritization of urinalysis tests in the event there is not enough sample for all tests. In the event that all assessments cannot be done at 1 visit (e.g., due to limited time, patient fatigue), allowance is provided to complete all assessments over 2 days instead of 1 day and prioritization of assessments is provided.

The change regarding urine total protein assessment also affects new Appendix B (Laboratory Analytes).

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were revised throughout the protocol.
- Background information on SMA and the clinical experience with nusinersen were updated and sources were added to references.
- Numbering of the Appendices was updated due to deletion of previous Appendix B (Schedule of Procedures for Subjects Who Discontinued Nusinersen but Agree to Remain in the Study).
- Minor editorial changes were made throughout the document.
- Typographical errors and formatting were corrected.

LIST OF ABBREVIATIONS

AE	adverse event
CRF	case report form
DHA	Directions for Handling and Administration
ECG	electrocardiogram
IT	intrathecal
LP	lumbar puncture
MMDR	Modified Maintenance Dosing Regimen
PK	pharmacokinetic(s)
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2

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AMENDMENT SUMMARY

Biogen Protocol ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Version 5.0

Date: 24 March 2020

EUDRA CT Number: 2015-001870-16

Version 5.0 of the protocol has been prepared for this amendment, which supersedes Version 4.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol ISIS 396443-CS11 is to change the standard neurological examination to a focused neurological examination.

Section 6.3.8, Neurological Examinations

Now reads:

Focused ~~N~~**n**eurological examinations will be performed predose **and** approximately 1 hour postdose at every onsite visit throughout the study. **Please note:** If sedation was used, please allow sufficient recovery time for the subject to be fully engaged in the examination because change from baseline in neurological examinations outcome is a primary study endpoint. It is important that the data collected truly reflect the subject's neurological performance.

…

For all subjects >24 months of age, ~~standard~~**focused** neurological examinations, which include assessments of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes, will be conducted.

…

Rationale:

The focused neurological examination will allow the collection of sufficient data on neurological status with a significant reduction in burden for participants in this long-term extension study.

This change also affects Section 6.10, Study Assessments to be Repeated Due to Delayed Dosing: Section 8.9, Discontinuation of Study Treatment; Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule; and Appendix B, Schedule of Procedures for Subjects Who Discontinued Nusinersen but Agree to Remain in the Study.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Protocol Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 6.3.5, Growth Parameters

Change: Ulnar length was added as a growth parameter measurement for a subset of participants whose height, body length, and arm span cannot be measured.

Now reads:

…

In subjects with scoliosis, the Investigator (or designee) may measure arm span in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. **If arm span cannot be measured due to contractures, the investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist.**

…

Rationale: Height, body length, and arm span measurements in participants with scoliosis may not be possible in those who have severe contractures. The inclusion of ulnar length allows investigators a viable option to include a growth parameter measurement for these participants.

This change also affects Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule; and Appendix B, Schedule of Procedures for Subjects Who Discontinued Nusinersen but Agree to Remain in the Study.

[redacted]

[redacted]

[redacted]

[redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were revised throughout the protocol.
- On the Sponsor Signature Page, the signatory's role and name and were updated. The Sponsor name was updated to align with the current protocol template.
- The date was removed from the headings.
- The List of Abbreviations and abbreviations in text were updated.
- Minor editorial changes were made throughout the document.
- Typographical errors and formatting were corrected.
- [redacted]
- In Section 11.4.1, Subject Data Protection, the collection of the full date of birth and the rationale to include these data were added to the protocol.
- [redacted]

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AMENDMENT SUMMARY

Biogen Protocol ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Version 4.0

Date: 19 November 2019

EUDRA CT Number: 2015-001870-16

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.0 dated 30 October 2017.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol ISIS 396443-CS11 is to change the interval of clinical assessment visits after the Modified Maintenance Dosing Regimen (MMDR) Day 720 Visit from every 8 months to every 12 months.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 6.5, Study Assessments for Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 8 Months Until MMDR Day 720 and Every 12 Months Thereafter, and the End-of-Study Evaluation/Early Termination Visit

Now reads:

6.5. Study Assessments for Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 8 Months **Until MMDR Day 720 and Every 12 Months** Thereafter ~~(Every Other Modified Maintenance Dosing Regimen Visit)~~, and the End-of-Study Evaluation/Early Termination Visit

Section 6.5.1, Motor Milestones

For all subjects, motor milestones will be assessed using the World Health Organization (WHO) Motor Milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004] at Screening and/or **predose at** MMDR Day 1, every 8 months **until MMDR Day 720 (inclusive) [i.e., predose at MMDR Days 240, 480, and 720] and every 12 months** thereafter (i.e., **predose at** MMDR Days **1080 and 1440**~~240, 480, 720, and so on~~), and at the EOS Evaluation **(MMDR Day 1800 [±14 days])**/ET Visit. **If the WHO motor milestones assessment has already been performed at Day 960 for a participant prior to approval of this protocol version at a site, the WHO motor milestones assessment will still need to be performed at Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit.**

…

Section 6.5.2, Motor Function Assessments

Motor function assessments include all assessments listed in Section 6.5.2.1, Section 6.5.2.2, Section 6.5.2.3, ~~and~~ Section 6.5.2.4, **and Section 6.5.2.5**. Motor function assessments will be performed at Screening and/or **predose at** MMDR Day 1, every 8 months **until MMDR Day 720 (inclusive) [i.e., predose at MMDR Days 240, 480, and 720] and every 12 months** thereafter (i.e., **predose at** MMDR Days **1080 and 1440**~~240, 480, 720, and so on~~), and at the EOS Evaluation **(MMDR Day 1800 [±14 days])**/ET Visit. **If motor function assessments have already been performed at Day 960 for a participant prior to approval of this protocol version at a site, motor function assessments (i.e., CHOP INTEND, HFMSE, Revised Upper Limb Module [RULM], 6-Minute Walk Test [6MWT], and contracture assessment)**

will still need to be assessed at Days 1080, 1440, and 1800. Assessment can be performed up to 7 days prior to the dosing visit.

Rationale: Frequency of motor milestones and motor function assessments were reduced from every 8 months to every 12 months to minimize burden for subjects and their families (thus potentially helping with trial retention), while maintaining meaningful intervals between assessments. This change in frequency of assessments is to begin after Day 720, as most subjects have already had assessments until Day 720. To account for the variable availability of this protocol version at sites, language was added to emphasize that if a subject has had assessments on MMDR Day 960, he/she will also need to be assessed on MMDR Days 1080, 1440, and 1800 to ensure consistent collection of data for all subjects at these less frequent time points in Year 3 and beyond of participation in this study.

This change also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Protocol Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 3.4.2, Treatment

Change: The window for each MMDR dosing visit was extended from ±7 days to ±14 days. In addition, a sentence for the schedule of other MMDR dosing visits was added.

Now reads:

Subjects who entered the study after completing the double-blind studies ISIS 396443-CS3B and ISIS 396443-CS4 (i.e., subjects in Groups 1A, 1B, 2A, and 2B) completed a blinded loading dose period and then transitioned to the open-label MMDR period. Subjects who were already enrolled in ISIS 396443 CS11 (SHINE) and had already participated in the blinded loading dose period continued their blinded loading dose/sham schedule through the last scheduled dose in that loading dose period and then transitioned to the open-label MMDR dosing schedule at their next study visit, which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). **The schedule for other MMDR dosing visits should be based on MMDR Day 1.**

…

Subjects who entered the study after completing open-label studies ISIS 396443-CS12 and ISIS 396443-CS3A (i.e., subjects in Groups 3 and 4) will enter directly into the open-label MMDR period at MMDR Day 1. Subjects who were already enrolled in ISIS 396443-CS11 and were already receiving maintenance doses according to the original maintenance schedule transitioned to MMDR Day 1 at their next study visit (regardless of how many maintenance doses already received in the original schedule), which was scheduled as close as possible to 120 days from the date of the last dosing visit (i.e., date of last dosing visit + 120 days = MMDR Day 1). Subjects entering the study after completing open-label Study 232SM202 (i.e., subjects in Group 5) will enter directly into the open-label MMDR period at MMDR Day 1. **The schedule for other MMDR dosing visits should be based on MMDR Day 1.**

The MMDR dosing schedule will consist of MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, **960, 1080, 1200, 1320, 1440, 1560, and 1680** ~~and so on every 4 months~~ (±~~7~~**14** days) until the EOS Evaluation/Early Termination (ET) Visit. The EOS Evaluation Visit will occur 4 months after the last open-label maintenance dose of nusinersen on approximately MMDR Day 1800 (±~~7~~**14** days).

Rationale: The window for each MMDR dosing visit was extended to ±14 days, as this extended window allows for reduction in participant burden (thus potentially helping with trial retention), while maintaining acceptable intervals between dosing visits. Text was added to clarify that the schedule for other MMDR dosing visits should be based on MMDR Day 1 to further ensure consistent calculation of dosing visit days across participants and sites.

The extension in window for each MMDR dosing visit was also applied to Section 3.4.3, Post-Treatment Follow-Up; Section 3.5, End of Study; Section 6.9.1, Telephone Assessments; Figure 2, Study Design and Treatment Schema: Groups 1A and 1B; Figure 3, Study Design and Treatment Schema: Groups 2A and 2B; Figure 4, Study Design and Treatment Schema: Groups 3, 4, and 5; and Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

Section 6.6.3.3, Clinical Global Impression – Improvement

Change: Section 6.6.3.3 was deleted.

Now reads:

~~Section 6.6.3.3, Clinical Global Impression – Improvement~~

~~The Clinical Global Impression of Change Rating Scale (CGI) was developed as a brief, stand-alone assessment of the clinician's view of the patient's global functioning after initiating a study medication[Guy 1976]. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. CGI is administered by an experienced clinician who is familiar with the disease under study and the likely progression of treatment. The clinician makes a judgment about the total picture of the patient at each visit: the severity of illness, the patient's level of distress and other aspects of impairment, and the impact of the illness on functioning. The CGI is rated without regard to the clinician's belief that any clinical changes are or are not due to medication and without consideration of the etiology of the symptoms.~~

~~The Clinical Global Impression – Improvement (CGI-I) scale is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and is rated as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. For assessment of CGI-I, the baseline state is defined as follows:~~

- ~~Groups 1, 3, and 4: Baseline is defined as the CGI-I score at Screening for the present extension study.~~
- ~~Group 2: Baseline is defined as the CGI-I score at Screening in the index study ISIS396443-CS4.~~
- ~~Group 5: Baseline is defined as the CGI-I score at Screening in the index study 232SM202.~~

~~CGI-I is to be administered consistently by the same rater for each study subject. Separate CGI-I assessment will be administered to the Investigator (Principal Investigator or Subinvestigator) and caregiver.~~

Rationale: The Clinical Global Impression – Improvement (CGI-I) scale was removed from participants' schedule of assessments because the data collected from this assessment would likely be difficult to reliably interpret. The CGI-I assessment requires comparison of a subject's current state to a baseline state. The duration of time since initiation of treatment (upward of 3 years for most participants in this study) compromises the quality of the data collected and the interpretation of the results. Furthermore, there have been inconsistencies across participants in the definition of "baseline." Given these concerns in addition to the goal of reducing participant burden in the trial, the decision was made to stop assessing CGI-I.

This change also affected Section 10.1.2, Efficacy Endpoints; Section 10.6.3, Efficacy Analysis; and Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

Section 6.10, Study Assessments to be Repeated Due to Delayed Dosing

Change: A new section for repeated procedures due to a delay in dosing was added.

Now reads:

If a dosing visit is delayed, the following predose procedures should be repeated at the delayed dosing visit:

- **Vital signs (resting blood pressure, pulse, pulse oximetry, respiratory rate, and temperature)**
- **Weight**
- **Growth parameters**
- **Ventilator use**
- **Physical examination**
- **Neurological examination**
  - **General neurological examination for subjects >24 months of age**
  - **HINE Section 1 and 3 for subjects ≤24 months of age**
- **Safety laboratory evaluations:**
  - **Chemistry (central laboratory)**
  - **Hematology (central laboratory)**
  - **Urinalysis (central laboratory)**
  - **Urine total protein (local laboratory)**
- **Coagulation parameters (local laboratory)**
- [redacted]
- [redacted]
- **Urine/serum pregnancy test**

- **ECG (predose at applicable visits: MMDR Days 1, 360, 720, 1080, and 1440)**
- **Concomitant medications assessment**
- **Ancillary procedure recording**
- **AE collection**

All procedures should be performed predose (within 7 days of dosing). Vital signs and neurological examination should also be performed at approximately 1-hour postdose. The purpose of repeating these assessments is to ensure the safety of the subject prior to dosing and to collect important study information pertaining to each dose.

At the discretion of the Investigator, additional visit-specific assessments may be repeated as needed, as long as they are performed predose within 7 days of the rescheduled dosing visit.

Rationale: The text was added to ensure the safety of the subject prior to dosing and to collect important study information pertaining to each dose.

This change also affected Section 6.3.1, Ventilator Use Diary Recording; Section 6.3.3, Urine Pregnancy Tests; Section 6.3.4, Weight; Section 6.3.5, Growth Parameters; Section 6.3.6, Physical Examinations; Section 6.3.7, Vital Signs; Section 6.3.8, Neurological Examinations, Section 6.4.1, Clinical Safety Laboratory Evaluations; Section 6.4.2, Coagulation Parameters; [redacted] and Section 6.6.1, Electrocardiograms.

Section 8.9, Discontinuation of Study Treatment

Change: Text was added for study assessments that need to be performed when a subject stops treatment but agrees to continue in the study.

Now reads:

A subject must permanently discontinue study treatment for any of the following reasons:

- The subject or subject's parent/guardian withdraws consent.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.

The reason for discontinuation of study treatment must be recorded in the case report form (CRF) and source documentation.

Subjects who discontinue treatment ~~will continue follow-up through scheduled study visits, unless consent is withdrawn~~ **and do not agree to continue in the study should have an ET Visit performed** (Appendix A).

Subjects who discontinue treatment but agree to continue in the study should have an ET visit performed (Appendix A). Subsequently, the first follow-up assessment will be planned approximately 4 months (±14 days) after the last open label maintenance dose of nusinersen. Afterward, annual (±30 days) follow-up assessments will be performed (Appendix B). Telephone contact will occur every 4 months (±14 days), except for months when in-clinic visits occur. During these calls, changes in concomitant medications, ancillary procedures, AEs, and ventilator use/status will be recorded.

The following assessments will be conducted at these follow-up visits:

- **Assessment of ventilator support/use**
- **Weight**
- **Growth parameters**
- **Physical examination**
- **Vital signs**
- **Neurological examination**
- **Motor milestones**
- **Motor function assessments, as appropriate per Investigator's discretion, including CHOP INTEND, HFMSE, RULM, and/or 6MWT (optional)**
- [redacted]

The following assessments will be collected on a continuous basis:

- **AEs and serious adverse events (SAEs) (see Section 10.6.2 for analysis of AEs)**
- **Use of concomitant medications**
- **Ancillary procedure recording**

Rationale: Subjects are given the option to continue participation in the study even after discontinuation of nusinersen treatment, which allows for the collection of valuable follow-up information after nusinersen treatment. Subjects who choose to remain in the study despite discontinuing nusinersen treatment should continue to have a predefined set of safety and efficacy assessments to ensure consistent collection of data.

This change also affected Section 3.4.2, Treatment; Section 10.6.2, Safety and Tolerability Analysis; and Appendix B, Schedule of Procedures for Subjects Who Discontinued Nusinersen but Agree to Remain in the Study.

Section 8.11.1, Concomitant Therapy

Change: Updated to revise the requirements for allowed and disallowed concomitant therapy.

Now reads:

...

Allowed Concomitant Therapy

Throughout the study, the Site Investigators or designated licensed physicians may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care. **At the time of the implementation of this protocol amendment (version 4.0), subjects will be allowed to take concomitant Food and Drug Administration-approved and/or country-specific approved therapies and experimental therapies for SMA (at the Investigator's discretion).** In addition, a mild sedative (e.g., midazolam) and a local anesthetic (e.g., lidocaine) may be used for the LP procedure (per institutional guidance).

Disallowed Concomitant Therapy

~~Study subjects are prohibited from receiving other experimental agents during the study. This includes marketed agents being used off-label and/or at experimental doses that are being tested for the treatment of SMA (e.g., riluzole, creatine, sodium phenylbutyrate, valproate, or hydroxyurea).~~**None.**

Rationale: Aside from nusinersen, there are other therapies approved or anticipated for approval for SMA. There are also investigational therapies for SMA that are under development. Given this real-world scenario in which combination therapy is an option, and given the longitudinal safety profile that is already available for nusinersen, participants in this study are now allowed to have concomitant approved or investigational therapies for SMA while continuing to be monitored for safety and efficacy within this study.

[redacted]

[redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were revised throughout the protocol.
- On the Sponsor Signature Page, the signatory's role and name were updated.
- The List of Abbreviations and abbreviations in text were updated.
- In Section 2.3.4, Clinical Experience, the list of completed and ongoing studies was updated
- In Section 3.2, Number of Study Centers, the number of study centers was updated to 50 sites.
- In Section 3.4, Overall Study Duration and Follow-Up, MMDR visits after Day 840 to Day 1680 were listed in Figure 2: Study Design and Treatment Schema: Groups 1A and 1B; in Figure 3: Study Design and Treatment Schema: Groups 2A and 2B; and in Figure 4: Study Design and Treatment Schema: Groups 3, 4, and 5.
- In Section 6.3.1, Ventilator Use Diary Recording, text was updated to clarify the conditions and period for which ventilator use should be recorded.
- In Section 6.3.2, Dysphagia Assessment, text was revised to indicate the survey used for assessment and the time period for assessment of dysphagia and to specify the questions to be assessed in tube-fed subjects. This change also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.
- In Section 6.3.5, Growth Parameters, text was updated to indicate that body length or height will be measured.
- In Section 6.3.6, Physical Examinations; Section 6.5.1, Motor Milestones; and Section 6.5.2, Motor Function Assessments, text was updated to clarify that videotaping of physical examinations, WHO and/or HINE motor milestone assessments, and all motor function assessments will occur only if the consent is provided.
- In Section 6.4.2, Coagulation Parameters, assessment of prothrombin time was deleted. This change also affected Section 10.1.1, Safety and Tolerability Endpoints and Appendix C: Laboratory Analytes.

- In Section 6.5.1, Motor Milestones, text was updated to clarify that the WHO motor milestone assessment should be performed even if the subject is not ambulatory. This change also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

- In Section 6.5.1, Motor Milestones, and Section 6.5.2, Motor Function Assessments, text was updated to include that assessments can be performed up to 7 days prior to the dosing visit. This change also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

- In Section 6.6.2, X-ray of Spine, protocol-required assessments were updated to include X-ray assessments as standard of care if the image acquisition guidelines are met and the X-ray was obtained within 4 months prior to the scheduled visit. This change also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

- In Section 6.6.3, Quality of Life Questionnaires, text was revised to allow a subject's caregiver to complete the applicable quality of life questionnaires at home up to 7 days prior to dosing visit, if needed. In addition, if a quality of life questionnaire is not completed at a visit, it should be collected at the next scheduled dosing visit. These changes also affected Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

- In Section 6.6.3.2, Assessment of Caregiver Experience With Neuromuscular Disease, text was revised to note that all subjects should not complete the quality of life questionnaires intended for completion by a caregiver.

- In Section 6.9.1, Telephone Assessments, the schedule and window for safety monitoring telephone calls was updated. This change also affected Section 3.4.2, Treatment; Section 3.4.3, Post-Treatment Follow-Up; and Appendix A, Schedule of

Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule.

- In Section 8.11.2, Concomitant Procedures, additional examples of therapeutic intervention of non-drug related treatment were provided.

- In Section 9.5.5, Medical Emergency, the Investigator's ability to unblind the study treatment assignment in a medical emergency was deleted.

- In Section 10.1.2, Efficacy Endpoints, text was updated to include contracture assessment as a motor function assessment. Compound muscle action potential was presented in a separate bullet point. In addition, a sentence was added to clarify that the definition for acute reversible events is provided in the SHINE Ventilation Endpoint Guidance.

- In Section 10.3, Populations, the Per-Protocol Set was removed. This change also affected Section 10.6, Planned Methods of Analysis.

- In Appendix A, Schedule of Procedures: Groups 1A/1B and 2A/2B Blind Loading Dose Period and All Groups MMDR Schedule, a footnote was provided to indicate that motor function assessment includes Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease, Hammersmith Functional Motor Scale - Expanded, Revised Upper Limb Module, 6-Minute Walk Test, and contracture assessment.

- [redacted]

- Minor editorial changes were made throughout the document.

- Typographical errors and formatting were corrected.

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AMENDMENT SUMMARY

Biogen Protocol ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Version 3.0

Date: 30 October 2017

EUDRA CT Number: 2015-001870-16

Version 3.0 of the protocol has been prepared for this amendment, which supersedes Versions 1.0, 1.1, 1.3, and 2.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol ISIS 396443-CS11 is to allow enrollment of subjects from the newly added index study 232SM202 into this extension study. As a result of this change, the approximate number of subjects has increased from 239 to 292 subjects, the approximate number of study sites from 37 up to 45 sites, and the approximate number of countries from 14 up to 15 worldwide.

Subjects entering the extension study from the index study 232SM202 will be enrolled into a new cohort, Group 5. Subjects will enter directly into the open-label period at Modified Maintenance Dosing Regimen (MMDR) Day 1.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3.1, Study Design

Now reads:

This is an open-label extension study in subjects with SMA who previously participated in investigational studies of ISIS 396443. For the purposes of this protocol, investigational studies of ISIS 396443, henceforth referred to as "index" studies, include Studies ISIS 396443-CS3A, ISIS 396443-CS3B, ISIS 396443-CS4, ~~and I~~SIS 396443-CS12**, and 232SM202**. ~~Subjects from other studies of ISIS 396443 may be included into the current long-term extension study with future amendments of the protocol.~~

Rationale:

Subjects from Study 232SM202 are being enrolled to enable collection of long-term safety and efficacy data from these subjects. At the present time, no other studies are planned to be added as index studies into the extension study. The study design summary was revised accordingly.

This change also affects Section 3.2. Number of Study Centers; Section 3.3, Number of Subjects; Section 3.4, Overall Study Duration and Follow-Up; Section 3.4.2, Treatment; and Figure 4. In addition, text listing the applicable index studies and subject groups for this extension study was updated throughout the protocol to include Study 232SM202 and Group 5.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Signature Page

Change:

The signatory of the Protocol ISIS 396443-CS11 was changed from [redacted]

Now reads:

Protocol ISIS 396443-CS11 was approved by:

_____ _____

[redacted] Date

[redacted]

Late Stage Clinical Development

Biogen MA Inc.

Rationale:

The signature page was revised due to changes in the personnel responsible for managing this extension study. This change also affects page 2 of the protocol.

Protocol Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 3.6, Safety Monitoring

Change:

Text describing formation and function of the Data Monitoring Safety Board (DSMB) was deleted. New text summarizing ongoing monitoring of safety data was added.

Now reads:

3.6 Safety Monitoring ~~and Data and Safety Monitoring Board~~

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor**, with data cuts at regular intervals**. ~~Safety may also be reviewed by an independent Data and Safety Monitoring Board (DSMB). It is anticipated that meetings may occur approximately 4 times per year (i.e., approximately every 3 months). The DSMB will review safety, tolerability, and efficacy data collected on nusinersen during this study. The details of the DSMB operation and the data reviewed will be outlined in the DSMB Charter. Based on its ongoing assessment of the data, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study. The DSMB may be discontinued at the Sponsor's discretion.~~

Rationale:

A DSMB will no longer be used in this study; therefore, text describing its formation and function is no longer applicable. Safety data in the study will continue to be reviewed by the Sponsor and the Medical Monitor on an ongoing basis.

This change also affects Section 9.2, Regulatory Requirements.

Section 4.1, Screening

Change:

Text summarizing assignment of subject identification numbers was revised.

Now reads:

Before a subject's participation in the study, the Investigator will be responsible for obtaining written informed consent from the parent(s) or legal guardian(s) and, in cases where institutional guidelines or the subject's age dictate, informed assent from the subject. Consent/assent must be signed before any study procedures, including screening procedures, are performed. If all eligibility criteria are met and the subject is enrolled into the study, ~~subjects will maintain~~ the ~~same~~**extension study** subject identification ~~numbers that were assigned in the~~ **number will be maintained from, or linked to, the** index study ~~throughout this extension study~~**subject identification number. This will be outlined in the ISIS 396443-CS11 data management documentation**.

Rationale:

The procedure for maintenance of subject identification numbers from the index study upon enrollment into the extension study was clarified.

Section 4.4, Unblinding of Treatment Assignment

Change:

Text describing procedures for unblinding of index studies ISIS 396443-CS3B and ISIS 396443-CS4 was added.

Now reads:

During the blinded loading **dose** period of this study, subjects ~~will receive~~**received** either blinded injections of nusinersen (Groups 1A and 2A) or a combination of nusinersen and sham procedures (Groups 1B and 2B) in order to allow subjects who previously participated in a sham procedure group of the index studies to obtain a loading regimen of nusinersen while maintaining the blind of the treatment assignment in the index study. Following that, during the open-label maintenance period of the study, all study subjects ~~will receive~~**received** nusinersen in an unblinded manner using a maintenance dosing regimen of once every 4 months.

~~Since the key study site personnel will be blinded to the subjects' treatment assignments during the loading dose period of the study, in case of a medical emergency where knowing the subject's treatment assignment may influence the subject's clinical care, the Investigator has the ability to unblind the treatment assignment (as defined in Section 9.5.5) using the Interactive Voice/Web Response System (also known as the IxRS system). The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to the personnel involved with the analysis and conduct of the study.~~**Index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, and treatment assignments for subjects in the applicable groups (Groups 1A, 2A, 1B, and 2B) were released. Therefore, there was no longer any reason to continue the blinded loading dose period in a blinded fashion. Procedures for subjects still attending visits within the blinding loading dose period at the time of unblinding were revised as follows:**

- **For subjects in Group 1A and Group 2A who were receiving active drug (i.e., nusinersen) within the blinding loading dose period, visits occurred as scheduled, with all predose and postdose assessments performed.**
- **For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period, all visits and predose assessments were continued per the protocol; however, the sham procedure and all postdose procedures were not performed for those applicable visits. The required assessments for sham visits performed after the time of unblinding are described in Section 8.2.**

~~In addition~~**During the blinded loading dose period**, all suspected unexpected serious adverse reactions (SUSARs) ~~will be~~**were** unblinded by the Sponsor's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting ~~(Section 9.2)~~. **As index studies**

ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, SUSARs will be submitted to regulatory agencies and Investigators in an unblinded fashion (Section 9.2).

Rationale:

A clarification letter was previously distributed to Investigators describing unblinding of index studies ISIS 396443-CS3B and ISIS 396443-CS4. As a result of the unblinding, there was no longer any reason to continue procedures in a blinded fashion for subjects who were in the blinded loading dose period at the time of unblinding. Study assessments, including those for sham visits, and safety reporting procedures were revised accordingly.

This change also affects Section 8.1, Study Drug Administration; Section 8.2, Sham Procedure; and Section 9.2, Regulatory Requirements.

Section 5.2, Exclusion Criteria

Change:

New text defining the applicable standard of care guidelines in spinal muscular atrophy (SMA) was added to exclusion criterion #4.

Now reads:

4. The subject's parent or legal guardian is not willing or able to meet ~~standard of care guidelines (including vaccinations and respiratory syncytial virus prophylaxis, if available)~~ **guidelines in the consensus statement for standard of care in SMA [Wang 2007]** or provide nutritional and respiratory support throughout the study. **NOTE: Routine vaccinations and respiratory syncytial virus (RSV) prophylaxis are recommended per consensus guidelines on standard of care [Wang 2007] but are not required for study enrollment. Subjects who are not current on vaccinations or who are not receiving RSV prophylaxis, but otherwise meet study inclusion criteria, will be considered eligible for study enrollment.**

Rationale:

A clarification letter was previously distributed to Investigators clarifying the applicable SMA standard of care guidelines being referred to in this exclusion criterion, as well as guidance for enrollment of subjects not current on routine vaccinations or respiratory syncytial virus prophylaxis. These clarifications were incorporated into exclusion criterion #4.

[redacted]

Section 6.3.1, Ventilator Use Diary Recording

Change:

New text summarizing the procedure for ventilator data collection and dispensation of the ventilator diary was added.

Now reads:

For all subjects, ventilator **support**/use~~/status~~ will be assessed. This assessment will document whether respiratory support is being used (or not), what type of respiratory support is being used (noninvasive [i.e., bilevel positive airway pressure (BiPAP)/continuous positive airway pressure (CPAP)] or permanent ventilation), the number of hours per day, and the number of days the support is being used. This information will be obtained from the caregivers during onsite study visits and every-other-month telephone contacts.

Ventilator use should be recorded if the subject's daily ventilator support increases to ≥16 hours/day. Once ventilator use increases to ≥16 hours/day, ventilator use should continue to be recorded within the diary for a minimum of 30 days, even if ventilator use

subsequently decreases to <16 hours/day during the 30-day period. Investigators may instruct caregivers to continue recording in the ventilator use diary for an additional 30 or more days based on clinical judgment. The ventilator use diary should be dispensed during onsite study visits as needed.

Once the caregiver is instructed by the Investigator to stop recording ventilator use, the caregiver may discontinue collecting the subject's daily ventilator use. If the subject's ventilator use increases to ≥16 hours/day again at another time, the subject's daily ventilator support use should be recorded as described above.

Rationale:

The requirements for ventilator use diary recording and dispensation, including when diary use is initiated and the duration of recording, were clarified within the protocol based on current guidelines stated within the ventilator diary instructions.

This change also affects Appendix A, Schedule of Procedures.

Section 6.3.2, Dysphagia Assessment

Change:

New text was added describing dysphagia assessment in subjects.

Now Reads:

6.3.2 Dysphagia Assessment

Caregivers will be asked a series of questions regarding mealtime behavior of the subject.

Rationale:

Beginning with this protocol amendment, changes in mealtime behavior during the 7 days prior to each study visit will be assessed in study subjects in order to detect potential dysphagia that may occur during study treatment.

This change also affects Appendix A, Schedule of Procedures.

Section 6.3.5, Growth Parameters

Change:

New text specifying the timing of growth parameter measurement, alternative procedures for subjects with scoliosis, and the analysis plan for growth parameter data was added.

Now reads:

Growth parameters of body length and/or height (for all subjects), head circumference (for subjects up to 36 months of age), chest circumference (for subjects up to 36 months of age), and arm circumference (for subjects up to 36 months of age) will be measured **predose (within 7 days) by the Investigator (or designee)** at every onsite visit throughout the study.

In subjects with scoliosis, the Investigator (or designee) may measure arm span in lieu of body length and/or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body.

Additional parameters of weight-for-age, weight-for-length, and head-to-chest circumference ratio will be calculated **by the Sponsor during the analysis as described in the Statistical Analysis Plan (see Section 10.1.2)**.

Rationale:

Scoliosis or lower limb contractures can interfere with body length and/or height measurement. Arm span is an alternative measurement for height; therefore, it is considered an appropriate alternative in subjects with scoliosis or other conditions that prevent body length or height measurement. The timing for growth parameter data collection and the summary of the planned analysis was also clarified.

Section 6.5.2.3, Revised Upper Limb Module

Change:

New text describing performance of the Revised Upper Limb Module (RULM) in subjects was added, and the age range that the RULM has been evaluated in was revised.

Now reads:

All nonambulatory subjects ≥30 months of age will be evaluated using the Revised Upper Limb Module (RULM) **[Mazzone 2016]**. **The RULM will continue to be performed should subjects subsequently become ambulatory.**

The RULM is an outcome measure developed to assess upper limb functional abilities in patients with SMA, including young children, and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The RULM is quickly administered and has been evaluated in patients with SMA ~~30 months~~ **2** to ~~27~~ **52** years of age **[Mazzone 2016]**.

Rationale:

The procedure for performing the RULM in subjects who subsequently become ambulatory was clarified. In addition, the age range that the RULM has been evaluated in was updated to reflect currently available information.

Section 6.5.2.5, Contracture Assessment

Change:

New text for contracture assessment was added.

Now reads:

6.5.2.5. Contracture Assessment

Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be affected by muscle strength, contractures, and maturational development (puberty). All subjects will be evaluated for contractures.

Rationale:

Motor performance during motor function assessments can be affected by a variety of factors, including contractures, among others; a summary of these potential relevant factors was added for clarity. Assessment for contractures was added to monitor for its occurrence.

Section 6.6.3.1, Pediatric Quality of Life Inventory (Generic Core Scales and Neuromuscular Module)

Change:

The upper age limit for the Pediatric Quality of Life Inventory (PedsQL) was revised.

Now reads:

Subjects 2 to ~~18~~**25** years of age will be evaluated using the Pediatric Quality of Life Inventory (PedsQL™) Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular [Varni 1999]. This assessment has been validated by the American Spinal Muscular Atrophy Randomized Trials group [Iannaccone 2009].

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. The PedsQL consists of brief, practical, generic core scales, as well as condition-specific modules for use in designated clinical populations. Pediatric self-report is measured in children**,** ~~and~~ adolescents**, and young adults** 5 to ~~18~~**25** years of age,

and parent proxy-report of child HRQOL is measured for children ~~and~~**,** adolescents**, and young adults** 2 to ~~18~~**25** years of age. The PedsQL 4.0 Generic Core Scales include assessment of physical functioning, emotional functioning, social functioning, and school functioning. The PedsQL 3.0 Neuromuscular Module was designed to measure HRQOL dimensions specific to children**, adolescents, and young adults** 2 to ~~18~~**25** years of age with neuromuscular disorders, including SMA.

Rationale:

The upper age limit for collection of the PedsQL was broadened to allow collection of quality of life data in subjects who turn age 19 years or older during the study duration. Quality of life measures will continue to be surveyed in young adult subjects and their caregivers.

Section 6.6.3.3, Clinical Global Impression – Improvement

Change:

Text defining baseline for the Clinical Global Impression – Improvement (CGI-I) scale assessment during study visits was added.

Now reads:

The Clinical Global Impression – Improvement (CGI-I) scale is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and is rated as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. **For assessment of CGI-I, the baseline state is defined as follows:**

- **Groups 1, 3, and 4: Baseline is defined as the CGI-I score at Screening for the present extension study.**
- **Group 2: Baseline is defined as the CGI-I score at Screening in the index study ISIS396443-CS4.**
- **Group 5: Baseline is defined as the CGI-I score at Screening in the index study 232SM202.**

Rationale:

The baseline for CGI-I assessment during study visits varies according to study group within the present extension study and was therefore clarified.

Section 6.7.1, Compound Muscle Action Potential

Change:

The timing of compound muscle action potential (CMAP) assessment was revised, and the location of the section was moved to reflect this change. Additionally, the requirement for CMAP measurement was revised.

Now reads:

6.7. Study Assessments to be Performed at Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 16 Months Thereafter (Every Fourth Modified Maintenance Dosing Regimen Visit), and the End-of-Study Evaluation/Early Termination Visit

~~6.5.3~~**6.7.1.** Compound Muscle Action Potential

For all subjects, measurements of ulnar and peroneal CMAP will be conducted at Screening and/or MMDR Day 1, **approximately every 16 months thereafter (i.e., MMDR Days 480, 960, and so on)**, and at the EOS Evaluation/ET Visit. **If CMAP measurements are not approved as a mandatory outcome measure by local authorities, they will be considered optional in the respective country.**

CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles. CMAP is a well-validated method for tracking disease progression in neuromuscular disorders such as SMA [Lewelt 2010; Swoboda 2005] and amyotrophic lateral sclerosis [Shefner 2011] and has been proposed as a potential biomarker of a therapeutic effect in SMA.

Rationale:

Based on investigator feedback, the timing of CMAP was revised from 8 to 16 months, which remains consistent with the timing of assessments for other efficacy endpoints. A new section, Section 6.7, was created to reflect this change, and the summary for CMAP was moved as a result. Section numbering within Section 6 was updated accordingly. In addition, to comply with local regulations, CMAP measurements will be considered optional in regions where such measurements are not approved. These changes also affect Appendix A, Schedule of Procedures.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Section 8.1, Study Drug Administration

Change:

The summary for nusinersen administration was updated to reflect changes in the status of the blinded loading dose period. Redundant text for procedures described elsewhere in the protocol was removed.

Now reads:

Details regarding the LP dosing injection procedure are provided in the Dosing Administration Manual, also known as the ~~Drug~~**Directions for** Handling and Administration (DHA) guidelines.

The DHA guidelines supersede all other references (e.g., protocol).

Nusinersen will be administered as an IT LP injection. All subjects will receive the full 12-mg dose of nusinersen (5 mL).

During the blinded loading **dose** period, the study treatment dosing or sham procedures ~~will be~~**were** performed in a dedicated room and administered by dedicated study personnel who ~~are~~**were** unblinded to the treatment assignment; this ~~cannot be~~**was not** administered by any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors), and the key study site personnel or the parents ~~should~~**were** not ~~be~~ present during the procedure to ensure blinding.

After the loading **dose** period has been completed **(and/or after unblinding of index studies ISIS 396443-CS3B and ISIS 396443-CS4; see Section 4.4)**, subsequent doses of

nusinersen will not involve a sham procedure and, with the agreement of the Sponsor, may be administered by the Principal Investigator or Subinvestigator.

Nusinersen will be administered as an IT slow bolus (1 to 3 minutes) LP injection. Nusinersen will be administered using a "spinal anesthesia" needle and syringe. A 22G to 25G spinal anesthesia needle is recommended, but a 21G may be used if indicated by subject size or clinical condition. The target site for needle insertion is the L3/L4 space but may be 1 segment above or 1 to 2 segments below this level, if needed. [redacted]

Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure, following institutional procedures. ~~If anesthesia or sedation is to be used for the LP procedure in nusinersen-treated subjects at an individual study center, in order to maintain the blind, minimal sedation (i.e., a low dose of an anxiolytic) should be used for the sham procedure, following institutional procedures. Subjects who receive the sham procedure will be kept in the procedure room for the same amount of time as that for subjects who are administered study treatment, thus simulating the time period of a study treatment administration procedure.~~ Subjects will be encouraged to lie flat for 1 hour following dosing, if possible.

[redacted]

Rationale:

Index studies ISIS 396443-CS3B and ISIS 396443-CS4 were unblinded, and treatment assignments were released as of 24 April 2017. As a result, there was no longer any reason to continue procedures in a blinded fashion for subjects who were in the blinded loading dose period at the time of unblinding. Text summarizing procedures specific to the blinded loading dose period was updated accordingly. In addition, redundant text for procedures described elsewhere in the protocol was removed to avoid repetition.

Section 8.2, Sham Procedure

Change:

Study procedures for subjects in Groups 1B and 2B attending and receiving treatment at sham visits within the blinded loading dose period at the time of unblinding were added.

Now reads:

During the blinded loading **dose** period of this study, subjects ~~**will receive**~~ **received** blinded injections of either nusinersen or sham procedures, to allow subjects who previously participated

in a sham procedure group of the index studies to obtain a loading dose regimen of nusinersen and maintain the blind on the regimen that was administered in the index study. Details of the sham procedure ~~are~~**were** provided in the Dosing Administration Manual (or DHA guidelines). The sham procedure ~~will be~~**was** performed in a dedicated room and administered by dedicated study personnel who **were**~~are~~ unblinded to the treatment group; this ~~cannot be~~**was not** administered by any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors), and the key study site personnel or the parents ~~should~~**were** not ~~be~~ present during the sham procedure to ensure blinding.

The sham procedure ~~will~~ consiste**d** of a small needle prick on the lower back at the location where the LP injection ~~is~~**was** normally made. The needle ~~will break~~**broke** the skin, but no LP injection or needle insertion ~~will~~ occurr**ed**. The site of the needle prick ~~will be~~**was** covered in the same manner as that of the LP injection, thus simulating the appearance of an LP injection. If anesthesia or sedation ~~is to be~~**was** used for the LP procedure in nusinersen-treated subjects at an individual study center, in order to maintain the blind, minimal sedation (i.e., a low dose of an anxiolytic) ~~should be~~**was** used for the sham procedure, following institutional procedures. Subjects who received the sham procedure ~~will be~~**were** kept in the procedure room for the same amount of time as that for subjects who ~~are~~**were** administered study treatment, thus simulating the time period of a study treatment administration procedure.

Study treatment and sham kits **were**~~are~~ packaged in a blinded fashion. [redacted]

As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, there was no longer any reason to continue the blinded loading dose period in a blinded fashion (see Section 4.4). For subjects in Groups 1B and 2B who were still attending visits and receiving treatment (i.e., nusinersen and sham procedures) within the blinded loading dose period since the time of unblinding, the sham procedure and all postdose procedures described above were not performed for those applicable visits. The procedure at sham visits was recorded as "NOT DONE" in the eCRF, and the reason was specified as "subject is in Group 1B or Group 2B; visit occurred after treatment assignments were released by study Sponsor." During these visits, study drug was not administered, and these visits were considered safety visits. The visit was still registered in the Interactive Voice/Web Response System (also known as the IxRS system) to allow for all future visits to be recorded without issue; however, the dispensed study drug was set aside, marked as "Not Used," recorded as such in the site and/or patient drug accountability log, and then returned for destruction. Safety assessments of predose vital signs and neurological examination were performed, and AEs, concomitant medications, general health, and ventilator use/status were reviewed.

Rationale:

Index studies ISIS 396443-CS3B and ISIS 396443-CS4 were unblinded, and treatment assignments were released as of 24 April 2017. As a result, there was no longer any reason to continue procedures in a blinded fashion for subjects who were in the blinded loading dose

period at the time of unblinding. The sham procedure was no longer performed in affected subjects, and sham visits were considered safety visits. Study procedures for the sham visit were revised accordingly.

Section 8.10, Withdrawal of Subjects From the Study

Change:

New text listing initiation of commercial treatment was added as a withdrawal criterion.

Now reads:

Other reasons for withdrawal of subjects from the study might include the following:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- **Initiation of commercial nusinersen treatment**
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor

Rationale:

Initiation of commercial nusinersen treatment is currently included within the case report form as a potential reason for study withdrawal and was added to the protocol accordingly.

Section 8.11.1, Concomitant Therapy

Change:

Oral albuterol/salbutamol and carnitine were removed as disallowed concomitant therapies.

Now reads:

Disallowed Concomitant Therapy

Study subjects are prohibited from receiving other experimental agents during the study. This includes marketed agents being used off-label and/or at experimental doses that are being tested for the treatment of SMA (e.g., ~~oral albuterol/salbutamol,~~ riluzole, ~~carnitine,~~ creatine, sodium phenylbutyrate, valproate, or hydroxyurea).

Rationale:

Based on investigator feedback, oral albuterol/salbutamol and carnitine are now permitted as concomitant therapy during the study.

Section 9.2, Regulatory Requirements

Change:

The procedure for reporting of serious adverse reactions (suspected unexpected serious adverse reactions [SUSARs]) was revised based on the unblinding of index studies ISIS 396443-CS3B and ISIS 396443-CS4.

Now reads:

During the blinded loading dose period, ~~Appropriate personnel at Biogen will unblind~~ SUSARs **were unblinded by appropriate Sponsor personnel** for the purpose of regulatory reporting. ~~Biogen will~~**The Sponsor** submit**ted** SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law **and**~~. Biogen will~~ submit**ted** SUSARs to Investigators in a blinded fashion.

As index studies ISIS 396443-CS3B and ISIS 396443-CS4 have been unblinded, this unblinding is no longer needed. SUSARs will be submitted to regulatory agencies and Investigators in an unblinded fashion.

IRBs/IECs will be notified of any SAE according to applicable regulations. ~~The DSMB will be notified of any SAE as specified in the DSMB charter.~~

Rationale:

Index studies ISIS 396443-CS3B and ISIS 396443-CS4 were unblinded, and treatment assignments were released as of 24 April 2017. As a result, there was no longer any reason to continue procedures in a blinded fashion for subjects who were in the blinded loading period at the time of unblinding. Study procedures for SUSAR reporting were revised accordingly. Additionally, a DSMB will no longer be used in this study; therefore, text describing its formation and function is no longer applicable and was removed.

[redacted]

[redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The Study Glossary was updated.
- Typographical and formatting errors were corrected.
- The term "date of the last visit" was revised to "date of the last dosing visit" throughout the protocol.
- The term "blinded loading period" was revised to "blinded loading dose period" throughout the protocol.
- When discussing the blinded loading dose period, the verb tense was changed from the present to past tense throughout the protocol, as this study stage has completed.
- An abbreviations list was added to the footnotes for each table and figure throughout the protocol to align with Biogen style guidelines.
- Throughout the protocol, the term "clinical chemistry" was revised to "blood chemistry" to align with Biogen style guidelines.
- On the title and sponsor pages, the sponsor address was corrected due to a change in the corporate address.
- In Section 2.3.3, "preclinical" was replaced with "nonclinical" to align with Biogen style guidelines.
- In Section 2.3.4, Clinical Experience, the summary of nusinersen clinical studies was revised to reflect changes in study status. The clinical study summary was reorganized to group completed studies together in order to improve readability.
- In Section 2.4, Rationale for Dose and Schedule of Administration, study names for index studies ISIS 396443-CS3B (ENDEAR) and ISIS 396443-CS4 (CHERISH) were added.
- In Section 3.4, Overall Study Duration and Follow-Up, Figures 2, 3, and 4, the "Baseline Day 1" box was removed for clarification. Upon completion of screening, subjects immediately proceed into the blinded loading dose period or MMDR period, as appropriate, with no additional Day 1 visit.
- Throughout Section 6 and the entire protocol where applicable, the visit windows were clarified for specific study procedures as follows: [redacted]; Section 6.3.1, Ventilator Use Diary Recording; Section 6.3.3, Urine Pregnancy Tests; Section 6.3.4, Weight; Section 6.3.5, Growth Parameters; Section 6.3.6, Physical Examinations; Section 6.3.7, Vital Signs; Section 6.3.8, Neurological Examinations; Section 6.4.1, Clinical Safety Laboratory Evaluations; Section 6.4.2, Coagulation Parameters; [redacted]; Section 6.6.1, Electrocardiograms; Section 6.6.2, X-Ray of Spine; Section 6.6.3, Quality of Life

Questionnaires; [redacted];
Section 6.9.1, Telephone Assessments; Figures 2, 3, and 4; and Appendix A, Study Procedures footnotes.

- In Section 6.4.1, Clinical Safety Laboratory Evaluations, Screening was added as a time point for clinical safety laboratory evaluations. In addition, it was clarified that repeating these evaluations is not required on MMDR Day 1 if the visit is within 7 days of Screening. This change also affects the section heading for Section 6.4, Study Assessments for Screening and/or Modified Maintenance Dosing Regimen Day 1, Every 4 Months Thereafter (Every Modified Maintenance Dosing Regimen Visit) and the End-of-Study Evaluation/Early Termination Visit and Appendix A, Schedule of Procedures.
- In Section 6.4.2, Coagulation Parameters, the coagulation parameter of partial thromboplastin time was replaced with prothrombin time. This change also affects Section 10.1.1, Safety and Tolerability Endpoints and Appendix B, Laboratory Analytes.
- [redacted]
- In Section 8.1, Study Drug Administration, the term "Drug Handling and Administration" was corrected to "Directions for Handling and Administration."
- In Section 10.1.6, Future Scientific Research Assessments, [redacted] was added as a potential sample that may be stored for future analysis, consistent with the stated policy elsewhere in the protocol.
- [redacted]
- In Appendix A, Schedule of Procedures, the visit day was clarified for procedures occurring annually.
- In Appendix A, Schedule of Procedures, the quality of life questionnaires were specified.
- In Appendix A, Schedule of Procedures, the time frame for Screening assessments to be completed at the index End-of-Study Visit was revised from 3 to 4 months, consistent with enrollment requirements stated elsewhere in the protocol.

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AMENDMENT SUMMARY

Biogen Protocol ISIS 396443-CS11

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Version 2.0

Date: 31 January 2017

EUDRA CT Number: 2015-001870-16

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Versions 1.0 and 1.3.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol ISIS 396443-CS11 is to transition the dosing regimen for the open-label maintenance dosing period for all index studies (ISIS 396443-CS3B [Groups 1A and 1B], ISIS 396443-CS4 [Groups 2A and 2B], ISIS 396443-CS12 [Group 3], and ISIS 396443-CS3A [Group 4]) to the Modified Maintenance Dosing Regimen (MMDR) schedule, during which maintenance doses of nusinersen are administered every 4 months.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3.4.2, Treatment

Now reads:

Subjects who **are** ~~meet the eligibility criteria will be admitted to the study center on study Day 1 to begin their Treatment Period. For~~ subjects entering the study after completing the double-blind studies ISIS 396443-CS3B and ISIS 396443-CS4 (i.e., **subjects** ~~those~~ in Groups 1A, 1B, 2A**,** and 2B**) will complete a** ~~below), the Treatment Period in the current study will consist of~~ the blinded loading **dose period** ~~phase~~ and **then be transitioned to the** ~~an~~ open-label **MMDR period. Subjects already enrolled in Study ISIS 396443-CS11 (SHINE)** ~~maintenance phase (Figure 2~~ and **already participating in the blinded loading dose period will continue their blinded loading dose/sham schedule through the last scheduled dose in that loading period and then be transitioned to the** ~~Figure 3). For subjects entering the study after completing the~~ open-label **MMDR dosing schedule at their next study visit, which should be scheduled as close as possible to 120 days from the date of the last visit** ~~study ISIS 396443~~ CS12 (i.e., **date** ~~those in Group 3 below), the Treatment Period in the current study will consist~~ of **last visit + 120 days = MMDR Day 1).** ~~an open-label maintenance phase only.~~

During the blinded loading **period** ~~phase of the study~~, subjects who previously **received the** ~~participated~~ in a sham procedure **during** ~~group of~~ the index study will receive blinded injections of **nusinersen**ISIS 396443 in order to achieve the full loading regimen of **study treatment** ~~drug~~, and subjects who previously received **nusinersen** ~~ISIS 396443~~ during the index study will receive a combination of **nusinersen** ~~ISIS 396443~~ injections and sham procedures. This design is necessary to protect the full blind of the treatment assignment in the ongoing index studies. ~~Following the loading phase, during the maintenance period of the study, all study subjects will receive drug in an unblinded manner using a maintenance dose regimen received by the treatment arm during the corresponding index study, as detailed below.~~

Subjects entering the study after completing open-label studies ISIS 396443-CS12 and ISIS 396443-CS3A (i.e., subjects in Groups 3 and 4) will enter directly into the open-label MMDR period at MMDR Day 1. Subjects already enrolled in ISIS 396443-CS11 and already receiving maintenance doses according to the original maintenance schedule will transition to MMDR Day 1 at their next study visit (regardless of how many maintenance

doses already received in original schedule), which should be scheduled as close as possible to 120 days from the date of the last visit (i.e., date of last visit + 120 days = MMDR Day 1).

The MMDR dosing schedule will consist of MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, and so on every 4 months (±7 days) until the EOS Evaluation/Early Termination (ET) Visit. The EOS Evaluation Visit will occur 4 months after the last open-label maintenance dose of nusinersen on approximately MMDR Day 1800 (±7 days).

Rationale: The frequency of nusinersen dosing for Groups 2A and 2B consists of 3 and 2 blinded loading doses of 12 mg nusinersen, respectively, on Days 1, 29, and 85 (Group 2A) or Days 1 and 85 (Group 2B) followed by maintenance doses of 12 mg every 4 months in the MMDR. The frequency of nusinersen dosing for Group 3 will transition from every 6 months to every 4 months in the MMDR. The recommended dosing regimen is strongly supported by the following considerations:

- The robust efficacy and safety data from Study ISIS 396443-CS3B, in which subjects received maintenance doses every 4 months.
- Although central nervous system (CNS) tissue half-life cannot be measured in humans, the median terminal elimination half-life was measured in the CNS tissue of adult monkeys and found to be 116 days, approximately 4 months. Because the site of action of nusinersen is within the CNS, these findings support the revised regimen with maintenance doses administered every 4 months.
- Population pharmacokinetics (PK) analyses suggest that higher cerebrospinal fluid (CSF) exposure leads to improvements in motor milestones; in compound muscle action potential (CMAP), a measure of motor neuron health; and Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND), a measure of motor strength in symptomatic infants with infantile-onset SMA treated with nusinersen. While the clinical endpoints differ between populations, the relationship between increased CSF trough concentration or overall exposure and improved functional outcomes is also anticipated in older subjects.
- No additional safety concerns are anticipated with administration of the proposed dosing regimen in the later-onset population in light of the fact that the majority of adverse events (AEs) in the clinical studies have been considered to be related to the natural history of the disease or intrathecal administration procedure rather than to nusinersen, and the maximum observed concentration and partial area under the concentration-time curve values of nusinersen in CSF are predicted to be lower in older children than in infants receiving the same regimen.

In light of these data and the severity of the disease, irrespective of phenotype, the ongoing extension study in patients with infantile-onset and later-onset SMA (Study ISIS 396443-CS11) will be amended so that all subjects, including those with later-onset SMA, will receive the same maintenance dosing regimen.

This change also affects Section 2.4, Rationale for Dose and Schedule of Administration; Section 3.4, Overall Study Duration and Follow-Up; Section 3.5, End of Study; Section 6, Study

Procedures; Section 8.1, Study Drug Administration; Section 10.6.2, Safety and Tolerability Analysis; and Appendix A, Schedule of Procedures and resulted in the creation of Section 3.1.1, Important Study Design Update.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Signature Page

Change: The Sponsor of Protocol ISIS 396443-CS11 was changed from Ionis Pharmaceuticals Inc. to Biogen.

Now reads:

Trial Sponsor:

~~Isis Pharmaceuticals, Inc.~~
~~2855 Gazelle Court~~
~~Carlsbad, CA 92010~~
~~Phone: +01 760 931 9200~~
~~Fax: +01 760 603 2700~~

Biogen MA Inc.
250 Binney Street
Cambridge, MA 02142
United States

[redacted]

Key Sponsor Contact:

[redacted]

Refer to the Study Reference Guide for complete contact information, including that for the unblinded Medical Monitor

Rationale: Biogen assumed sponsorship of Study ISIS 396443-CS11 in September 2016. In addition to listing Biogen as the Sponsor, this amendment adds safety and administrative language, making this protocol consistent with Biogen's protocol template.

This change also affects Pages 1 and 2 and the following sections: Section 9.1, Sponsor Review of Safety Information; Section 9.2, Regulatory Requirements; Section 9.4.1, Serious Adverse Events; Section 9.5.3, Dosing Errors; Section 9.5.4, Contraception and Pregnancy; Section 9.5.5, Medical Emergency; Section 11.1, Informed Consent/Assent; Section 11.2, Ethical Conduct of the Study; Section 11.3, Institutional Review Board/Institutional Ethics Committee/Research Ethics Board; Section 11.4.1, Subject Data Protection; Section 12.7, Conflict of Interest; Section 12.8, Registration of Study and Disclosure of Study Results; Section 12.9, Study Funding; Section 12.10, Publications; and Section 15, Signed Agreement of the Study Protocol.

Protocol Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 1, Objectives

Change: Text was added to the objectives section to provide further details regarding the open-label extension study and to clarify the use of "nusinersen," "study drug," and "study treatment" in the protocol.

Now reads:

The objective~~s~~ of this **open-label extension** study **is**~~are~~ to gather additional information on the long-term safety, tolerability, and efficacy of repeated **12-mg** doses of ISIS 396443 (**also known as BIIB058 and nusinersen**~~12 mg~~) administered as intrathecal (IT) injections by lumbar puncture (LP) in subjects **with spinal muscular atrophy (SMA)** who previously participated in investigational studies of ISIS 396443.

Note: For the purposes of this protocol, when referring to "study drug," nusinersen will be used in place of ISIS 396443. When referring to the Protocol Title or previous ("index") studies, ISIS 396443 will be used. The term "study treatment" refers to administration of nusinersen or the sham procedure during the blinded portion of the study.

Rationale: This language was added to provide clarity regarding the use of "nusinersen," "study drug," and "study treatment" in the protocol.

Section 2.4, Rationale for Dose and Schedule of Administration

Change: Text in this section was updated to reflect the change in maintenance dose from every 6 months to every 4 months and to provide justification for the change in frequency.

Now reads:

The proposed study will test the clinical efficacy, safety, tolerability, and PK of multiple doses of **nusinersen** ~~ISIS 396443~~ administered ~~as~~ **by** IT injection~~s~~ to subjects with SMA who previously participated in investigational studies of ISIS 396443. A single dose level of 12 mg ~~equivalent~~ of **nusinersen** ~~ISIS 396443~~ will continue to be evaluated in this long-term extension study.

The **nusinersen** ~~ISIS 396443~~ dose level and dose interval were selected based on ~~pre~~**non**clinical toxicology and **PK** ~~pharmacokinetic~~ observations from ~~monkey~~ studies **in monkey** utilizing single- and repeat~~-~~dosing IT administration, consideration of the target tissue concentration anticipated for drug pharmacology, severity of SMA phenotype, and safety data in the completed and ongoing clinical studies of ISIS 396443 to date. Based **on the** ~~upon~~ pharmacology and **PK** ~~pharmacokinetic~~ results in SMA transgenic mice, **it was** ~~we~~ estimat**ed** that the target tissue concentration to produce 50**%** to 90% SMN2 ~~Exon~~ **exon** 7 inclusion is between **2**~~1~~ and 10 µg/g spinal cord tissue. Nonclinical studies in juvenile monkeys receiving IT doses of **nusinersen** ~~ISIS 396443~~ showed a resulting gradient of distribution of **nusinersen** ~~ISIS 396443~~ along the spinal cord, with mean lumbar spinal cord concentrations ranging from 1.6- **to** 2.3-fold and 2.0- **to** 3.5-fold higher than thoracic and cervical spinal cord levels, respectively. The dose level selected for this multiple-dose clinical study (12 mg **nusinersen**~~ISIS 396443~~) is predicted to achieve levels at the high end of this range (approximately 10 µg/g lumbar and 3 **µg**~~ug~~/g cervical spinal cord tissue concentrations), following the first dose.

The loading dose interval was selected **as the dose interval** based on the nonclinical **PK**~~pharmacokinetic~~ and pharmacology data ~~as the dose interval~~ to achieve and maintain **nusinersen** ~~ISIS 396443~~ spinal cord tissue levels that are predicted to be within the upper end of the pharmacologically active range by Day 64 in **subjects** ~~patients~~ with the more severe infantile-onset SMA phenotype **(predicted to be approximately 30 µg/g lumbar and 10 µg/g cervical spinal cord tissue concentrations)** and by Day 85 in **subjects** ~~patients~~ with the less severe later-onset SMA phenotype (predicted to be approximately 24 µg/g lumbar and 8 µg/g cervical **spinal cord** tissue concentration**s**), while at the same time considering subject safety and convenience for repeated LP **IT**~~intrathecal~~ injections. ~~Similarly, the maintenance dose interval, once every 4 months for patients with the more severe infantile-onset SMA phenotype and once every 6 months for patients with the less severe later-onset SMA phenotype, was selected based on the estimated spinal tissue and CSF drug half-life (4-6 months) with the goal of maintaining the spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range.~~

The maintenance dose intervals were selected based on nonclinical PK and pharmacology data and clinical PK data from subjects in ongoing and completed clinical studies with the goal of maintaining the spinal cord tissue levels of nusinersen at a steady-state level within the estimated pharmacologically active range. The elimination half-life of nusinersen from human CSF is approximately 135 to 177 days and was estimated based on a limited number of postdose levels. Although CNS tissue half-life cannot be measured in humans, the median terminal elimination half-life was measured in the CNS tissue of adult monkeys and found to be 116 days, approximately 4 months. Because the site of action of nusinersen is within the CNS tissues, these findings support maintenance doses administered every 4 months.

The maintenance dosing regimen of 12 mg every 4 months was implemented in a sham-controlled study in infantile-onset SMA (Study ISIS 396443-CS3B), an open-label study in presymptomatic SMA (Study 232SM201 [NURTURE]), an open-label study in infantile-onset SMA (Study ISIS 39644-CS3A), and a sham-controlled study in both infantile-onset and later-onset SMA (Study 232SM202 [EMBRACE]). For subjects in a sham-controlled study in later-onset SMA (Study ISIS 396443-CS4) and an open-label study in later-onset SMA (Study ISIS 396443-CS12) who are eligible to enroll in this open-label extension study (Study ISIS 396443-CS11), the maintenance dose schedule is shortened from every 6 months to every 4 months. The change is further supported by available data on the exposure-response relationship as well as efficacy and safety data from the clinical studies. Data from the population PK analyses suggest that higher CSF exposure leads to improvements in compound muscle action potential (CMAP), a measure of motor neuron health; Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND), a measure of motor strength; and motor milestones in symptomatic infants with infantile-onset SMA treated with nusinersen. While the clinical endpoints differ between populations, the relationship between increased CSF trough concentration or overall exposure and improved functional outcomes is also anticipated in older subjects receiving more frequent maintenance doses. Because the majority of adverse events (AEs) in the clinical studies have been more likely related to the natural history of the disease rather than to nusinersen, any additional safety concerns associated with the Modified Maintenance Dosing Regimen (MMDR) are expected to be mostly limited to procedure-related AEs, such as post lumbar puncture syndrome and back pain.

Additional details on ~~dose scaling~~**dosing** and expected CSF and tissue concentrations are summarized in the Investigator's Brochure.

Rationale: This update was necessary to clarify the change in dosing frequency and to provide relevant data to support the change.

Section 3.1, Study Design

Change: Protocol ISIS 396443-CS11 now allows inclusion of subjects who completed an additional index study, ISIS 396443-CS3A.

Now reads:

This is an open-label extension study ~~(OLE) for patients~~ **in subjects** with ~~Spinal Muscular Atrophy~~**SMA** who previously participated in investigational studies of ISIS 396443. For the purposes of ~~the current~~ **this** protocol, investigational studies of ISIS 396443, henceforth referred to as **"**index**"** studies, include ~~s~~**S**tudies **ISIS 396443-CS3A,** ISIS 396443-CS3B, ISIS 396443-CS4, and ISIS 396443-CS12. Subjects from other studies of ISIS 396443 may be included into the current long-term extension study with future amendments of the protocol.

Rationale: The addition of the index Study ISIS 396443-CS3A will provide subjects from this study with the opportunity to continue to receive open-label nusinersen through the current study, Study ISIS 396443-CS11, which assesses the clinical efficacy, safety, tolerability, and PK of multiple doses of nusinersen.

This change also affects Study Design and Treatment Schema and the following sections: Section 2.3.4, Clinical Experience; Section 2.4, Rationale for Dose and Schedule of Administration; Section 3, Experimental Plan; Section 6.5.1, Motor Milestones; Section 10.2, Sample Size Considerations; Section 10.3, Populations; Section 10.6.3, Efficacy Analysis; and Appendix A, Schedule of Procedures.

Section 3.4, Overall Study Duration and Follow-Up

Change: The language describing the duration of study was updated.

Now reads:

T~~he~~**is** ~~S~~**s**tudy will consist of ~~s~~**S**creening, ~~t~~**T**reatment, and ~~p~~**P**ost-~~t~~**T**reatment ~~f~~**F**ollow-~~u~~**U**p ~~p~~**P**eriods**, and an End-of-Study (EOS) Evaluation Visit**. The total duration of participation in the study is ~~approximately31 (Groups 1A, 1B and 3) to 34 (Groups 2A and 2B) months~~**5 years from MMDR Day 1 (EOS Evaluation Visit to occur at approximately MMDR Day 1800) or as determined by the Sponsor (via early termination or amendment to extend)**. **A study schematic for Groups 1A and 1B, Groups 2A and 2B, and Groups 3 and 4 are provided in Figure 2, Figure 3, and Figure 4, respectively.** Please refer to the Schedule of Procedures in Appendix A.

Rationale: The duration of study was updated to reflect changes to the overall study period that resulted from the implementation of MMDR schedule and to provide clarification regarding decisions made by the Sponsor.

This change also affects the Study Design and Treatment Schema for Groups 1A and 1B, Groups 2A and 2B, and Groups 3 and 4 (Figures 2, 3, and 4, respectively).

Section 5.1, Inclusion Criteria

Change: Criterion #2 was updated to allow subjects to enroll in the study up to 16 weeks after completion of the index study.

Now reads:

2. Completion of the index study in accordance with the study protocol **or as a result of Sponsor decision (e.g., early termination of the index study)** within **the** preceding **16**~~12~~ weeks.

Rationale: The window of time between the completion of the index study and enrollment in Study ISIS 396443-CS11 was extended up to 16 weeks to accommodate subjects who are rolling over from studies that will have been completed by the time this amendment is in place.

Section 6.3.4, Growth Parameters

Change: A section describing growth parameter assessments for subjects in Group 4 was added to clarify the timing and extent of the assessments.

Now reads:

6.3.4 Growth Parameters

Growth parameters of body length and/or height (for all subjects), head circumference (for subjects up to 36 months of age), chest circumference (for subjects up to 36 months of age), and arm circumference (for subjects up to 36 months of age) will be measured at every onsite visit throughout the study.

Additional parameters of weight-for-age, weight-for-length, and head-to-chest circumference ratio will be calculated.

Rationale: These assessments were added because they are standard assessments for young children and are collected in other studies of nusinersen.

This change also affects Appendix A, Schedule of Procedures.

Section 6.3.7, Neurological Examinations

Change: Text specifying the Hammersmith Infant Neurological Examination (HINE) assessments to be performed for subjects ≤24 months was added.

Now reads:

Sections 1 and 3 of the ~~Hammersmith Infant Neurological Examination (~~HINE~~)~~ will be conducted ~~in~~**on** all subjects ≤24 months of age.

Rationale: This language was clarified to specify that all subjects <24 months of age will be assessed using Sections 1 and 3 of the HINE.

Section 6.4.2, Coagulation Parameters

Change: Coagulation parameters were added to the list of assessments that are performed at MMDR Day 1, every 4 months thereafter, and at the EOS Evaluation/ET Visit.

Now reads:

6.4.2 Coagulation Parameters

Coagulation parameters (activated partial thromboplastin time [aPTT], partial thromboplastin time [PTT], and international normalized ratio [INR]) will be collected at MMDR Day 1, every 4 months thereafter (i.e., MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, and so on), and at the EOS Evaluation/ET Visit.

The coagulation testing must be performed and reviewed prior to dosing.

Rationale: These assessments were added to thoroughly evaluate coagulation parameters in study subjects receiving nusinersen.

This change also affects Appendix A, Schedule of Procedures, and Appendix B, Laboratory Analytes.

Section 6.5.1, Motor Milestones

Change: Text was added specifying the HINE assessments to be performed for subjects <2 years who have not achieved independent walking.

Now reads:

6.5.1 ~~6.2.6~~ Motor Milestones

Subjects will be evaluated for motor milestones at the times shown in the Schedule of Procedures (Appendix A). In Groups 2 and 3, motor milestones will be assessed with the WHO Motor Milestone Criteria. In Groups 1 and 4, motor milestones will be assessed using Section 2 of the Hammersmith Infant Neurological Exam (HINE) for all subjects. In those subjects of Groups 1 and 4 who achieve the motor milestone of independent sitting, WHO Motor Milestone criteria will be assessed, too (Wijnhoven et al. 2004; WHO Multicentre Growth Reference Study Group 2006).

For all subjects, motor milestones will be assessed using the World Health Organization (WHO) Motor Milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004] at Screening and/or MMDR Day 1, every 8 months thereafter (i.e., MMDR Days 240, 480, 720, and so on), and at the EOS Evaluation/ET Visit.

For subjects <2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the HINE.

Rationale: This language was clarified to state that all subjects <2 years of age who have not achieved independent walking will be assessed using Section 2 of the HINE.

Section 6.5.2.1, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease

Change: Text clarifying the criterion for performing CHOP INTEND assessment was added.

Now reads:

6.5.2.1 ~~6.2.4~~ Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease

CHOP INTEND will be assessed in subjects with infantile-onset SMA until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed.

The ~~Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (~~CHOP INTEND~~)~~ test was specifically designed to evaluate the motor skills of infants with significant motor weakness, including infants with SMA [Glanzman 2010]. The CHOP INTEND test captures neck, trunk, **and** proximal and distal limb strength in 14 elicited and 2 observational items. The CHOP INTEND has been established as a safe and reliable infant motor measure in infantile-onset SMA~~, but its validity has not been established~~ **and has been validated [Glanzmann 2011].** ~~CHOP INTEND will be assessed in subjects in Groups 1A, 1B, and 4 at the times shown in the Schedule of Procedures (Appendix A).~~

Rationale: The criterion for performing CHOP INTEND until a maximum score of 64 is achieved was validated, and the criterion in effect for this protocol was revised accordingly. This change also affects Section 6.5.2.2, Hammersmith Functional Motor Scale - Expanded.

Section 6.5.2.2, Hammersmith Functional Motor Scale - Expanded

Change: Text clarifying the criteria for performing Hammersmith Functional Motor Scale – Expanded (HFMSE) and CHOP INTEND assessment was added.

Now reads:

6.5.2.2 ~~6.2.5~~ Hammersmith Functional Motor Scale - Expanded

~~All subjects in Groups 2A, 2B and 3, and any subject in Group 1A, 1B, or 4 who has maintained a CHOP INTEND total score of ≥ 50 for 2 consecutive study visits (including post baseline visits of the index study), will be evaluated using the Hammersmith Functional Motor Scale – Expanded (HFMSE) at the times shown in the Schedule of Procedures (Appendix A).~~ **All subjects ≥2 years of age will be evaluated using the HFMSE for the duration of the study. Subjects who are ≥2 years of age but have not yet achieved the maximum score of 64 with CHOP INTEND will be assessed with both until a CHOP INTEND maximum score of 64 is**

achieved. The HFMSE should be performed after the CHOP INTEND with an approximately 15-minute rest period in between to allow the subject to be fully engaged with both assessments.

Note: Any subjects currently being assessed with both the CHOP INTEND and HFMSE under a previous version of this protocol will continue to have both assessments performed under the current Version 2.0 of this protocol (even if they are <2 years of age) until they achieve a CHOP INTEND maximum score of 64.

Rationale: The criterion for performing CHOP INTEND until a maximum score of 64 is achieved was validated, and the criterion in effect for this protocol was revised accordingly. The procedure for subjects currently undergoing CHOP INTEND assessment based on criteria in effect in a previous protocol version (e.g., subjects <2 years of age undergoing CHOP INTEND assessment) was also clarified to align with the criterion in effect for the current Version 2.0 protocol.

Section 6.5.2.3, Revised Upper Limb Module

Change: The Revised Upper Limb Module (RULM) was added as a motor function assessment, and the Upper Limb Module was removed.

Now reads:

6.5.2.3 ~~6.2.8 Upper Limb Module~~ **Revised Upper Limb Module** ~~Test~~

~~Subjects will be evaluated using the Upper Limb Module Test (Mazzone et al. 2011) at the times shown in the Schedule of Procedures (Appendix A). The Upper Limb Module Test is an outcome measure specifically developed to assess upper limb functional abilities in SMA patients, including young children and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The Upper Limb Module Test is quickly administered and has been evaluated in SMA patients age 30 months to 27 years (Mazzone et al. 2011).All nonambulatory subjects ≥30 months of age will be evaluated using the Revised Upper Limb Module (RULM) [Mazzone 2011].~~

All nonambulatory subjects ≥30 months of age will be evaluated using the Revised Upper Limb Module (RULM) [Mazzone 2011].

The RULM is an outcome measure developed to assess upper limb functional abilities in patients with SMA, including young children~~,~~ and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a

box, remove the lid of a container). The RULM Test is quickly administered and has been evaluated in patients with SMA 30 months to 27 years of age [Mazzone 2011].

The purpose of an upper limb scale for use in SMA is to assess change that occurs in motor performance of the upper limb over time. Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be impacted by muscle strength, contractures, and maturational development (puberty) and the RULM aims to incorporate performance of the shoulder, elbow, wrist, and hand.

Rationale: The RULM Test was used to assess limb mobility in subjects entering from Study ISIS 396443-CS4 and was added to enable long-term evaluation of limb mobility in these subjects.

This change also affects Section 10.1.2, Efficacy Endpoints, and Appendix A, Schedule of Procedures.

Section 6.6.1, Electrocardiograms

Change: Language describing second ECG reads for subjects who have QTc values ≥500 milliseconds was added.

Now reads:

6.6.1 Electrocardiograms

ECGs will be performed for all subjects at Screening and/or MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, and so on), and at the EOS Evaluation/ET Visit.

After the ECG is completed, an initial local read of the ECG should occur before the ECG is sent for a central read (all ECGs will be centrally read). If the subject's initial ECG results show a QTc interval of ≥500 milliseconds, then the ECG should be repeated prior to the subject leaving the visit. If the second ECG QTc again reads ≥500 milliseconds, the Investigator should use best clinical judgment to address the condition.

Additional ECGs may be performed per the judgment of the Investigator, as deemed clinically necessary.

Rationale: This language was added to thoroughly monitor ECG readings for study subjects receiving nusinersen.

Section 6.6.2, X-Ray of Spine

Change: Text was added to the description of the X-ray of spine to indicate that this assessment is not required for sites participating in Germany. Language describing the timing of the assessment as it pertains to the MMDR was also added.

Now reads:

~~For subjects in Group 2 all~~ **Subjects currently ≥2 years of age or upon turning 2 years of age (with the exception of subjects treated at German sites**) will have an X-ray of the thoracolumbar spine ~~is acquired at the following visits: Screening, Day 445, and End of Study Day 960)~~ on **Screening and/or MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, and so on), and at the EOS Evaluation/ET Visit**. The X-rays will be used to determine the severity of scoliosis by measuring the Cobb-angle. **The s**pine X-ray was performed in the index **studies** ~~study~~, and the image acquisition guidelines will remain consistent between the index study and the current extension study. The technical details for image acquisition will be outlined in a separate document provided to the sites.

Rationale: This text was added so that the country-specific changes to this study for Germany could be captured in the global amendment. The frequency of the assessment was updated to align with the MMDR schedule.

[redacted]

[redacted]

Section 6.8.1, Telephone Assessments

Change: The frequency of follow-up safety monitoring telephone calls was updated to 1 to 7 days postdose and every other month for the duration of the study.

Now reads:

Follow-up safety monitoring telephone calls will occur **1 to 7 days postdose and every other month** ~~on a monthly basis~~ for the duration of the study, except for the months when in-clinic visits occur. During these calls, changes in concomitant medications, ~~adverse events~~ **AEs,**

ventilator use/status, and contraceptive methods that have occurred since the last phone call or study visit will be recorded. ~~In addition, the extent of ventilatory support used since the last phone call or study visit will be collected.~~

Rationale: The frequency of follow-up safety monitoring telephone calls was updated to 1 to 7 days postdose and every other month for the duration of the study to reduce the overall burden of study participation on study subjects and their families.

This change also affects Section 3.4.2, Treatment; Section 3.4.3, Post-Treatment Follow-Up; Section 6.3.1, Ventilator Use Diary Recording; and Appendix A, Schedule of Procedures.

Section 8.1, Study Drug Administration

Change: The regimen for study drug administration was revised to state that all subjects, regardless of age, will receive the full 12 mg dose of nusinersen.

Now reads:

Nusinersen~~ISIS 396443~~ will be administered as an **IT**~~intrathecal~~ LP injection. **All S**~~s~~ubjects ~~who are older than 24 months (>730 days) on the day of dosing~~ will receive the full 12-mg dose of **nusinersen**~~ISIS 396443~~ (5 mL). ~~For subjects who are 24 months of age or younger, the volume of the injection will be adjusted based on the subject's age on the day of dosing per Table 2, such that each subject will receive a 12 mg equivalent dose based on CSF volume scaling.~~

~~**Table 2 ISIS 396443 Dose Volume to be Administered**~~

~~Age~~	~~Estimated CSF Volume*~~	~~Injection Volume (mL)~~	~~Dose (mg)~~
~~0-3 months (0-90 Days)~~	~~120 mL~~	~~4 mL~~	~~9.6~~
~~3-6 months (91-180 Days)~~	~~130 mL~~	~~4.3 mL~~	~~10.3~~
~~6-12 months (181-365 Days)~~	~~135 mL~~	~~4.5 mL~~	~~10.8~~
~~12-24 months (366-730 Days)~~	~~140 mL~~	~~4.7 mL~~	~~11.3~~
~~> 24 months (> 730 days)~~	~~150 mL~~	~~5 mL~~	~~12~~

~~*Matsuzawa et al. 2001~~

Rationale: The current regimen for study drug administration is that all subjects will receive the full 12-mg dose of nusinersen at a dosing regimen of 4 loading doses followed by maintenance dosing every 4 months thereafter. Over the course of the clinical development program, data from early studies have informed the dose regimens used in later studies.

The population PK model supports the conclusion that fixed dosing is appropriate. This model suggests that there is a similar area under the concentration-time curve (AUC) across all age groups, but a higher maximum concentration (C_{max}) in the youngest age group (i.e., subjects <3 months of age) with the fixed dose (relative to the age-adjusted dose). There was high variation in the prediction of C_{max} as a result of only trough CSF data being available for population PK model analysis and distribution of parameters across age groups that largely overlap, regardless of whether fixed dosing or age-adjusted dosing was used. Given that the AUC is similar regardless of whether fixed dosing or age-adjusted dosing is used and the substantial overlap in the range of estimates for each age group, neither method is likely to produce clinically relevant differences in exposure across different age groups. As a result, a fixed-dosing regimen is deemed appropriate to reduce the likelihood of dosing errors.

Population PK analysis predicts higher trough concentration and partial AUC values in CSF in subjects who receive the 4 loading dose/every 4-month maintenance dose regimen compared with subjects receiving less frequent doses. The Sponsor considers the more frequent dose regimen appropriate for all subjects, regardless of age and SMA type. This judgment is based on safety and efficacy data observed in Studies ISIS 396443-CS3B and 232SM201, as well as results from the PK analysis that showed greater improvement in motor function in subjects with a higher concentration of nusinersen. Although available safety and efficacy data from Study ISIS 396443-CS4 support a positive risk:benefit profile for subjects with a less frequent dosing regimen, the favorable safety and efficacy data from Studies ISIS 396443-CS3B and 232SM201, along with the PK analysis results, suggest potentially even greater benefit without any significantly increased risk with the proposed dosing dose regimen for all subjects.

Therefore, a dose regimen of 4 loading doses of 12 mg nusinersen delivered on Days 0, 15, 29, and 64 followed by maintenance dosing of 12 mg nusinersen every 4 months thereafter is considered appropriate for all subjects, regardless of age or SMA type.

Section 9.1, Sponsor Review of Safety Information

Change: Language clearly defining the responsibilities of the Investigator and the Sponsor was added to this section.

Now reads:

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical ~~trial~~ **study**.

The Investigator's responsibilities include the following:

- **Monitor and record all AEs, including SAEs, regardless of the severity or relationship to the study treatment.**
- **Determine the seriousness, relationship, and severity of each event.**
- **Determine the onset and resolution dates of each event.**
- **Complete an SAE form for each serious event and fax it as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the event.**
- **Pursue SAE follow-up information actively and persistently. Follow-up information must be reported as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of new information.**
- **Ensure that all AE and SAE reports are supported by documentation in the subjects' medical records.**
- **Pursue AE follow-up information, if possible, until the event has resolved or become stable.**
- **Report SAEs to local ethics committees, as required by local law.**

The Sponsor's responsibilities include the following:

- **Before study site activation and subject enrollment, the Clinical Monitor (or designee) is responsible for reviewing with study site staff the definitions of AE and SAE as well as the instructions for monitoring, recording, and reporting AEs and SAEs.**
- **The Sponsor (or designee) is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.**

Rationale: This text was added to adequately collect safety information across the study population.

Section 9.2, Regulatory Requirements

Change: Language defining a suspected unexpected serious adverse reaction (SUSAR) was added to this section, and the definition for International Council for Harmonisation (ICH) was updated.

Now reads:

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of SAEs including ~~suspected unexpected serious adverse reactions (~~SUSARs~~)~~ per the International ~~Conference on Harmonization~~ **Council for Harmonisation** (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines. **SUSARs are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered**.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

Rationale: The ICH definition was updated for accuracy, and the language pertaining to SUSARs was added to describe the collection of safety information that is consistent with internationally recognized standards.

Section 9.5.3, Dosing Errors

Change: This section was updated to include instructions for mediating the event of a study treatment overdose.

Now reads:

~~Study drug~~ **All dosing** errors **(including but not limited to route of** ~~defined as errors in~~ administration**, wrong** ~~or the administered~~ dose**, etc.) must** ~~should~~ be **reported** ~~documented~~ as **protocol deviations** ~~Protocol Deviations.~~ A brief description should be provided in the deviation, including **information about** whether the subject was symptomatic **or not.** ~~(list symptoms) or asymptomatic.~~ Dosing details should be captured on the Dosing CRF.

A dosing error will be considered an overdose when any of the following conditions are met:

- **Any single dose given exceeds the dose level described in the protocol and Drug Handling and Administration (DHA) Guidelines.**
- **Dosing frequency exceeds 4 doses in a 60-day period.**
- **Study drug is administered less than 14 days from the previous dose.**

Overdoses are not considered AEs and should not be recorded as an AE on the CRF unless an AE or an SAE occurs. All overdoses (regardless of whether or not they result in an AE) must be recorded on an overdose form and faxed to Biogen or designee within 24 hours of the site becoming aware of the overdose. If an overdose results in an SAE, both the SAE and overdose forms must be completed and faxed to Biogen or designee. Should an overdose occur, the Investigator or designee must contact the Medical Monitor within 24 hours**; refer to the Study Reference Guide for complete contact information**.

Rationale: There was no text in the previous version of the protocol that addressed a study treatment overdose. This text was added to address this potential event and to collect information on overdoses.

Section 9.5.4, Contraception and Pregnancy

Change: Language was added to define childbearing potential and to describe acceptable contraception methods. A sentence was added to clarify how congenital abnormalities and birth defects in the offspring of study subjects should be reported.

Now reads:

Female subjects of **childbearing**~~child bearing~~ potential **(defined as any female who has experienced menarche)** must have a negative pregnancy test at **every study visit as described in Section 6.3.2** ~~Screening~~ and must either be abstinent or practice adequate contraception during the study~~, as described in Section 6.3~~.

Male subjects must remain abstinent during the study or **must** be using an acceptable contraceptive method.

For the purposes of the study, acceptable contraception methods are abstinence, barrier contraceptives, intrauterine contraceptive devices, licensed hormonal products, and the use of ~~(i.e, use~~ a condom together with spermicidal foam/gel/film/cream/suppository. **Abstinence is only acceptable as true abstinence (i.e., when this is representative of the preferred and usual lifestyle of the subject).**~~)~~ **Periodic abstinence (e.g., abstinence for the duration of the study) and withdrawal are not acceptable methods of contraception.**

If a subject becomes pregnant or a pregnancy is suspected, or if a male subject makes or believes that he has made someone pregnant during the study, then the **study** site staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of **(possible)** pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and **is** reported within 24 hours **of the study site staff becoming aware.**

Payment for all aspects of obstetrical ~~care~~, child**,** or related care will be the subject's responsibility.

Female **subjects** ~~patients~~: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The **subject** ~~patient~~ with a confirmed pregnancy will be immediately withdrawn from **study drug** treatment~~ with study drug~~. However, the **subject** ~~patient~~ will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the **subject** ~~patient~~ in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the study center ~~Study Center~~ and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male **subjects** ~~patients~~: The progress of the pregnancy in a male **subject's** ~~patient's~~ partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by relevant guidelines (e.g., **Health Insurance Portability and Accountability Act [**HIPAA**]**) and privacy considerations.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the conduct of the study (including follow-up).

Rationale: This text was added to provide clarity regarding the appropriate way to report congenital abnormalities and birth defects for subjects who conceive a child during the study treatment period.

Section 9.5.5, Medical Emergency

Change: Text providing guidance to address a medical emergency was added.

Now reads:

9.5.5 Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. In case of a medical emergency where knowing the subject's treatment assignment may influence the subject's clinical care, the Investigator has the ability to unblind the treatment assignment. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's official study contact list for complete contact information.

Rationale: This text was added to provide guidance in the event of a medical emergency.

Section 10.1.1, Safety and Tolerability Endpoints

Change: Physical examinations were removed as an endpoint and urine total protein was added as a clinical laboratory assessment.

Now reads:

Safety **and**~~/~~ Tolerability Endpoints

- AEs ~~adverse events~~ and SAEs
- Vital signs and weight
- Neurological examinations
- ~~Physical examinations~~
- Clinical laboratory tests (serum chemistry, hematology, urinalysis**, and urine total protein**)
- **Coagulation parameters (aPTT, PTT, and INR)**
- ~~Electrocardiograms (~~**ECGs**~~)~~
- Use of concomitant medications

Rationale: Physical examinations were removed as an endpoint because no data related to the examinations are collected (any findings are reported as AEs). Urine total protein collection is a standard laboratory assessment and was added to ensure adequate collection of subject's samples to monitor the safety of nusinersen. Coagulation parameters were added to thoroughly evaluate coagulation parameters in study subjects receiving nusinersen.

This change also affects Section 6.3.5, Physical Examinations; Section 6.4.1, Clinical Safety Laboratory Evaluations; Appendix A, Schedule of Procedures, and Appendix B, Laboratory Analytes.

Section 10.1.2, Efficacy Endpoints

Change: The efficacy endpoints for each study group were revised and resulted in the generation of a subsection titled [redacted].

Now reads:

~~Groups 1A and 1B~~ **For all groups/subjects:**

- **Achievement of motor milestones (WHO motor milestones and/or Section 2 of HINE)**
- Time to death or permanent ventilation (tracheostomy **or** ≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event)
- ~~Survival rate~~
- ~~Proportion~~ **Percentage** of subjects not requiring permanent ventilation
- Change from baseline in **applicable motor function assessments:** CHOP INTEND**, HFMSE, RULM, 6MWT, and CMAP**
- **Growth parameters**
- Proportion of **CMAP responders** ~~patients achieving a CHOP INTEND score of at least 50~~
- ~~Hammersmith Functional Motor Scale – Expanded (HFMSE) total score and change~~ ~~**from** first to last assessment~~
- ~~Proportion of subjects that achieve any new motor milestone~~
- ~~Proportion of patients achieving all maximum motor milestones in HINE (Hammersmith Infant neurological Examination)~~
- ~~Proportion of subjects that achieve standing alone~~
- ~~Proportion of subjects that achieve walking with assistance~~
- ~~CMAP total and change from baseline~~
- ~~Change from baseline in CSF SMN protein concentration~~
- ~~Clinical Global Impression – Improvement~~
- ~~Disease-related hospitalizations and adverse events~~
- ~~Change from baseline in HFMSE (Hammersmith Functional Motor Scale – Expanded)~~
- ~~Proportion of subjects that achieve any new motor milestone~~
- Number of motor milestones achieved per subject
- Proportion of subjects ~~that achieve~~ **who achieved** standing alone
- **Proportion of subjects who** achieved ~~that achieve~~ walking with assistance
- ~~CMAP total and change from baseline~~
- ~~Change from baseline in cerebrospinal fluid (CSF) SMN protein concentration~~
- **Number of serious respiratory events**

- **Number and length of hospitalizations**
- Change from baseline in Cobb-**Angle ~~angle~~ on X~~x~~**-ray of the thoracolumbar spine
- **Changes in quality of life assessments: CGI-I, PedsQL, and/or ACEND**
- Disease-related hospitalizations and **AEs**
- **Survival rate**

[redacted]

~~**Groups 2A and 2B**~~

- ~~Change from baseline in Upper Limb Module Test~~
- ~~Change from baseline in 6 Minute Walk Test (6MWT) (ambulatory subjects only)~~
- ~~Change from baseline in CSF SMN protein concentration~~
- ~~Change from baseline in PedsQL~~
- ~~Change from baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)~~
- ~~Change from baseline in Cobb-angle on x-ray of the thoracolumbar spine~~
- ~~CGI-I~~
- ~~Disease-related hospitalizations and AEs~~

~~**Group 3**~~

- ~~Change from baseline in HFMSE (Hammersmith Functional Motor Scale – Expanded)~~
- ~~Change from baseline in Upper Limb Module Test (non-ambulatory subjects)~~
- ~~Change from baseline in 6 Minute Walk Test (ambulatory subjects only)~~
- ~~CMAP and multipoint incremental MUNE total and change from baseline (subjects who had these assessments performed in ISIS 396443-CS12 study)~~
- ~~Myometry (subjects ≥5 years old only)~~
- ~~Change from baseline in CSF SMN protein concentration~~
- ~~Change from baseline in PedsQL (Pediatric Quality of Life Inventory)~~

- ~~Change from baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)~~
- ~~Clinical Global Impression - Improvement~~
- ~~Disease-related hospitalizations and adverse events~~

[redacted]

[redacted]

Section 10.1.6, Future Scientific Research Assessments

Change: A section for future scientific research assessments was added to allow for the possibility of future research to be conducted on [redacted] collected from patients who provided consent.

Now reads:

10.1.6 Future Scientific Research Assessments

In subjects who provide additional optional consent, [redacted] may be stored for future, unspecified, [redacted]. Subjects will sign a separate written ICF if they opt for samples to be retained and used in this way.

The samples collected may be utilized to identify or verify putative, prognostic, and predictive markers associated with the disease as well as markers of therapeutic response to treatment and/or develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated [redacted] data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

Rationale: [redacted]ify [redacted], and/or develop diagnostic and analytical tests, which can then be used to predict disease progression, identify high-risk patients, and identify predictors of response to treatment.

Section 10.3, Populations

Change: The definition for the Intent-to-Treat Set was updated and the definition for the Per-Protocol Set for Group 4 was added.

Now reads:

Intent-to-Treat (ITT) Set: All subjects who are enrolled **and received at least 1 dose of nusinersen**.

Per-Protocol Set (PPS): For **Groups** ~~Group~~ 1A and 2A, PPS will include the subset of the ITT who complete the loading period in this study and who have no significant protocol deviations that would be expected to affect efficacy assessments. For **Groups** ~~**Group**~~ 1B and 2B, PPS will include **the** subset of the ITT who complete the loading period in index studies and who have no significant protocol deviations that would be expected to affect efficacy assessments. For **Groups** ~~Group~~ 3 **and 4**, PPS will include the subset of the ITT who have no significant protocol deviations that would be expected to affect efficacy assessments.

Rationale: The definition for PPS was updated for all groups to align with the updated statistical plan for this study.

Section 10.4, Definition of Baseline

Change: The definition for baseline was revised.

Now reads:

Definitions of baseline are given below for the purposes of the final analysis.

The analyses will focus on the ISIS 396443-CS11 data. The baseline will be the last non-missing assessment prior to the first dose of study treatment in the ISIS 396443-CS11 study. If any integration of data with the index study is conducted, the following definitions of baseline will be used:

For safety, baseline for subjects on active treatment in the index study will be the index study baseline. For subjects on sham in the index study, baseline for safety will be the last non-missing assessment prior to the first dose of **study treatment** ~~Study Drug~~ in this study.

For efficacy, **2** ~~two~~ baselines are defined for each subject: index study baseline and the baseline in this study, which is defined as the end-of-treatment assessment in index studies or **the** last non-missing assessment before the first dose of **study treatment** ~~Study Drug~~ in this study.

Rationale: The definition for baseline was revised to provide clarity regarding baseline for the ISIS 396443-CS11 study and baseline if the data will be integrated with data from the index studies.

Section 10.5, Interim Analysis

Change: The text was updated to reflect that interim analyses may be performed.

Now reads:

Interim analyses may be performed to provide content for regulatory submissions and to support nusinersen drug development planning and business activities. ~~No formal interim analysis is planned for this study.~~

Rationale: The purpose of interim analyses would be to provide study Sponsors and regulators with information on the status of this ongoing study.

Section 10.6.2, Safety and Tolerability Analysis

Change: Text was added to describe the evaluation of AEs for subjects in Groups 2A, 2B, and 3.

Now reads:

All treatment-emergent **AEs**~~-adverse events~~ and **SAEs**~~-serious adverse events~~ will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system, by system organ class, preferred term, relationship to **study treatment**~~-Study Drug~~, and severity. Narratives of deaths **and**~~,~~ **SAEs**~~-serious adverse events~~, including early withdrawals from **the study treatment**~~-Study Drug~~ and from **the** study due to **AEs**~~-adverse events~~, will also be provided.

When applicable, for Groups 2A, 2B, and 3, the incidence of AEs will be evaluated by treatment phase (original dosing schedule phase versus MMDR).

Rationale: The description of evaluation of AEs for Groups 2A, 2B, and 3 was updated to align with the statistical plan for this study.

Section 10.6.3, Efficacy Analysis

Change: This section was updated to align with the most recent statistical analyses and the current efficacy endpoints for this study.

Now reads:

For subjects <2 years of age who have not yet achieved independent walking, motor milestones will be assessed using Section 2 of the HINE, which is composed of 8 motor milestone categories as follows: voluntary grasp, ability to kick in supine position, head

control, rolling, sitting, crawling, standing, and walking. Within each motor milestone category, there are 3 to 5 levels that can be achieved. All 8 motor milestones will be tested during each assessment. A subject whose results after testing all appear in the first column (no grasp, No kicking, Unable to maintain head upright, and so on) has not achieved any motor milestone. Motor milestone achievement is depicted by movement from the left side of Table 3 to the right side of the table, as denoted by the Milestone Progression arrow in the table [Haataja 1999].

Table 3 Hammersmith Infant Neurological Examination Section 2 - Motor Milestones

Motor Milestone Category	Milestone Level Progression (Age Expected in Heathy Infants[a]) →				
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb; immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) [3 months]	Touches leg (4 to 5 months)	Touches toes (5 to 6 months)
Head control	Unable to maintain upright (<3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolling to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sit with support at hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) [10 months]
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4 to 5 months)	Crawling flat on abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4 to 5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) [11 months]	Walking independently (15 months)	

***Values for healthy infants in [Haataja 1999].**

The proportion of motor milestone responders is defined based on the 7 motor milestones categories, with the exclusion of voluntary grasp using the assessment at the later study visits, as follows:

- **Subject demonstrates at least a 2-point increase in the motor milestone category of ability to kick or achievement of the maximal score on that category (touching toes) or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND**
- **Among the 7 motor milestone categories with the exclusion of voluntary grasp, subject demonstrates improvement (defined in [i]) in more categories than worsening. Note: For the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease.**

Subjects who die or withdraw from the study will be counted as nonresponders and will be included in the denominator for the calculation of the proportion. As a result, mortality will be accounted for in the motor milestone analysis. For subjects on permanent ventilation, because motor milestone assessment continues, functional scores after permanent ventilation has been achieved will be used to assess improvement in motor milestones.

The median time to death or permanent ventilation, survival rates over time, and the **percentage** ~~proportion~~ of subjects requiring permanent ventilation ~~in Group 1A and 1B at end of treatment~~ will be estimated using Kaplan-Meier method.

Change from baseline in CHOP INTEND total score and HFMSE score **for subjects as described in Section 6.5.2.1 and Section 6.5.2.2, respectively**, proportion of subjects **who achieved** ~~that achieve~~ any new motor milestone, number of motor milestones achieved per subject, proportion of subjects **who achieved** ~~that achieve~~ standing alone milestone, proportion of subjects **who achieved** ~~that achieve~~ walking with assistance milestone, change from baseline in RULM~~Upper Limb Module Test~~, change from baseline in **6MWT** ~~6 MWT~~ distance, CMAP~~,~~ ~~MUNE, and myometry~~ parameters, change from baseline in ~~CSF SMN protein concentration, change from baseline in~~ PedsQL, change from baseline in ACEND, **CGI-I** ~~clinical global impression improvement~~, and disease-related hospitalizations and **AEs** ~~adverse events~~ will be summarized.

The proportion of CMAP responders is defined as the proportion of subjects with peroneal CMAP amplitude increasing to or maintained at ≥1 mV, comparing to the baseline, based on assessment at the later study visits.

Rationale: The text pertaining to efficacy analyses was updated to align with the revised endpoints. Myometry and motor unit number estimation assessments were removed to reduce the burden of study participation on subjects and their families.

This change also affects Section 10.1.2, Efficacy Endpoints.

[redacted]

Section 11.3, Institutional Review Board/Institutional Ethics Committee/Research Ethics Board

Change: Text clarifying the processes to be completed before subjects can be recruited for the study, the timing of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) progress reports, and the processes for study completion or termination have been added.

Now reads:

A copy of the protocol, proposed **ICF and optional genetics and future research ICFs** ~~informed consent form~~, proposed informed assent form (if applicable), other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval **by the Investigator**. A copy of the **IRB/IEC** written approval ~~of the protocol and informed consent/assent forms~~ must be received **and approved** by the Sponsor before recruitment of subjects into the study and shipment of **study drug** ~~Study Drug~~**.** ~~A copy of the written approval of any other items/materials that must be approved by the Study Center or IRB/IEC must also be received by the Sponsor before recruitment of subjects into the study and shipment of Study Drug.~~ The Investigator's Brochure must be submitted to the IRB/IEC for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent/assent documents. The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IRB/IEC of **SAEs** ~~serious adverse events~~ occurring at the **study center** ~~Study Center~~ and other **AEs** ~~adverse events~~ reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. **A progress report must be submitted to the ethics committee at required intervals and not less than annually**. Copies of the Investigator's reports, all IRB/IEC submissions**,** and the IRB/IEC continuance of approval must be sent to the Sponsor. **At**

the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and the Sponsor (or designee).

Rationale: This information was added to clarify when progress reports will be submitted during the study and the responsibilities of the investigational site after the completion or the termination of the study.

Section 11.4.1, Subject Data Protection

Change: A section describing subject data protection was added to the protocol.

Now reads:

11.4.1 Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, the subjects' race and ethnicity may be collected for the purposes of data analysis.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Rationale: This text was added to align with the most current version of the Biogen protocol template.

This change also affects Section 11.1, Informed Consent/Assent.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The Ionis logo was replaced with the Biogen logo on the title page.
- The Sponsor Information was updated.
- The Sponsor Signatory information was updated, and a signature page was added.
- The Study Glossary was updated.
- Typographical errors and formatting were corrected.
- "Subject" replaced most instances of "Patient" to align with Biogen style (1 exception is the protocol title).
- "Study" replaced most instances of "Trial" throughout the protocol, except on pages 2, 43, and 68.
- When referring to "study drug," nusinersen is used in place of ISIS 396443. When referring to the Protocol Title or previous ("index") studies, ISIS 396443 is used. The term "study treatment" refers to administration of nusinersen or the sham procedure during the blinded portion of the study.
- Information in the Confidentiality Statement was updated to align with the most recent version of the Biogen protocol template.
- Section 2.1, Spinal Muscular Atrophy, was updated to include "5 nucleotides" instead of "11 nucleotides."
- Section 2.3.4, Clinical Experience, was updated to align with the most recent version of the Investigator's Brochure.
- Section 3.2, Number of Study Centers, was revised to include approximately 37 sites in 14 countries.
- Section 3.3, Number of Subjects, was revised to include up to 289 subjects who previously participated in investigational studies with ISIS 496443.
- Section 3.5, End of Study, was updated with language to reflect the MMDR schedule and early termination.
- Section 3.6, Safety Monitoring and Data and Safety Monitoring Board (DSMB), was updated to include text stating that the DSMB may be discontinued at the Sponsor's discretion.
- Section 6, Study Procedures, was reorganized to present study assessments according to their timing within the study (on injection day only; screening only; every study visit and the EOS Evaluation Visit; MMDR Day 1, every 4 months thereafter [every MMDR visit], and the EOS Evaluation/ET Visit; screening and/or MMDR Day 1, every 8 months thereafter [every other MMDR visit], and the EOS Evaluation/ET

Visit; screening and/or MMDR Day 1, annually, and the EOS Evaluation/ET Visit; MMDR Day 1 and the EOS Evaluation/ET Visit; and continuously throughout the study).

[redacted]

- Section 6.3.2, Urine Pregnancy Tests, was created to address urine and serum pregnancy tests for women of childbearing potential.
- Section 6.3.3, Weight, was created to indicate when this information will be collected in the study.
- Section 6.3.5, Physical Examinations, was created to describe the timing of the examinations and the capturing of abnormal findings as AEs.
- Section 6.3.6, Vital Signs, was created to address the timing of data collection for these parameters in the study.
- Section 6.3.7, Neurological Examinations, was updated to include the predose and postdose time frame for this assessment as well as the time frame for sufficient recovery if sedation is used.

[redacted]

- Section 6.5.1, Motor Milestones, was updated with text that indicates videotaping of motor milestone assessments will be optional.
- Section 6.5.2, Motor Function Assessments, was updated with text that indicates videotaping of motor function assessments will be optional and to include a definition for the term "ambulatory."
- Section 7.3, Study Drug Accountability, was revised.
- Section 8.1, Study Drug Administration, was updated with information pertaining to the DHA guidelines and to provide information regarding the room in which the procedures will be performed.
- Section 8.8, Adjustment of Dose and/or Treatment Schedule, was revised.
- Section 8.10, Withdrawal of Subjects From the Study, was updated with language clarifying the withdrawal of consent by the subject or the subject's parent/guardian.
- Section 10.1.1, Safety and Tolerability Evaluations, was updated to include "Tolerability" in the section title.
- Section 11.1, Informed Consent/Assent, was updated to include a sentence that states that subjects will be informed that their race and ethnicity may be collected and may be used during analysis of study results.
- Section 11.2, Ethical Conduct of the Study, was updated.

- Section 12.3, Study Documentation and Storage, was updated for clarity.
- Sections 12.7, Conflict of Interest; 12.8, Registration of Study and Disclosure of Study Results; 12.9, Study Funding; and 12.10, Publications were added.
- Appendix A, Schedule of Procedures, was updated to combine the schedules for all groups under the MMDR schedule, and footnotes describing vital signs, ECGs, [redacted], and X-ray of spine were removed from the Schedules of Procedures and added to Section 6, Study Procedures.
- Appendix B, Laboratory Analytes, was updated to include gamma glutamyl transferase as a clinical chemistry assessment, and urine total protein and coagulation assessments were added as assessments that will be assessed by local laboratory only.