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PROTOCOL NUMBER: 232SM202/ NCT02462759

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

EUDRA CT NO **2014-003657-33**

DATE: 16 June 2017
Version 4
Final

Supersedes previous Version 3 dated 01 June 2016.

SIGNATURE OF BIOGEN MA INC. THERAPEUTIC AREA HEAD

Neurology

Protocol 232SM202, Version 4, was approved by:

[redacted]

[redacted] MD

Biogen MA Inc.

16-June-2017

Date

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1. SPONSOR INFORMATION

Biogen Idec Research Limited is the Sponsor of the study in the United States and the Rest of World. Biogen Idec Research Limited (or designee) will be responsible for managing the study globally.

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

2. LIST OF ABBREVIATIONS

2′ MOE	2′ O (2 methoxyethyl)
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
Bi-PAP	bi-level positive airway pressure
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
GCP	Good Clinical Practice
HINE	Hammersmith Infant Neurological Examination
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRT	interactive response technology
LP	lumbar puncture
mRNA	messenger ribonucleic acid
OLE	open-label extension
PK	pharmacokinetic(s)
PTT	partial thromboplastin time
RNA	ribonucleic acid
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to reach maximum observed concentration
US	United States
WHO	World Health Organization

3. SYNOPSIS

This is a brief summary. For details, refer to the body of the protocol.

Protocol Number:	232SM202
Protocol Title:	A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
Version Number:	4
Name of Study Treatment:	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.
Study Indication:	Spinal muscular atrophy (SMA)
Phase of Development:	2
Study Rationale:	The rationale of Part 1 of the study is to assess the safety and tolerability and evaluate the utility of selected exploratory efficacy endpoints in subjects with SMA treated intrathecally with Nusinersen who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 (the open-label extension phase) prior to completion of all Part 1 evaluations. The rationale of Part 2 of the study is to assess the long-term safety and tolerability of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.
Study Objectives and Endpoints:	**Part 1** Primary objective: The primary objective of Part 1 of this study is: • To assess the safety and tolerability of Nusinersen in subjects

with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The primary endpoints that relate to this objective are:

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline in neurological examination outcomes

Secondary objective:

The secondary objective and endpoint of Part 1 of this study are as follows:

- To examine the pharmacokinetics (PK) of Nusinersen in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
- Nusinersen concentrations in plasma and cerebrospinal fluid (CSF)

Part 2

Primary objective:

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The primary endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline in clinical laboratory parameters, ECGs, vital signs, and growth parameters
- Change from baseline in neurological examination outcomes
- Coagulation parameters (activated partial thromboplastin time, partial thromboplastin time, and international normalized ratio) and urine total protein

Secondary objective:

The secondary objective and endpoint of Part 2 of this study are as follows:

- To examine the PK of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments

- Nusinersen concentrations in plasma and CSF

Exploratory objectives and endpoints are listed in Section 6.3.

Study Design:

This is a Phase 2 multicenter study conducted in 2 parts:

Part 1 was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered Nusinersen over a period of approximately 14 months (from the first dose until the End of Part 1 Evaluation). Up to 21 subjects will be randomized in a ratio of 2:1 to receive Nusinersen by intrathecal lumbar puncture (LP) injection or a sham-procedure control. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months.

After informed consent is obtained, subjects will undergo a screening evaluation no greater than 28 days prior to administration of the first dose of study treatment. Subjects who meet the eligibility criteria will be randomized to receive Nusinersen or sham procedure. Subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of study treatment or sham procedure. Subjects will return to the study site on Days 15, 29, 64, 183, and 302 for follow-up evaluations and subsequent injections or sham procedures. For subjects receiving Nusinersen or sham procedure, a CSF sample will be taken predose on each injection day in a manner that maintains the blind.

After the study treatment dosing or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours for safety monitoring. Following all subsequent injections, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring.

Safety monitoring will occur on the day following each injection of study treatment or sham procedure. Subjects receiving the dosing or sham procedure on Days 15, 29, 64, 183, and 302 will be monitored by telephone contact on Days 16, 30, 65, 184, and 303.

In addition, subjects will also be monitored through telephone contact throughout the duration of the study.

An End of Part 1 Evaluation will occur up to 4 months after the last dose of Nusinersen or sham procedure, or sooner (if the Sponsor decides to terminate Part 1 early based on emergent data from the Nusinersen clinical development program, as described below). Subjects who terminate early from Part 1 of the study will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal.

After completing End of Part 1 Evaluation assessments according to the study schedule or sooner, if emergent data from the Nusinersen clinical

development program necessitate the early termination of Part 1 by the Sponsor, all eligible subjects may elect to enroll in Part 2. All subjects enrolled in the study at the time that the Sponsor terminates Part 1 will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an open-label extension (OLE) phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered Nusinersen for approximately 24 additional months.

Part 2 study procedures will be determined based on the treatment assignment in Part 1.

Subjects who were randomized to receive Nusinersen in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving Nusinersen in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of Nusinersen in Part 1. On Part 2 Day 1, subjects will undergo predose evaluations according to the schedule of events and then receive their first dose of Nusinersen for Part 2 (next maintenance dose). Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 for follow-up evaluations and subsequent maintenance dose injections. All subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment. Subjects will be monitored by telephone contact on Days 2, 121, 240, 359, 478, 597, and 716.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 of the study will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine eligibility for Part 2 of the study. For subjects who were receiving sham

procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following the End of Part 1 Evaluation, in the event of early termination due to emergent data from the Nusinersen clinical development program. On Part 2 Day 1, subjects will undergo predose evaluations according to the schedule of events and then receive their first dose of Nusinersen (first loading dose). Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 for follow-up evaluations and subsequent injections. Subjects will remain at the study site for at least 24 hours on Day 1. Following all subsequent injections, all subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment after Day 1. Subjects will be monitored by telephone contact on Days 16, 30, 65, 184, 303, 422, 541, 660, and 779.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Rationale for Dose and Schedule Selection:	In Part 1, a scaled equivalent dose of 12 mg Nusinersen will be administered at each of the 6 doses (i.e., on Study Days 1, 15, 29, 64, 183, and 302) over a dosing period of approximately 10 months to subjects randomized to receive active treatment. In Part 2, a scaled equivalent dose of 12 mg Nusinersen will be administered at each dose over a dosing period of approximately 24 months. The volume of the injection will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower absolute mg dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for 2 years of age to adult. The dose regimen and the dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dose intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of Nusinersen to date. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 μg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal 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 selected for this multiple-dose clinical study (equivalent to 12 mg of 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain Nusinersen spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 μg/g lumbar and 10 μg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who were not

eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of Nusinersen at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving Nusinersen in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1 will receive maintenance doses starting on Day 183 of Part 2.

Table 1 Nusinersen Dose Volume To Be Injected

Age	Estimated CSF Volume (mL)	Injection Volume (mL)	Dose (mg)
0-3 months (0-90 days)	120	4	9.6
3-6 months (91-182 days)	130	4.3	10.3
6-12 months (183-365 days)	135	4.5	10.8
12-24 months (366-730 days)	140	4.7	11.3
>24 months (>730 days)	150	5.0	12.0

Source: [Matsuzawa 2001]
CSF = cerebrospinal fluid.

Study Location: Global, multicenter

Number of Planned Subjects: In Part 1, up to 21 subjects are planned (14 Nusinersen; 7 sham procedure).

In Part 2, up to 21 subjects are planned (21 Nusinersen).

Study Population: Part 1 of this study will be conducted in subjects who have clinical signs and symptoms of SMA at ≤6 months of age or at >6 months of age and who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

Part 2 will include only subjects who participated in Part 1 and completed their End of Part 1 Evaluation assessments. Subjects enrolling in Part 2 must meet the Part 2-specific criteria.

Detailed eligibility criteria are described in Section 8.

Treatment Groups:	In Part 1, subjects will receive either Nusinersen intrathecally or sham-procedure control in a 2:1 ratio. Randomization will be balanced for the stratification factor (age of symptom onset >6 months versus ≤6 months). A single dose level of 12 mg Nusinersen will be scaled by age at the time of dosing for each subject. In Part 2, all subjects will receive open-label Nusinersen. A single dose level of 12 mg Nusinersen will be scaled by age at the time of dosing for each subject.
Duration of Treatment and Follow-up:	For subjects who meet the eligibility criteria and enroll in Part 1 of the study, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations. For subjects who meet the eligibility criteria and enroll in Part 2 of the study, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment. Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.
Criteria for Evaluation:	The criteria for evaluation for Part 1 and Part 2 include:
Safety:	• Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes) • AEs, including SAEs • Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide) • Growth parameters • Physical examinations • Medical history • 12-Lead ECGs

- Use of concomitant medications
- Clinical laboratory tests (blood chemistry, hematology, urinalysis, urine total protein, and coagulation parameters)

Pharmacokinetics:

- Plasma Nusinersen concentrations
- CSF Nusinersen concentrations

Efficacy:

- Ventilator use
- World Health Organization motor milestones and Hammersmith Infant Neurological Examination (HINE, Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment) and Assessment of Caregiver Experience With Neuromuscular Disease

Immunogenicity:

- Anti-Nusinersen plasma antibody concentrations

Statistical Methods:

Analysis Population

The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure in Part 1.

The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure in Part 1.

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

Part 1

Safety Analysis

The analysis of safety will be performed on the safety population. The incidence of treatment-emergent AEs and SAEs will be tabulated. Changes from baseline in clinical laboratory parameters, vital signs, and ECG parameters will be summarized. Incidence of clinically relevant changes from baseline in vital signs and ECGs will be summarized. Laboratory parameters will also be summarized using shift tables, as appropriate.

PK Analysis

Summary statistics for plasma and CSF concentrations of Nusinersen will be provided.

Exploratory Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

Part 2

No formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

Interim Analysis:

No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

Sample Size Determination:

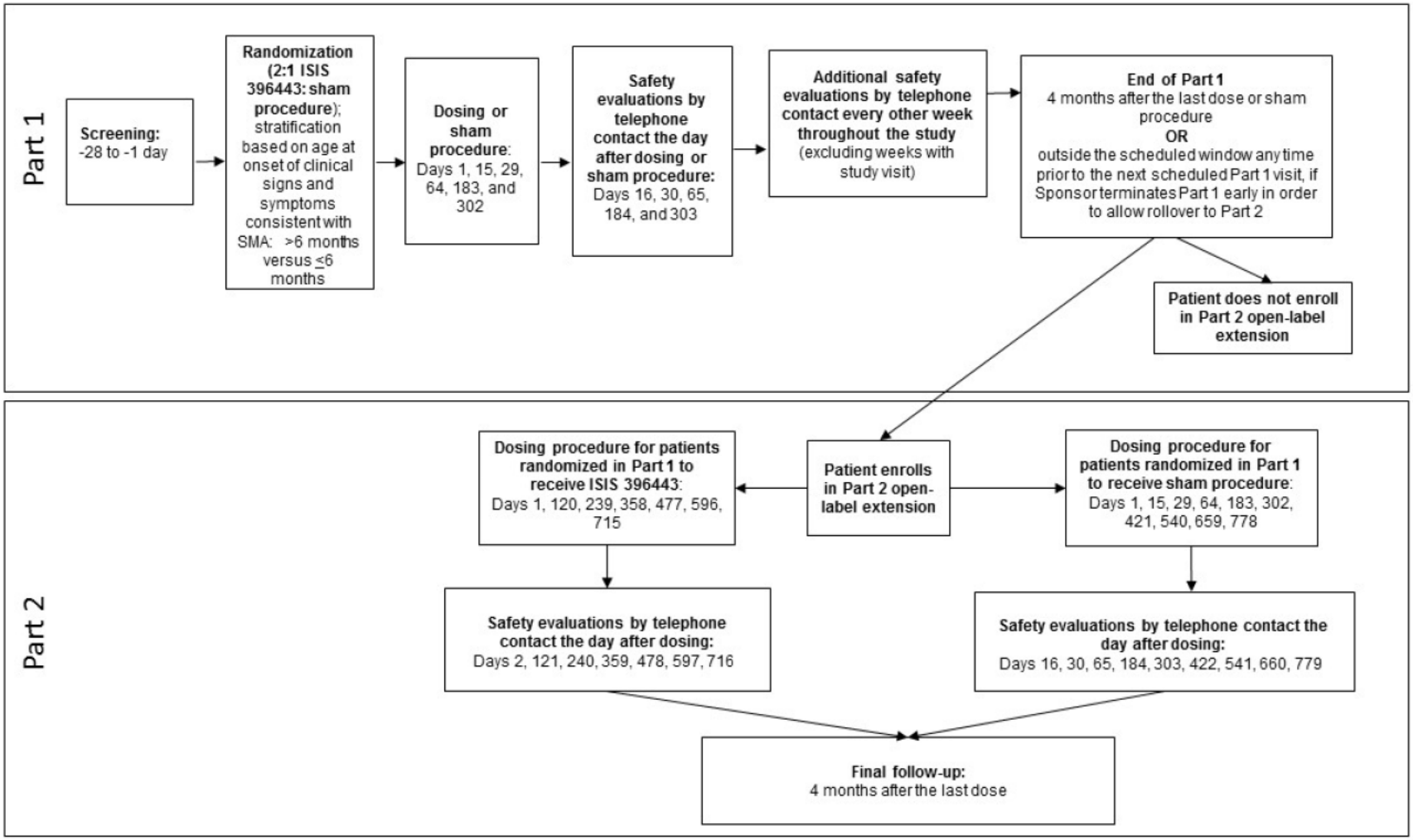
Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

Study Stopping Rules:	The Sponsor may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 232SM202

4.1. Study Schematic

Figure 1: Study Schematic



4.2. Schedule of Events

4.2.1. Schedule of Events: Part 1

Table 2: Part 1 Schedule of Activities

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3,4,5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Vital Signs[6]	X	X		4X[7]	X[8]	X		X		X		4X[7]		X		4X[7]		X
Weight	X	X			X	X				X				X				X
Growth Parameters[9]	X	X				X				X				X				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
Neurological Examination[10]	X	X		X[11]	X	X		X[11]		X		X[11]		X		X[11]		X
ECG	X				X							X						X
Safety Laboratory Tests[12]	X													X[13]				X[14]
Coagulation Laboratory Tests	X																	
Immunogenicity Sample		X												X				X
CSF PK[15]		X				X				X				X				
Plasma PK				X[16]										X[17]				X
Study Treatment Injection or Sham			X				X				X				X			

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3,4,5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Procedure																		
Inpatient Stay[18]				X														
Telephone Contact for Safety Monitoring[2]									X				X				X	
HINE Motor Milestone		X												X				X
Clinical Global Impression of Change														X				X
Con Med Recording[19]	X ---------- X																	
Adverse Event Collection[20]	X ---------- X																	

AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

[1] A blood sample will be collected at Screening for *SMN2* copy number only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

[2] After the injection of study treatment or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. On the day following the injection of study treatment or sham procedure on Days 15, 29, 64, 183, and 302, there will be safety monitoring through telephone contact. During that telephone contact (i.e., Days 16, 30, 65, 184 and 303), changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[3] End of Part 1 is one of the following: Part 1 Final Follow-up Evaluation (Day 422 [±7 days]) according to the study schedule, early Part 1 Final Follow-up Evaluation to allow for rollover into Part 2, or Early Termination Evaluation for subjects who withdraw from the study during Part 1.

[4] For subjects not transitioning into Part 2, the date of the End of Part 1 Evaluation assessments will be the end of study. For subjects who transition to Part 2, the date of the End of Part 1 will be the date of first dose in Part 2.

[5] At the End of Part 1 evaluation, in order to allow transition to Part 2, subjects will be unblinded.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected within 20 to 24 hours after the injection of study treatment or sham procedure.

[9] At the evaluations scheduled for injection of study treatment or sham procedure, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference.
[10]Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
[11]Neurological examinations will occur between 4 to 6 hours after the injection of study treatment or sham procedure.
[12]Blood chemistry, hematology, and urinalysis panels.
[13]Samples for safety laboratory tests will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only.
[14]End of Part 1 safety laboratory tests may be performed locally in addition to centrally to accommodate the Part 2 Day 1 dosing.
[15]Refer to Table 5 for CSF PK sample schedule. The CSF samples will be analyzed for Nusinersen concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[16]Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment or sham procedure only on Day 1. Refer to Table 5 for the plasma PK sample schedule.
[17]Blood samples for PK assessment will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only. Refer to Table 5 for the plasma PK sample schedule.
[18]Overnight stay (at least 24 hours) is required after the first injection of study treatment or sham procedure. Following all subsequent injections or sham procedures, a stay of at least 6 hours at the study site is required; overnight stays are optional on these days.
[19]In addition to concomitant medications, ancillary procedures will be recorded.
[20]AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

4.2.2. Schedule of Events: Part 2

Table 3: Part 2 Schedule of Activities for Subjects Randomized to Receive Nusinersen in Part 1

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X[5]								
Inclusion/ Exclusion Criteria	X[5]								
Vital Signs[6]	X[7]		X[8]		X		X[8]		X
Weight	X[7]				X				X
Growth Parameters[9]	X[7]				X				X
Physical Examination	X[7]				X				X
Ventilator Use	X[7]			X	X			X	X
Neurological Examination[10]	X[7,11]		X[11]		X[11]		X[11]		X
ECG	X[7]				X[12]				X[12]
Safety Laboratory Tests[13]	X[7]				X[14]				X
Immunogenicity Sample	X[7]				X[15]				X
CSF PK[16]	X[5, 7]				X				
Plasma PK[17]			X[17]		X[17]				X
Study Treatment Injection		X				X			
Telephone Contact for Safety Monitoring (+3 Days)				X				X	
HINE and WHO Motor Milestone					X				X
Clinical Global Impression of Change					X				X

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
and ACEND									
Optional Sibling SMA Data Collection[18]	X								X
Con Med Recording[19]	X----------								----------X
Adverse Event Collection[20]	X----------								----------X

ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; WHO = World Health Organization.

[1] There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 2, 121, 240, 359, 478, 597, and 716). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[2] If the study continues beyond Year 2 (i.e., beyond Day 715), then from Day 835 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the assessments for those additional timepoints to alternate between the assessments done on Day 120 and those done on Day 239. Day 120 assessments would be performed at Day 835 and Day 239 assessments would be performed at Day 954. The alternating pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 716 or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, and CSF PK must be performed on Part 2 Day 1.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation.

[7] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after the End of Part 1 visit, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, and CSF PK. If Part 2 Day 1 study treatment injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, or if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, ECG, CSF PK, and safety laboratory tests. Immunogenicity testing must also be repeated predose if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected 1 hour (±15 minutes) after the injection of study treatment.

[9] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.

[10] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes. 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.

[11] Predose and postdose.
[12] ECG will be performed on Days 239, 477, and 715, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.
[13] Blood chemistry, hematology, urinalysis, urine total protein panels, and coagulation parameters. Urine total protein and coagulation parameters will be assessed by local laboratories.
[14] Samples for safety laboratory tests will be collected before the injection of study treatment at each dosing visit.
[15] Blood samples for immunogenicity testing will be collected before the injection of study treatment on Days 239, 477, and 715.
[16] Refer to Table 6 for CSF PK sample schedule. The CSF samples will be analyzed for Nusinersen concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[17] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 6 for the plasma PK sample schedule. Plasma PK samples will be collected predose on Days 239, 477, and 715.
[18] The optional assessment of sibling SMA data collection will be performed only after obtaining consent.
[19] In addition to concomitant medications, ancillary procedures will be recorded.
[20] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 4: Part 2 Schedule of Activities for Subjects Randomized to Receive Sham Procedure in Part 1

Study Period	Part 2 Treatment/Follow-Up																
Study Day	Day 1			Day 2[1]	Day 15 (±1 day)			Day 16[1]	Day 29 (±1 day)			Day 30[1]	Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]			Days 65, 184, 303, 422, 541, 660, 779[1]	Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X[5]																
Inclusion/Exclusion Criteria	X[5]																
Vital Signs[6]	X[7]		X[8]	X[9]	X		X[8]		X		X[8]		X		X[8]		X
Weight	X[7]			X	X				X				X				X
Growth Parameters[10]	X[7]				X				X				X				X
Physical Examination	X[7]				X				X				X				X
Ventilator Use	X[7]			X	X			X	X			X	X			X	X
Neurological Examination[11]	X[7]		X[12]	X	X		X[12]		X		X[12]		X		X[12]		X
ECG	X[7]			X							X		X[13]				X[13]
Safety Laboratory Tests[14]	X[7]				X				X				X[15]				X
Immunogenicity Sample	X[7]												X[16]				X
CSF PK[17]	X[5, 7]				X				X				X				
Plasma PK[18]			X[18]										X[18]				X
Study Treatment Injection		X				X				X				X			
Inpatient Stay[19]			X														
Telephone Contact for Safety Monitoring								X				X				X	

Study Period	**Part 2 Treatment/Follow-Up**																
Study Day	**Day 1**			**Day 2[1]**	**Day 15 (±1 day)**			**Day 16[1]**	**Day 29 (±1 day)**			**Day 30[1]**	**Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]**			**Days 65, 184, 303, 422, 541, 660, 779[1]**	**Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]**
	Predose[5]	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		
(+3 Days)																	
HINE and WHO Motor Milestone													X				X
Clinical Global Impression of Change and ACEND													X				X
Optional Sibling SMA Data Collection[20]	X																X
Con Med Recording[21]	X----------X																
Adverse Event Collection[22]	X----------X																

ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; WHO = World Health Organization.

[1] After the injection of study treatment on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 16, 30, 65, 184, 303, 422, 541, 660, and 779). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[2] If the study continues beyond Year 2 (i.e., beyond Day 778), then from Day 897 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the schedule of events for those additional timepoints to alternate between the assessments done on Day 183 and those done on Day 302. Day 302 assessments would be performed at Day 897 and Day 183 assessments would be performed at Day 1016. That pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 778 or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, and CSF PK must be performed on Part 2 Day 1 predose.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation.

[7] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after the End of Part 1 visit, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, and CSF PK. If Part 2 Day 1 study treatment injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, or if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, ECG, CSF PK, and safety laboratory tests. Immunogenicity testing must also be repeated if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment only on Part 2 Day 1. On subsequent study days, vital signs will be collected 1 hour after the injection of study treatment.

[9] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected on Day 2 within 20 to 24 hours after the injection of study treatment only.

[10] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.

[11] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes. 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.

[12] Predose and postdose.

[13] ECG will be performed at Days 64, 183, 540, and 778, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.

[14] Blood chemistry, hematology, urinalysis, urine total protein panels, and coagulation parameters. Urine total protein and coagulation parameters will be assessed by local laboratories.

[15] Samples for safety laboratory tests will be collected before the injection of study treatment at each dosing visit.

[16] Blood samples for immunogenicity testing will be collected before the injection of study treatment on Days 64, 183, 302, 421, 540, 659, and 778.

[17] Refer to Table 7 for CSF PK sample schedule. The CSF samples will be analyzed for Nusinersen concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.

[18] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 7 for the plasma PK sample schedule. Plasma PK samples will be collected predose on Days 64, 183, 540, and 778.

[19] Overnight stay (at least 24 hours) is required after the first injection of study treatment. Following all subsequent injections, a stay of at least 1 hour at the study site is required; overnight stays are optional on these days.

[20] The optional assessment of sibling SMA data collection will be performed only after obtaining consent.

[21] In addition to concomitant medications, ancillary procedures will be recorded.

[22] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 5 Part 1 Pharmacokinetic Sampling Schedule[1]

Treatment Period	Part 1 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	End of Part 1	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of Nusinersen with plasma and CSF constituents.

Table 6 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive Nusinersen in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 120	Predose	NA	0.5
	Day 239	Predose	0.5	0.5
	Day 358	Predose	NA	0.5
	Day 477	Predose	0.5	0.5
	Day 596	Predose	NA	0.5
	Day 715	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of Nusinersen with plasma and CSF constituents.

Table 7 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive Sham Procedure in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	Day 421	Predose	NA	0.5
	Day 540	Predose	0.5	0.5
	Day 659	Predose	NA	0.5
	Day 778	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of Nusinersen with plasma and CSF constituents.

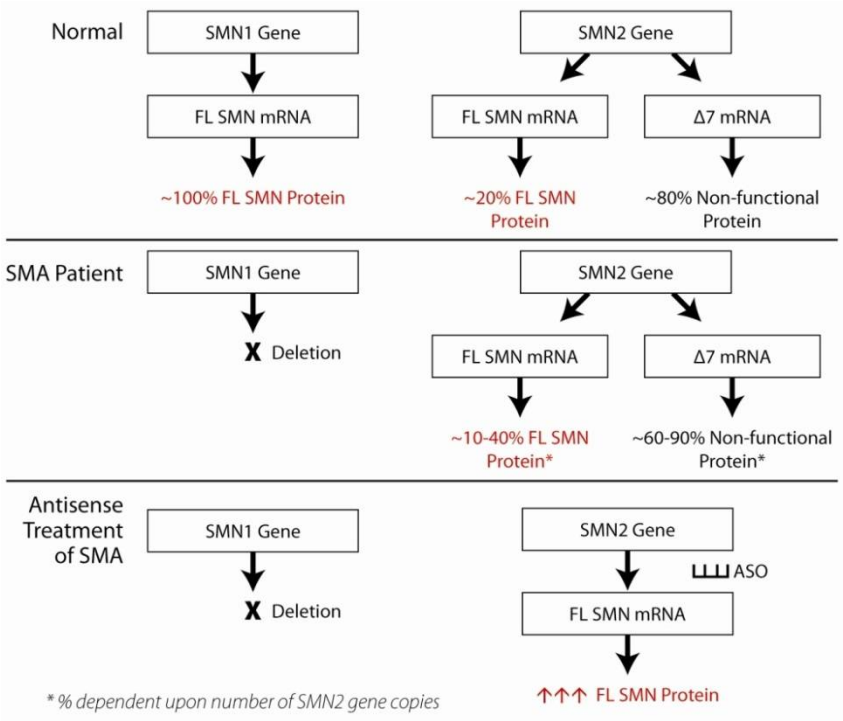
5. INTRODUCTION

Nusinersen (also known as ISIS 396443 or BIIB058) is a uniformly modified second generation, 2′-*O*-(2-methoxyethyl) (2′-MOE), antisense oligonucleotide (ASO) drug in development for the treatment of spinal muscular atrophy (SMA) due to genetic defects in the survival motor neuron 1 (*SMN1*) gene.

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.

ASOs are short synthetic strings of nucleotides designed to alter the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein. In patients with SMA, the number of survival motor neuron 2 (*SMN2*) gene copies and the resulting amount of survival motor neuron (SMN) protein are correlated with disease onset and severity. A therapeutic approach predicted to benefit patients with SMA is to increase the levels of full-length SMN2 pre-messenger ribonucleic acid (mRNA) by restoring the splicing pattern that gives rise to full-length SMN2 mRNA, thus increasing full-length SMN protein levels and SMN protein activity. Nusinersen is designed to bind to intron 7 of the SMN2 pre-mRNA, restoring the splicing pattern that gives rise to full-length SMN2 mRNA and thus increases full-length SMN protein levels (Figure 2).

Figure 2: Antisense Oligonucleotide Therapeutic Approach for Treatment of Spinal Muscular Atrophy



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.

5.1. Overview of 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. With an incidence of 1:6000 to 1:10,000 live births, SMA is the most common genetic cause of infant mortality, and a major cause of childhood morbidity due to weakness, in developed countries. 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 I 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 the age of 2 years. Patients with Type II SMA are able to sit but never walk unaided, with symptoms typically presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but may become severely and increasingly disabled. Patients with Type IV or adult-onset SMA have an age of onset over 18 years and have normal life expectancies.

SMA is caused by loss of SMN protein due to a homozygous deletion or mutation or compound heterozygous mutation in the *SMN1* gene on chromosome 5q11-q13. Humans have a duplication of the chromosome region where *SMN1* is found, resulting in a second copy of the gene, *SMN2*. In *SMN2*, a C to T nucleotide substitution in exon 7 results in an alternative splicing event such that the majority of transcripts produced (~90%) lack exon 7, and a defective truncated protein is produced. The remainder, SMN2 transcripts containing exon 7, produces a full-length protein product identical to the SMN1 protein, since 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 full-length SMN protein expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlate with SMA disease severity; thus, *SMN2* is a key modifier of disease phenotype [Coovert 1997; Feldkötter 2002; Lefebvre 1997; Prior 2004].

5.2. Current Therapies for Spinal Muscular Atrophy

The first approval of Nusinersen for commercial use occurred in the United States (US) in December 2016 for the treatment of SMA in pediatric and adult patients. Nusinersen has since been approved in Europe. Current medical care is supportive and focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery [Wang 2007].

5.3. Profile of Previous Experience With Nusinersen

5.3.1. Nonclinical Experience

Nusinersen was identified after an extensive screen of greater than 500 2′-MOE oligonucleotides in reporter gene assays, in vitro splicing assays, and SMA patient fibroblasts [Hua 2007; Hua 2008]. Data have shown that Nusinersen promotes a concentration-dependent increase in full-length transcripts (including exon 7) in patient fibroblast cells, achieving >90% full-length SMN2 transcripts, and forms nuclear structures called gems, known to contain SMN protein [Liu and Dreyfuss 1996]. 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 2008]

and in central nervous system (CNS) tissue, including the spinal cord, when injected into the lateral ventricle [Hua 2010]. Nusinersen produced >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 CNS delivery of drug produced a dose-dependent effect on SMN2 exon 7 inclusion, SMN protein production, and survival. These mice treated with Nusinersen demonstrated improved weight gain; improvements in muscle morphology, muscle strength, and motor coordination; and improved morphology of the motor neuron junctions [Passini 2011]. Furthermore, Nusinersen was shown to distribute widely in the CNS after intrathecal administration in monkeys [Passini 2011].

The pharmacokinetics (PK) and toxicity of Nusinersen were assessed in adult monkeys (single intrathecal lumbar bolus injections of 1 to 7 mg) and in juvenile monkeys (repeated intrathecal lumbar bolus injections of 0.3 to 3 mg/dose [4/14-week study] or 0.3 to 4 mg/dose [53-week study]). In addition, a dedicated multiple-dose PK study in adult monkeys (3-week dosing period) was performed to assess the half-life of Nusinersen in cerebrospinal fluid (CSF), tissues, and plasma.

In the single-dose study, following intrathecal dose administration, Nusinersen distributed from the CSF into the spinal cord, brain, and systemic circulation via CSF turnover. Plasma concentrations of Nusinersen were relatively low compared to CSF concentrations.

In the multiple-dose PK study, concentrations of Nusinersen in both CSF and plasma exhibited multiphasic disposition following intrathecal administration. The terminal elimination half-life of Nusinersen in CSF was 102 days. CSF concentrations peaked 1 hour after intrathecal injection, while plasma concentrations peaked 4 hours after the intrathecal injection. Animals were sacrificed at multiple times after intrathecal administration, and analysis demonstrated that Nusinersen was slowly cleared from CNS tissues with terminal elimination half-lives between various brain and spinal cord regions ranging from 74 to 275 days (median: 116 days).

In the 14-week and 53-week repeat-dose studies, concentrations of Nusinersen in CSF, plasma, and tissue were consistent with the pattern established in the 4-week multiple dose PK study. CSF and plasma concentrations increased in a dose-dependent manner in both studies. Consistent with previous studies, the time to reach maximum observed concentration (T_{max}) in the plasma occurred approximately 2 to 5 hours after intrathecal bolus administration. Tissue concentrations were measured for CNS tissues, and consistent values were obtained between the 14- and 53-week studies of intrathecally administered Nusinersen after adjusting for the difference in dosing regimens.

In both repeat-dose toxicology studies, dose-dependent increases in tissue concentrations of Nusinersen were seen in the brain, spinal cord, and liver. In the 53-week study, during which Nusinersen was administered every 6 weeks, tissue concentrations were lower compared to the 14-week study, as expected. CNS tissues had half-lives of 117 to 195 days (median: 174 days), which is consistent with the range of elimination half-lives determined from the multiple-dose PK study. To provide additional safety data based on systemic exposure margins for use of Nusinersen in pediatric patients, a 13-week toxicity study using subcutaneous dose administration was conducted in juvenile mice.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience

Completed studies in subjects with SMA

Nusinersen has been evaluated in 4 completed open-label studies in subjects with SMA diagnosed during childhood: ISIS 396443-CS1, ISIS 396443-CS2, ISIS 396443-CS10, and ISIS 396443-CS12. Nusinersen has also been evaluated in 2 controlled studies in subjects with SMA diagnosed during infancy and childhood: ISIS 396443-CS3B and ISIS 396443-CS4.

Study ISIS 396443-CS1 was a single-ascending dose Phase 1 study designed to assess the safety, tolerability, and PK of Nusinersen in subjects with later-onset SMA. A single dose of Nusinersen was administered by intrathecal injection to subjects with SMA who were 2 to 14 years of age. Four doses (1, 3, 6, and 9 mg) were evaluated sequentially. Each dose was studied in a cohort of 6 or 10 subjects. All subjects received study treatment. Twenty-eight subjects were dosed in the clinical trial, and all subjects completed dosing and follow-up visits per protocol. Nusinersen was well tolerated, and no safety concerns were reported when administered as a single dose up to 9 mg. Mild adverse events (AEs) of headache were the most commonly reported events. The 2 events related to Nusinersen (palpitations and paresthesia) were mild in severity, were not dose related, and had resolved. No serious AEs (SAEs) and no discontinuations due to AEs were reported. There were no clinically significant changes in vital signs or safety laboratory parameters related to Nusinersen. CSF and plasma drug concentrations of Nusinersen were dose dependent and consistent with the nonclinical data.

Study ISIS 396443-CS2 was an open-label, multiple-ascending dose, Phase 1/2a study designed to assess the safety, tolerability, and PK of Nusinersen in subjects with later-onset SMA. Multiple doses of Nusinersen were administered by intrathecal injection to subjects with SMA who were 2 to 15 years of age. Four dose levels (3, 6, 9, and 12 mg) were evaluated sequentially. Each dose level was studied in a cohort of 8 or 9 subjects, where all subjects received study treatment. The 6 subjects who participated in Cohort 1 of ISIS 396443-CS1 were eligible to enroll in ISIS 396443-CS2; 3 of these subjects enrolled in ISIS 396443-CS2 Cohort 1 and the other 3 enrolled in ISIS 396443-CS2 Cohort 2. Thirty-four subjects were enrolled, and all but 1 subject completed the study. One subject in the 12-mg Nusinersen dose cohort discontinued treatment early because of the Investigator's decision. The Investigator concluded that the subject and the parents could not tolerate the study procedures associated with dosing and PK draws, and thus, the subject was withdrawn. Nusinersen was well tolerated, and no safety concerns were reported when Nusinersen was administered as multiple doses up to 12 mg. Post lumbar puncture (LP) syndrome was the most commonly reported AE. None of the AEs reported during the study were considered related to Nusinersen or resulted in discontinuation from the study or of the study treatment. Three SAEs were reported during the study; all were assessed as unrelated to Nusinersen. There were no clinically significant changes in vital signs, neurological or physical examination findings, or safety laboratory parameters related to Nusinersen. There were no dose-related safety concerns.

Study ISIS 396443-CS10 was a single-dose open-label study to assess the safety and tolerability of a single intrathecal dose in subjects with later-onset SMA who participated in ISIS 396443-CS1 Cohorts 2, 3, and 4 (3, 6, or 9 mg). Eighteen subjects (4 subjects at 6-mg dose and 14 subjects at 9-mg dose) were enrolled and received study treatment. All 18 subjects completed the study.

Study in subjects with infantile-onset SMA

Study ISIS 396443-CS3B was a pivotal, randomized, double-blind, sham procedure-controlled, Phase 3, multicenter study to assess the clinical efficacy and safety of Nusinersen in infants with SMA (onset of clinical signs and symptoms consistent with SMA at ≤6 months of age) who have 2 *SMN2* copies. Subjects were randomized in a 2:1 ratio to receive either a scaled equivalent 12-mg dose of Nusinersen or a sham procedure control, respectively. There were 121 subjects enrolled in this study, and 37 subjects completed the follow-up visit as of the end of study.

Studies in subjects with later-onset SMA

Study ISIS 396443-CS4 was a pivotal, randomized, multicenter, double-blind, sham procedure-controlled, Phase 3 study in subjects with later-onset SMA (onset of clinical signs and symptoms consistent with SMA at >6 months of age) conducted to assess the clinical efficacy and safety of Nusinersen. Subjects were randomized in a 2:1 ratio to receive either a scaled equivalent 12 mg dose of Nusinersen or a sham procedure control, respectively. There were 126 subjects who completed the study.

Study ISIS 396443-CS12 was an open-label study to assess the safety, tolerability, and PK of Nusinersen (12 mg) administered intrathecally to subjects with later-onset SMA who previously participated in either ISIS 396443-CS2 or ISIS 396443-CS10. There were 45 subjects who completed the study.

Ongoing studies in subjects with SMA

Nusinersen is also being evaluated in 4 ongoing studies: ISIS 396443-CS3A, 232SM201, ISIS 396443-CS11, and 232SM202 (the present study).

Studies in subjects with SMA diagnosed during infancy

Study ISIS 396443-CS3A is an ongoing, open-label, Phase 2 study to assess the efficacy, safety, tolerability, and PK of multiple doses of Nusinersen. Enrollment has been completed with 21 subjects enrolled. Two loading dose levels (scaled by infant age to be equivalent to either 6- or 12-mg dose for children >2 years of age based on CSF volume) were evaluated sequentially in symptomatic infants with SMA who were between ≥21 and ≤7 months of age at screening. Loading doses were administered on Days 1, 15, and 85. Maintenance dosing commenced 24 weeks following Day 85 and at 18-week intervals thereafter.

Study 232SM201 is an open-label, multicenter, global, single-arm study to assess the efficacy, safety, tolerability, and PK of multiple doses of Nusinersen in presymptomatic subjects with genetically diagnosed SMA. The study is being conducted in subjects ≤6 weeks of age with genetic documentation of 5q *SMA* homozygous gene deletion or mutation or compound heterozygous mutation, genetic documentation of 2 or 3 copies of the *SMN2* gene, CMAP ≥1 mV, and the absence of signs or symptoms of SMA. Up to 25 subjects are planned to be treated in the study. All subjects will receive a scaled equivalent 12-mg dose of Nusinersen.

Study in subjects with infantile-onset or later-onset SMA

Study ISIS 396443-CS11 is an ongoing OLE study being conducted to evaluate the long-term safety, tolerability, and efficacy of Nusinersen administered intrathecally to subjects with SMA

who previously participated in investigational studies of Nusinersen. Up to 274 subjects are planned to be treated in the study.

5.4. Study Rationale

There is reasonably high genotype-phenotype correlation such that the *SMN2* copy number can be used to predict the severity of disease (moderate or severe) with approximately 80% to 85% accuracy [Burghes and Beattie 2009; Prior 2010; Swoboda 2005]. Evaluation of relationship between categories of functional status and number of *SMN2* copies have indicated that as *SMN2* copy number increases so does functional status [Feldkötter 2002; Swoboda 2005]. However, assessment of various outcome measures over time have indicated that there is overlap among SMA types, and values vary widely with age and gross motor functional status with an overall age dependent decline [Swoboda 2005].

5.4.1. Rationale for Part 1

The intent of Part 1 of this study is to assess safety, tolerability, and explore the utility of selected efficacy endpoints in subjects who have onset of clinical signs and symptoms that are consistent with SMA at age ≤6 months or >6 months. These subjects have either 2 or 3 *SMN2* copies and were not eligible to participate in the 2 pivotal clinical studies, ISIS 396443-CS3B and ISIS 396443-CS4. ISIS 396443-CS3B was a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of Nusinersen in subjects with 2 *SMN2* copies who have onset of clinical signs and symptoms of SMA at ≤6 months of age. ISIS 396443-CS4 was a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of Nusinersen in subjects who have onset of clinical signs and symptoms of SMA at >6 months of age. To be consistent with the study design of the 2 pivotal clinical studies and to understand the safety and tolerability of Nusinersen compared with natural history, the present study is designed to include sham procedure control in Part 1 for an unbiased assessment of safety, tolerability, and selected efficacy endpoints in the study population that was not eligible to participate in Studies ISIS 396443-CS3B or ISIS 396443-CS4. The design of the present study will also allow exploration of the safety and tolerability of a higher dose regimen in subjects who have onset of clinical signs and symptoms at >6 months of age, but who were not eligible for Study ISIS 396443-CS4.

5.4.2. Rationale for Part 2: Open-Label Extension Phase

The rationale for Part 2 of this study is to assess the long-term safety and tolerability of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

5.5. Rationale for Dose and Schedule Selection

The Nusinersen dose and dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dosing intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of Nusinersen. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90%

SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal 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 selected for this multiple-dose clinical study (equivalent to 12 mg of 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain Nusinersen spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who were not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of Nusinersen at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving Nusinersen in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1, will receive maintenance doses starting on Day 183 of Part 2.

Nusinersen will be administered as an intrathecal injection. The volume of the injection, and thus the dose, will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower dose of drug, achieved by injecting a smaller volume that is proportional to the estimated CSF volume for age, such that the dose volume will be equivalent to 5 mL for a 2-year-old child to adult. Dosing instructions and details regarding administration will be provided in the Directions for Handling and Administration (DHA).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives and Endpoints

Part 1

The primary objective of Part 1 of this study is:

- To assess the safety and tolerability of Nusinersen in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline (see Section 16.1) in neurological examination outcomes

Part 2

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, ECGs, vital signs, and growth parameters
- Change from baseline (see Section 16.1) in neurological examination outcomes
- Coagulation parameters (activated partial thromboplastin time [aPTT], partial thromboplastin time [PTT], and international normalized ratio [INR]) and urine total protein

6.2. Secondary Objectives and Endpoints

Part 1

The secondary objective of Part 1 of this study is:

- To examine the PK of Nusinersen in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

The endpoint that relates to this objective is:

- Nusinersen concentrations in plasma and CSF

Part 2

The secondary objective of Part 2 of this study is:

- To examine the PK of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments

The endpoint that relates to this objective is:

- Nusinersen concentrations in plasma and CSF

The secondary immunogenicity endpoint is as follows:

- Plasma antibodies to Nusinersen

6.3. Exploratory Objectives and Endpoints

Part 1

The exploratory objective of Part 1 of this study is:

- To explore the efficacy of Nusinersen in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE)
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through final safety follow-up evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through final safety follow-up evaluation

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to Nusinersen

Part 2

The exploratory objective of Part 2 of this study is:

- To explore the efficacy of Nusinersen in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by World Health Organization (WHO) motor milestones and Section 2 of the HINE
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through Part 2 Final Follow-up Evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through Part 2 Final Follow-up Evaluation and Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2 multicenter study conducted in 2 parts. The study was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered Nusinersen up to approximately 14 months (from the first dose until End of Part 1 Evaluation). Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an OLE phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered Nusinersen for approximately 24 additional months. In Part 1 of the study, up to 21 subjects will be randomized in a ratio of 2:1 to receive Nusinersen by intrathecal LP injection (n = 14) or to a sham procedure-control (n = 7). Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months. In Part 2 of the study, all subjects who participated in Part 1, who completed their End of Part 1 Evaluation assessments, and who elected to enroll in Part 2 will receive Nusinersen by intrathecal injection.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

See Section 4.1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

Part 1 of the study will consist of a Screening Period, Treatment Period, and post-treatment End of Part 1 Evaluation. For subjects who meet eligibility criteria and enroll in Part 1, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations.

Part 2 will consist of a Treatment Period and a post-treatment Final Follow-up Evaluation. For subjects who meet eligibility criteria and enroll in Part 2, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment in Part 2.

Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.

7.2.1. Screening

Subject eligibility for Part 1 of the study will be determined within 4 weeks (Day -28 to Day -1) prior to the first injection of Nusinersen or administration of sham procedure and will be confirmed before randomization. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period at the discretion of the Investigator. End of Part 1 Evaluation assessments will be used to confirm subjects' eligibility for Part 2.

7.2.2. Treatment

Part 1

Eligible subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of Nusinersen or a sham procedure. After the injection on Day 1, subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, and 302 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of study treatment or sham procedure, for a total of 6 injections or sham procedures over a dosing period of 10 months. During these 5 evaluations, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment or sham procedure. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

After completing the End of Part 1 Evaluation assessments, all eligible subjects may elect to enroll in Part 2.

Based on emergent data from the Nusinersen clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 Evaluation assessments. All subjects enrolled in the study at the time of Sponsor termination will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Unblinding will occur in order for the subjects to transition from Part 1 to Part 2.

End of Part 1 Evaluation assessments are required to be done prior to the transition to Part 2. After performing the End of Part 1 Evaluation assessments, the subject may immediately transition to Part 2.

Part 2

Part 2 study procedures and schedules will be determined based on the subject's treatment assignment in Part 1.

Subjects who were randomized to receive Nusinersen in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving Nusinersen in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of Nusinersen in Part 1. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 3) and then receive their first dose of Nusinersen for Part 2 (next maintenance dose).

Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 (±7 days for all days) for follow-up evaluations and subsequent injections of Nusinersen over a dosing period of approximately 24 months. Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following their End of Part 1 Evaluation, in the event of early termination by the Sponsor due to emergent data from the Nusinersen clinical development program. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 4) and then receive their first injection of Nusinersen (first loading dose). Subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of Nusinersen over a dosing period of approximately 24 months. Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

For both groups of subjects, Part 2 of the study will continue for approximately 24 months and in accordance with applicable laws and regulations. From Year 2 onwards, subjects will maintain evaluations for injection of study treatment every 4 months as indicated in Table 3 and Table 4.

7.2.3. Follow-Up

Subjects who enroll in Part 1 but not Part 2 will return to the study site for an End of Part 1 Evaluation approximately 4 months after the last dose of study treatment (End of Part 1 on Day 422 [±7 days]).

In the event of a decision by the Sponsor to terminate the study earlier than the end of Part 1 based on emergent data from the Nusinersen clinical development program, subjects who do not elect to participate in Part 2 will complete their next evaluation after Part 1 is terminated and that visit will be the End of Part 1 Evaluation.

Subjects who enroll in Part 2 will have a Part 2 Final Follow-up Evaluation approximately 4 months after the last open-label dose of Nusinersen.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

7.3. Study Stopping Rules

For Part 1 and Part 2 of the study, the Sponsor may terminate the study at any time by informing Investigators (who will subsequently inform the corresponding ethics committees) and any other applicable regulatory agencies. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.4. End of Study

The end of the study is the last subject's completion of the last evaluation for Part 2.

7.5. Safety Monitoring and Data and Safety Monitoring Board

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor. Safety data will also be reviewed on a quarterly basis, throughout Part 1 of the study, by an independent Data and Safety Monitoring Board (DSMB; see Section 19.2).

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Genetic documentation of 5q *SMA* homozygous gene deletion, mutation, or compound heterozygote.
3. Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age and have documentation of 3 *SMN2* copies.

OR

Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age, >7 months of age (211 days) at screening, and have documentation of 2 *SMN2* copies.

OR

Onset of clinical signs and symptoms consistent with SMA at >6 months of age, are ≤18 months of age at screening, and have documentation of 2 or 3 *SMN2* copies.

4. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either the anesthesiologist or pulmonologist).
5. Medical care, such as routine immunizations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis [palivizumab] if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA, in the opinion of the Investigator.
6. Subjects with 2 *SMN2* copies must reside within approximately 9 hours' ground-travel distance from a participating study site for the duration of the study. Residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor.
7. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

For Part 2 only:

To be eligible to participate in Part 2 of this study, candidates must meet the following eligibility criteria at the time of consent to participate in Part 2:

1. Participation in Part 1 and completion of the End of Part 1 Evaluation assessments.
2. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and to provide signed and dated informed consent on the Part 2 informed consent form

(ICF) and authorization to use confidential health information in accordance with national and local subject privacy regulations.

3. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or at the time point specified in the individual criterion listed:

1. Any previous exposure to Nusinersen; previous dosing in this study or previous studies with Nusinersen.
2. Signs or symptoms of SMA present at birth or within the first week after birth.
3. Ventilation for ≥16 hours per day continuously for >21 days at screening.
4. Permanent tracheostomy, implanted shunt for CSF drainage, or implanted CNS catheter at screening.
5. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments.
6. Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 months prior to screening, or hospitalization for surgery planned during the study.
7. Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG, as assessed by the Investigator, at the Screening Visit that would render the subject unsuitable for inclusion.
8. Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening. Any history of gene therapy, prior ASO treatment, or cell transplantation.
9. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures.
10. 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 assessments.
11. Subject's parent or legal guardian is not willing to continue to meet standard of care guidelines for care (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study.
12. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the subject unsuitable for enrollment.

For Part 2 only:

Candidates will be excluded from the Part 2 if they meet the following exclusion criterion at the time of consent into Part 2 of the study:

1. Any significant change in clinical status, including laboratory tests that, in the opinion of the Investigator, would make them unsuitable to participate in Part 2. The Investigator must reassess the subject's medical fitness for participation and consider any diseases that would preclude treatment.

Note that subjects who have been previously exposed to Nusinersen in Part 1 of the study (Exclusion criterion 1 for Part 1) may participate in Part 2.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

The subject's legally authorized representative (e.g., parent or legal guardian) must provide informed consent for Part 1 before study-specific screening tests are performed and for Part 2 before study-specific procedures are performed (see Section 17.3). When a subject's parent/guardian signs the ICF, that subject is assigned a unique subject identification number through the interactive response technology (IRT) system and is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents, within the IRT system, and on the screening log. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period, at the discretion of the Investigator.

9.2. Registration and Randomization of Subjects

In Part 1 of the study, subjects will be registered and randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Section 8.1 and Section 8.2. No subject may begin treatment until the subject is documented as registered (assigned a unique identification number) and is randomized for the study in the IRT system. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

In Part 1 of the study, using an IRT system, eligible subjects will be randomized to receive Nusinersen:sham procedure in a 2:1 ratio. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus $\leq$6 months. Subjects who withdraw from the study may be replaced.

At the beginning of Part 2 of the study, the subject's treatment assignment will be unblinded via the IRT system. Part 2 is the OLE phase of the study in which all subjects receive Nusinersen.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

Part 1 of the study is a randomized, double-blind, sham-procedure controlled study. The Sponsor, parents and/or legal guardians, and key study site personnel will be blinded throughout Part 1 of the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or that of the Sponsor, except the unblinded site study staff (dedicated team) and the unblinded medical monitor or clinical research associate. The DSMB may be unblinded as described in the DSMB charter.

Before Part 2 Day 1, parents and/or legal guardians, key study site personnel, and the Sponsor will be unblinded to the treatment group to which the subjects were randomized in Part 1. This will be performed according to the unblinding plan, which will be finalized prior to unblinding. Of note, in the event that the Sponsor decides to rollover subjects to Part 2 early, unblinding for key study site personnel will occur prior to the End of Part 1 Evaluation in order to facilitate bringing subjects who were randomized to receive sham in Part 1 as soon as possible and to maintain the 4-month dosing interval for subjects who were randomized to receive Nusinersen in Part 2. Treatment in Part 2 will be open-label, and all study subjects will receive Nusinersen.

9.3.1. Emergency Unblinding of Treatment Assignment

In Part 1 of the study, if a subject has experienced an SAE (as defined in Section 15.1.2), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the IRT. However, prior to unblinding, the Investigator should attempt to contact the blinded Medical Monitor to discuss the emergency. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. Every reasonable attempt should be made to complete the End of Part 1 Evaluation assessments prior to unblinding, as knowledge of the treatment arm could influence subject assessment. 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, nor to personnel involved with the analysis and conduct of the study. In cases where there are ethical reasons to have a subject whose treatment assignment was unblinded for safety reasons remain in the study, the Investigator must obtain specific approval from the Sponsor and the Medical Monitor for the subject to continue in the study.

In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's (or designee) Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (Section 15.3.4).

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

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

- The subject's parent or legal guardian withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or the Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

In Part 1 of the study, subjects who discontinue treatment will continue follow-up evaluations (i.e., predose evaluations at regular study evaluations) but with no postdose safety monitoring telephone contacts (Section 4.2, Table 2) unless either consent is withdrawn (Section 10.2) or the Sponsor terminates Part 1 early, in the case of emergent data from the Nusinersen clinical development program. If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. At these evaluations or telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator use/bi-level positive airway pressure (Bi-PAP), and health status will be recorded. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document.

In Part 2 of the study, subjects who discontinue treatment will continue follow-up evaluations unless consent is withdrawn (Section 10.2). If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document. Follow-up evaluations for any subjects who discontinue treatment in Part 2 will continue through the end of Part 2.

10.2. Withdrawal of Subjects From Study

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

- The subject's parent or legal guardian withdraws consent.
- The subject's parent or legal guardian is unwilling or unable to comply with the protocol.
- The Sponsor terminates Part 1 early because of emergent data from the Nusinersen clinical development program, and the subject elects not to enroll in Part 2.
- The Investigator or Sponsor decides to withdraw the subject for administrative reasons.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments (see Section 4.2 [Table 2]) at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal (see Section 4.2 [Table 3 and Table 4]). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for complete details.

11.1.1. Study Treatment

In Part 1 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of Nusinersen or sham procedure on Days 1, 15, 29, 64, 183, and 302 by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, the study coordinator, or outcome assessors). The study treatment administration will be performed in a dedicated room, and key study personnel and the parents will not be present during the procedure to ensure blinding.

In Part 2 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of Nusinersen at the days determined by their Part 1 treatment assignment as specified in Table 3 and Table 4. Treatment administration will not be blinded.

Nusinersen will be administered using a "spinal anesthesia" needle and a 5-mL syringe. A 22G to 25G spinal anesthesia needle is recommended based on 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. Depending on institutional guidelines, anesthesia may be used for the LP procedure or for the sham procedure in Part 1, following institutional procedures. Spinal ultrasound or other imaging techniques may be used to guide the intrathecal administration of Nusinersen if deemed necessary, but these are not required. Subjects will be encouraged to lie down flat for 1 hour following injection of the study treatment, if possible. Prior to each injection, 0.5 mL of CSF fluid will be collected for analyses. CSF will be used for Nusinersen PK analyses. Upon consent, extra CSF and blood samples will be stored for optional future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel) or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or other actions of Nusinersen with CSF constituents. CSF analyses and data presentation will be conducted in a blinded manner in Part 1.

The volume of the injection, and thus, the dose, will be adjusted for the subject's age on the day of dosing, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling (Table 1). Thus, younger subjects will be given a lower dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for a 2-year-old child to adult.

11.1.2. Sham Procedure

In Part 1 of the study, subjects randomized to the sham procedure control group will undergo a sham procedure, rather than study treatment administration, on Study Days 1, 15, 29, 64, 183, and 302. Details regarding the sham procedure will be provided in the DHA. The sham procedure will be administered by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, study coordinator, or outcomes assessors). The sham procedure in Part 1 will be performed in a dedicated room, and key study personnel and the parent or legal guardian will not be present during the procedure to ensure blinding.

In general, the sham procedure in Part 1 will consist of a small needle prick on the lower back at the location where the LP injection is normally made. The needle will break the skin, but no LP injection or needle insertion will occur. The needle prick will be covered with the same bandage that is used to cover the LP injection normally, thus simulating the appearance of an LP injection. If institutional guidelines require the use of anesthesia or sedation for an LP procedure in Nusinersen-treated subjects, then in order to maintain the blind, minimal sedation (i.e., a low dose of an anxiolytic) should be used for the sham procedure in Part 1, following institutional procedures. The study subject will be kept in the procedure room for the same amount of time that subjects administered study treatment are kept, thus simulating the time period of the study treatment administration procedure.

Study treatment and sham kits will be packaged in a blinded fashion. Blinded kits for the sham procedure in Part 1 contain artificial CSF (5.0 mL solution per 6 mL vial) that will not be injected but will be used to simulate CSF samples for that subject.

11.2. Modification of Dose and/or Treatment Schedule

No adjustment of dose is permitted. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted but must be approved by the Medical Monitor. In this case, dosing will be resumed as soon as possible.

11.3. Precautions

There are no protocol-required treatment precautions.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Screening and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

Allowed Concomitant Therapy

Throughout the study, Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

Disallowed Concomitant Therapy

Subjects are prohibited from receiving other experimental agents, including gene therapy, during the study. This includes marketed agents at experimental doses that are being tested for the treatment of SMA (e.g., albuterol/ salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea).

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or medically qualified staff. Study treatment is to be dispensed only for subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial should not be used for another subject.

12.1. Study Treatment

Nusinersen is formulated as an isotonic solution at 2.4 mg/mL and is provided as a 5.0-mL fill volume in a 6-mL clear glass vial. Nusinersen drug product contains the heptadecasodium salt of an 18-base residue phosphorothioate oligonucleotide.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, drug identifier, and quantity of dosage units, lot number, and other pertinent information in accordance with local laws. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration date.

For Part 1 of the study, the study drug (Nusinersen) and sham kits will be packaged in a blinded fashion. Blinded kits for sham procedure contain artificial CSF provided as 5.0 mL solution per 6 mL vial that will not be injected but will be used to simulate CSF samples for a subject.

For Part 2 of the study, the study drug (Nusinersen) kits will be packaged in an open-label fashion.

12.1.1. Study Treatment Preparation

The individual preparing Nusinersen or artificial CSF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, do not use it. The vials in question should be saved at the study site and the problem immediately reported to the Sponsor (or designee).

12.1.2. Study Treatment Storage

Study treatment must be stored in a secure location.

Nusinersen is to be protected from light and stored long term at 2°C to 8°C in a locked refrigerator with limited access. For additional information on storage requirements, follow the instructions provided in the DHA.

12.1.3. Study Treatment Handling and Disposal

The Investigator must return all used and unused vials of Nusinersen and artificial CSF as instructed by the Sponsor (or designee).

If any used Nusinersen or artificial CSF supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor (or designee), by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor (or designee) must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Study Treatment Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of Nusinersen or artificial CSF supplied, dispensed, and subsequently destroyed or returned to the Sponsor (or designee). A written explanation must be provided for any discrepancies.

13. EFFICACY, PHARMACOKINETIC, AND IMMUNOGENICITY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all efficacy assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of Nusinersen:

- Ventilator use
- WHO motor milestones and HINE (Section 2). These assessments will be performed based on the subject's abilities, as appropriate.
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment) and ACEND

13.2. Pharmacokinetic (Nusinersen Concentration) Assessments

The following tests will be performed to assess the PK of Nusinersen:

- Plasma Nusinersen concentrations
- CSF Nusinersen concentrations

13.3. Immunogenicity Assessments

The following test will be performed to assess the immunogenicity of Nusinersen:

- Anti-Nusinersen plasma antibody concentrations

14. SAFETY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of Nusinersen:

- Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes)
- AEs, including SAEs
- Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide)
- Growth parameters
- Physical examinations
- Medical history
- 12-Lead ECGs
- Use of concomitant medications

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed to evaluate the safety profile of Nusinersen:

- Blood chemistry: total protein, albumin, creatinine, cystatin C, creatine phosphokinase, blood urea nitrogen, total serum bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, calcium, phosphorus, chloride, sodium, potassium, bicarbonate, creatine kinase (MB [isoenzyme expressed in the myocardium], BB [isoenzyme predominantly expressed in the brain], and MM [isoenzyme expressed in skeletal muscle]), gamma-glutamyl transferase
- Hematology: red blood cells, hemoglobin, hematocrit, platelets, white blood cells, white blood cell differential (% and absolute: neutrophils, eosinophils, basophils, lymphoctyes, monocytes)
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals
- Urine total protein
- Coagulation parameters: aPTT, PTT, INR

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject's legally authorized representative and/or main caregiver(s) must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Abnormal laboratory findings that are considered by the Investigator as not clinically significant should not be reported as AEs. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of >24 hours to a medical facility and does not qualify as an AE
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. 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 site 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 consent from the subject's parent or legal guardian to participate in the study.
- The condition requiring 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 parent's or legal guardian's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Related	There is clear evidence that the event is related to the use of the investigational drug (e.g., confirmation by positive re-challenge 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 administration of the investigational drug.
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 investigational drug 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; therefore, the Investigator believes no relationship exists between the event and the investigational drug.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
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.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor (or designee) according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

For subjects who receive study treatment, any AE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment injection or sham procedure in Part 1. For subjects who never receive study treatment, no AEs need to be recorded on the applicable CRF.

15.3.2. Serious Adverse Events

For subjects who receive study treatment, any SAE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on an SAE form and on the applicable CRF,

regardless of the severity of the event or its relationship to study treatment. For subjects who never receive study treatment, any SAE occurring between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment; however, the SAE does not need to be recorded on the applicable CRF.

SAEs must be reported to the safety vendor listed in the Study Reference Guide within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until their Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2). Thereafter, the event should be reported as described in the Study Reference Guide only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the safety contact as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject's parent or legal guardian has signed the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be reported as described in the Study Reference Guide, within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** as described in the Study Reference Guide regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form as described in the Study Reference Guide.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports as described in the Study Reference Guide. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor (or designee) to be related to the study treatment administered.

The Sponsor (or designee) will report SUSARs to the appropriate regulatory authorities and to Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Dosing Errors

All dosing errors (including, but not limited to, route of administration and wrong dose) must be reported as protocol deviations. A brief description should be provided in the deviation report, 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.

15.4.2. 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 [redacted], MD, Office: [redacted], Mobile: [redacted], Fax: [redacted] (or [redacted] medical emergency: [redacted] or [redacted]) or [redacted], MD at [redacted].

15.4.2.1. Unblinding for Medical Emergency

For Part 1 of this study, in a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator (or designee) should attempt to contact the blinded Biogen MA Inc. Medical Director or blinded [redacted] Medical Monitor to discuss the emergency within 24 hours. In these instances, the Investigator (or designee) may access the subject's treatment assignment by IRT.

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 personnel involved with the analysis and conduct of the study.

15.5. Safety Responsibilities

15.5.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to 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 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.

15.5.2. The Sponsor

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.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Part 1 and Part 2 will be analyzed separately. For Part 1, in general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category. For Part 2, no formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

For the Part 1 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 1. For the Part 2 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 2. In addition, a pooled analysis incorporating data from both Part 1 and Part 2 will be conducted to characterize the safety profile of Nusinersen. For subjects on active treatment in Part 1, safety data from both Part 1 and Part 2 will be included in the pooled analysis and the Part 1 baseline will used for those subjects in the pooled analysis. For subjects on sham procedure in Part 1, only safety data from Part 2 will be included in the pooled analysis and the Part 2 baseline will be used for those subjects in the pooled analysis.

Concomitant medication usage for each subject will be listed for review.

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

16.2. Safety and Tolerability

Safety is the primary objective for the study. All AEs, laboratory abnormalities, ECGs, and vital signs will be evaluated for safety.

16.2.1. Analysis Population

Safety analyses will be conducted in the safety population. This safety set will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure in Part 1. Treatment duration and amount of study treatment received will be summarized by treatment group.

16.2.2. Methods of Analysis

16.2.2.1. Neurological Examinations

Neurological examination findings will be listed for review, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal, and abnormal (not AE) will be summarized.

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.

16.2.2.2. Adverse Events

All AEs will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment emergent if it was present prior to the first dose of study treatment and subsequently worsened, or was not present prior to the first dose of study treatment but subsequently appeared. The incidence of treatment-emergent AEs will be summarized overall, by severity, and by relationship to study treatment. A subject having the same AE more than once will be counted only once in the incidence for that event. The occurrence of the AE with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the AE with the strongest relationship to study treatment will be used in the calculation of incidence by relationship to study treatment.

All treatment-emergent AEs and SAEs will be summarized for each treatment group 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, SAEs, early withdrawals from study treatment and from study due to AEs will be provided.

16.2.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented. Summary statistics for actual values and change from Baseline will also be presented.

16.2.2.4. ECGs

ECG results will be presented by subject, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal clinically significant, and abnormal (not clinically significant) will be summarized.

16.2.2.5. Clinical Laboratory Results

Clinical laboratory evaluations, including hematology, blood chemistry, urinalysis, and urine total protein, will be summarized using study visit for each treatment group. These safety variables will also be presented over time after study treatment administration, as appropriate. Laboratory parameters will also be summarized using shift tables, as appropriate.

For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.

16.2.2.6. Coagulation Parameters

Coagulation parameters (aPTT, PTT, and INR) will be collected. The coagulation testing must be performed and reviewed prior to dosing.

16.3. Efficacy

16.3.1. Analysis Population

The exploratory analysis of efficacy will be performed on the intent-to-treat population. The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure in Part 1.

16.3.2. Methods of Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

16.3.2.1. Sibling SMA Data Collection

If any subject has or had a sibling(s) with SMA and if consent is given, data for the sibling(s) will be collected at Day 1 and at the End of Study Evaluation/Early Termination Visit. Data to be collected from siblings with SMA will be nonbiologic and noninvasive and will include historical data for *SMN2* gene copy number and sibling treatment history.

16.4. Pharmacokinetics

16.4.1. Analysis Population

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

16.4.2. Methods of Analysis

Plasma PK parameters, as applicable, and Nusinersen concentrations in plasma and CSF for the PK population will be summarized using descriptive statistics and, where warranted, presented graphically.

16.5. Immunogenicity

16.5.1. Analysis Population

The analysis population for immunogenicity will include all subjects with available immunogenicity data.

16.5.2. Methods of Analysis

Results from the immunogenicity analyses for anti-Nusinersen plasma antibody status and titer will be summarized at the specified visits.

16.6. Interim Analyses

No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are

planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

16.7. Sample Size Considerations

Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

17. ETHICAL REQUIREMENTS

The Sponsor, [redacted] (the contract research organization [CRO] for this study), and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor (or designee) will submit documents on behalf of the investigational sites in countries other than the US.

If the Investigator makes any changes to the ICF, the Sponsor (or designee) must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor (or designee). After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor (or designee).

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor (or designee) must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

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).

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will not be collected for the purposes of data analysis during the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent, if applicable, must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent, if applicable, must also be documented in the subject's medical record.

17.4. 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, subjects' race and ethnicity will not 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. Sponsor, 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.

17.5. Compensation for Injury

The Sponsor (or designee) maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit conducted by the Sponsor (or designee). This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

CRFs will be not be used as source data. Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. 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 the Sponsor. Biogen will be responsible for managing the study globally. All financial details are provided in the separate contract(s) between the institution, Investigator, and the Sponsor.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

The Sponsor may transfer any or all of its study-related responsibilities to a CRO and other third parties; however, the Sponsor retains overall accountability for these activities.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool that is developed and supported by an electronic data capture vendor and configured by Sponsor or CRO.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory will be selected by the Sponsor to analyze all hematology, blood chemistry, urine, and CSF samples collected at all study sites. Local laboratories may be used to accommodate acute or urgent needs as discussed in in the Study Reference Guide.

During the Part 1 Screening Period, a blood sample will be collected for *SMN2* copy number analysis by the central laboratory only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

19.2. Study Committees

Safety data will be reviewed on an ongoing quarterly basis throughout Part 1 of the study by an independent DSMB. The DSMB will be assembled to review safety, tolerability, and efficacy (as needed) data collected on Nusinersen during the study. Based on its ongoing assessment of the safety and tolerability of Nusinersen, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the

investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor (or designee) may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Burghes AH, Beattie CE. Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nature reviews. 2009;10(8):597-609.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4" 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 (Print)

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
USA

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

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 232SM202

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

EUDRA CT NO **2014-003657-33**

DATE: 01 June 2016
Version 3
Final

Supersedes previous Version 2 dated 05 May 2016.

SIGNATURE OF BIOGEN MA THERAPEUTIC AREA HEAD

Neurology

Protocol 232SM202, Version 3, was approved by:

[redacted]

[redacted] MB, BCh, MMSC

[redacted]

Biogen MA Inc.

1st June 2016

Date

SIGNATURE OF IONIS PHARMACEUTICALS, INC. CHIEF CLINICAL DEVELOPMENT OFFICER

Chief Clinical Development Officer

Protocol 232SM202, Version 3, was approved by:

[redacted] 1 JUNE 2016

[redacted], MBBS Date

[redacted]

Ionis Pharmaceuticals, Inc.

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1. SPONSOR INFORMATION

Ionis Pharmaceuticals, Inc. (Ionis) is the Sponsor of the study in the United States. Biogen Idec Research Limited is the Sponsor of the study in the Rest of World. Biogen Idec Research Limited (or designee) will be responsible for managing the study globally.

Biogen MA Inc. 250 Binney Street Cambridge, MA 02142 United States	Biogen Idec Research Limited Innovation House 70 Norden Road Maidenhead, Berkshire SL6 4AY United Kingdom	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 USA

Primary contact for urgent medical issues:
[redacted]: [redacted], MD
Office: [redacted]
Mobile: [redacted]
Fax: [redacted]
[redacted]
[redacted] medical emergency: [redacted]
or [redacted]

Secondary contact for urgent medical issues:
Biogen MA [redacted]: [redacted], MD
Cell phone: [redacted]

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

2. LIST OF ABBREVIATIONS

2′ MOE	2′ O (2 methoxyethyl)
AE	adverse event
ASO	antisense oligonucleotide
Bi-PAP	bi-level positive airway pressure
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
GCP	Good Clinical Practice
HINE	Hammersmith Infant Neurological Examination
ICF	informed consent form
ICH	International Conference on Harmonisation
IRT	interactive response technology
LP	lumbar puncture
mRNA	messenger ribonucleic acid
OLE	open-label extension
PK	pharmacokinetic(s)
RNA	ribonucleic acid
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to reach maximum observed concentration

3. SYNOPSIS

This is a brief summary. For details, refer to the body of the protocol.

Protocol Number:	232SM202
Protocol Title:	A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
Version Number:	3
Name of Study Treatment:	ISIS 396443 (BIIB058)
Study Indication:	Spinal muscular atrophy (SMA)
Phase of Development:	2
Study Rationale:	The rationale of Part 1 of the study is to assess the safety and tolerability and evaluate the utility of selected exploratory efficacy endpoints in subjects with SMA treated intrathecally with ISIS 396443 who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 (the open-label extension phase) prior to completion of all Part 1 evaluations. The rationale of Part 2 of the study is to assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.
Study Objectives and Endpoints:	**Part 1** Primary objective: The primary objective of Part 1 of this study is: • To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. The primary endpoints that relate to this objective are: • Incidence of adverse events (AEs) and serious AEs (SAEs)

- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline in neurological examination outcomes

Secondary objective:

The secondary objective and endpoint of Part 1 of this study are as follows:

- To examine the pharmacokinetics (PK) of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
- ISIS 396443 concentrations in plasma and cerebrospinal fluid (CSF)

Part 2

Primary objective:

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The primary endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline in clinical laboratory parameters, ECGs, and vital signs
- Change from baseline in neurological examination outcomes

Secondary objective:

The secondary objective and endpoint of Part 2 of this study are as follows:

- To examine the PK of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments
- ISIS 396443 concentrations in plasma and CSF

Exploratory objectives and endpoints are listed in Section 6.3.

Study Design: This is a Phase 2 multicenter study conducted in 2 parts:

Part 1 was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 over a period of approximately 14 months (from the first dose until the End of Part 1 Evaluation). Up to 21 subjects will be randomized in a ratio of

2:1 to receive ISIS 396443 by intrathecal lumbar puncture (LP) injection or a sham-procedure control. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months.

After informed consent is obtained, subjects will undergo a screening evaluation no greater than 28 days prior to administration of the first dose of study treatment. Subjects who meet the eligibility criteria will be randomized to receive ISIS 396443 or sham procedure. Subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of study treatment or sham procedure. Subjects will return to the study site on Days 15, 29, 64, 183, and 302 for follow-up evaluations and subsequent injections or sham procedures. For subjects receiving ISIS 396443 or sham procedure, a CSF sample will be taken predose on each injection day in a manner that maintains the blind.

After the study treatment dosing or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours for safety monitoring. Following all subsequent injections, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring.

Safety monitoring will occur on the day following each injection of study treatment or sham procedure. Subjects receiving the dosing or sham procedure on Days 15, 29, 64, 183, and 302 will be monitored by telephone contact on Days 16, 30, 65, 184, and 303.

In addition, subjects will also be monitored through telephone contact throughout the duration of the study.

An End of Part 1 Evaluation will occur up to 4 months after the last dose of ISIS 396443 or sham procedure, or sooner (if the Sponsor decides to terminate Part 1 early based on emergent data from the ISIS 396443 clinical development program, as described below). Subjects who terminate early from Part 1 of the study will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal.

After completing End of Part 1 Evaluation assessments according to the study schedule or sooner, if emergent data from the ISIS 396443 clinical development program necessitate the early termination of Part 1 by the Sponsor, all eligible subjects may elect to enroll in Part 2. All subjects enrolled in the study at the time that the Sponsor terminates Part 1 will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and

transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an open-label extension (OLE) phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 for approximately 24 additional months (or until availability of commercial product).

Part 2 study procedures will be determined based on the treatment assignment in Part 1.

Subjects who were randomized to receive ISIS 396443 in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving ISIS 396443 in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of ISIS 396443 in Part 1. On Part 2 Day 1, subjects will undergo predose evaluations according to the schedule of events and then receive their first dose of ISIS 396443 for Part 2 (next maintenance dose). Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 for follow-up evaluations and subsequent maintenance dose injections. All subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment. Subjects will be monitored by telephone contact on Days 2, 121, 240, 359, 478, 597, and 716.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 of the study will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine eligibility for Part 2 of the study. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following the End of Part 1 Evaluation, in the event of early termination due to emergent data from the ISIS 396443 clinical development program. On Part 2 Day 1, subjects will undergo predose evaluations according to the schedule of events and then receive their first dose of ISIS 396443 (first loading dose). Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 for follow-up evaluations and subsequent injections. Subjects

will remain at the study site for at least 24 hours on Day 1. Following all subsequent injections, all subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment after Day 1. Subjects will be monitored by telephone contact on Days 16, 30, 65, 184, 303, 422, 541, 660, and 779.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Rationale for Dose and Schedule Selection:	In Part 1, a scaled equivalent dose of 12 mg ISIS 396443 will be administered at each of the 6 doses (i.e., on Study Days 1, 15, 29, 64, 183, and 302) over a dosing period of approximately 10 months to subjects randomized to receive active treatment. In Part 2, a scaled equivalent dose of 12 mg ISIS 396443 will be administered at each dose over a dosing period of approximately 24 months (or until availability of the commercial product). The volume of the injection will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower absolute mg dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for 2 years of age to adult. The dose regimen and the dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dose intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443 to date. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every

4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving ISIS 396443 in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1 will receive maintenance doses starting on Day 183 of Part 2.

Table 1 ISIS 396443 Dose Volume To Be Injected

Age	Estimated CSF Volume (mL)	Injection Volume (mL)	Dose (mg)
0-3 months (0-90 days)	120	4	9.6
3-6 months (91-182 days)	130	4.3	10.3
6-12 months (183-365 days)	135	4.5	10.8
12-24 months (366-730 days)	140	4.7	11.3
>24 months (>730 days)	150	5.0	12.0

Source: [Matsuzawa 2001]
CSF = cerebrospinal fluid.

Study Location: Global, multicenter

Number of Planned Subjects: In Part 1, up to 21 subjects are planned (14 ISIS 396443; 7 sham procedure).

In Part 2, up to 21 subjects are planned (21 ISIS 396443).

Study Population: Part 1 of this study will be conducted in subjects who have clinical signs and symptoms of SMA at ≤6 months of age or at >6 months of age and who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

Part 2 will include only subjects who participated in Part 1 and completed their End of Part 1 Evaluation assessments. Subjects enrolling in Part 2 must meet the Part 2-specific criteria.

Detailed eligibility criteria are described in Section 8.

Treatment Groups:	In Part 1, subjects will receive either ISIS 396443 intrathecally or sham-procedure control in a 2:1 ratio. Randomization will be balanced for the stratification factor (age of symptom onset >6 months versus ≤6 months). A single dose level of 12 mg ISIS 396443 will be scaled by age at the time of dosing for each subject. In Part 2, all subjects will receive open-label ISIS 396443. A single dose level of 12 mg ISIS 396443 will be scaled by age at the time of dosing for each subject.
Duration of Treatment and Follow-up:	For subjects who meet the eligibility criteria and enroll in Part 1 of the study, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations. For subjects who meet the eligibility criteria and enroll in Part 2 of the study, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months (or until availability of commercial product) and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment. Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.
Criteria for Evaluation:	The criteria for evaluation for Part 1 and Part 2 are as follows:
Safety:	• Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes) • AEs, including SAEs • Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide) • Weight • Physical examinations • Medical history • 12-Lead ECGs

- Use of concomitant medications
- Clinical laboratory tests (blood chemistry, hematology, and urinalysis)

Pharmacokinetics:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

Efficacy:

- Ventilator use
- Hammersmith Infant Neurological Examination (HINE, Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

Immunogenicity:

- Anti-ISIS 396443 plasma antibody concentrations

Statistical Methods:

Analysis Population

The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

Part 1

Safety Analysis

The analysis of safety will be performed on the safety population. The incidence of treatment-emergent AEs and SAEs will be tabulated. Changes from baseline in clinical laboratory parameters, vital signs, and ECG parameters will be summarized. Incidence of clinically relevant changes from baseline in vital signs and ECGs will be summarized. Laboratory parameters will also be summarized using shift tables, as appropriate.

PK Analysis

Summary statistics for plasma and CSF concentrations of ISIS 396443 will be provided.

Exploratory Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

Part 2

No formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

Interim Analysis: No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

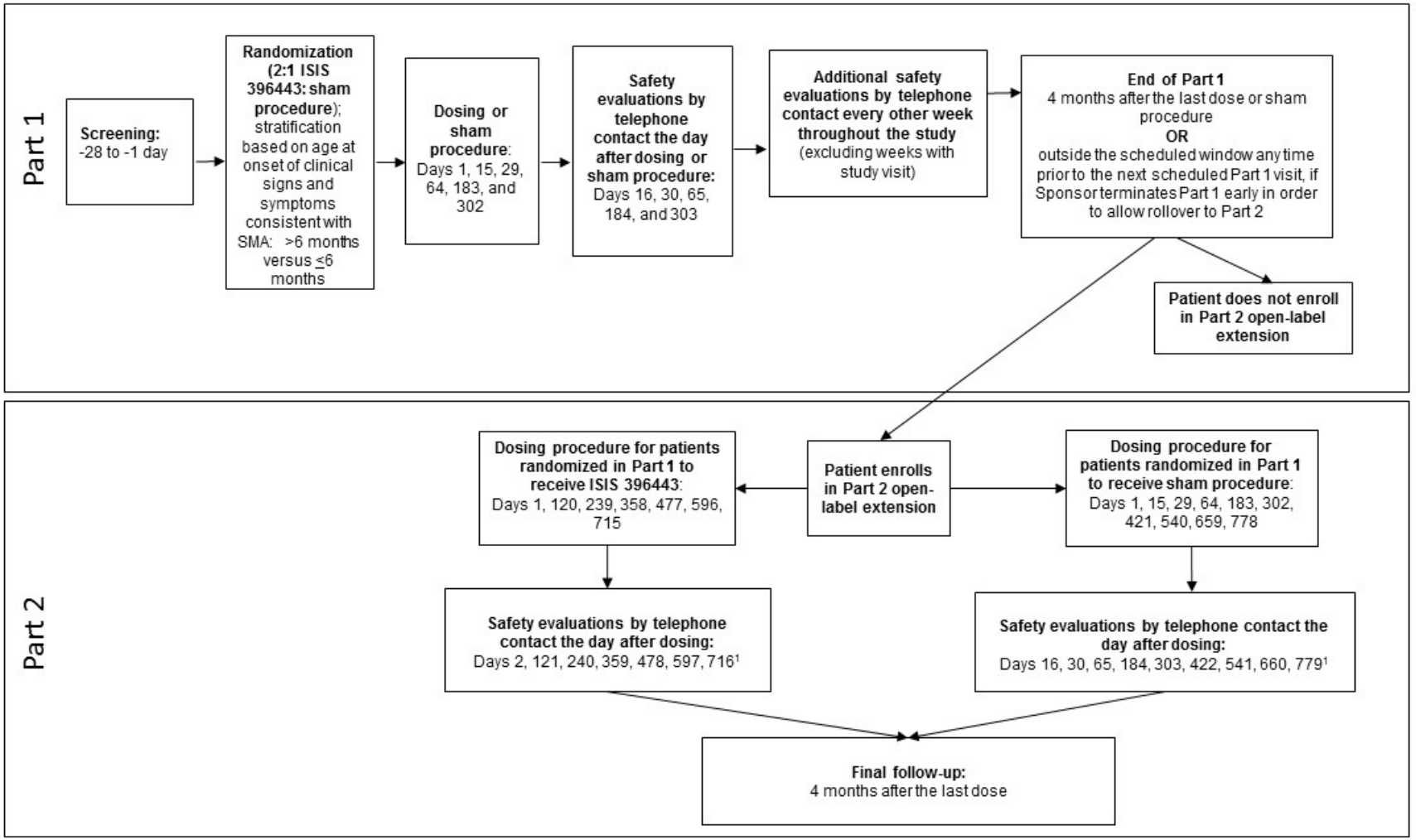
Sample Size Determination: Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

Study Stopping Rules:	The Sponsor may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 232SM202

4.1. Study Schematic

Figure 1: Study Schematic



[1]Study visits may continue every 4 months beyond Year 2 if commercial product is not yet available.

4.2. Schedule of Events

4.2.1. Schedule of Events: Part 1

Table 2: Part 1 Schedule of Activities

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3,4,5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Vital Signs[6]	X	X		4X[7]	X[8]	X		X		X		4X[7]		X		4X[7]		X
Weight	X	X			X	X				X				X				X
Growth Parameters[9]	X	X				X				X				X				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
Neurological Examination[10]	X	X		X[11]	X	X		X[11]		X		X[11]		X		X[11]		X
ECG	X				X							X						X
Safety Laboratory Tests[12]	X													X[13]				X[14]
Coagulation Laboratory Tests	X																	
Immunogenicity Sample		X												X				X
CSF PK[15]		X				X				X				X				
Plasma PK				X[16]										X[17]				X
Study Treatment Injection or Sham			X				X				X				X			

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3,4,5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Procedure																		
Inpatient Stay[18]				X														
Telephone Contact for Safety Monitoring[2]									X				X				X	
HINE Motor Milestone		X												X				X
Clinical Global Impression of Change														X				X
Con Med Recording[19]	X ---------- X																	
Adverse Event Collection[20]	X ---------- X																	

AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

[1] A blood sample will be collected at Screening for *SMN2* copy number only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

[2] After the injection of study treatment or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. On the day following the injection of study treatment or sham procedure on Days 15, 29, 64, 183, and 302, there will be safety monitoring through telephone contact. During that telephone contact (i.e., Days 16, 30, 65, 184 and 303), changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[3] End of Part 1 is one of the following: Part 1 Final Follow-up Evaluation (Day 422 [±7 days]) according to the study schedule, early Part 1 Final Follow-up Evaluation to allow for rollover into Part 2, or Early Termination Evaluation for subjects who withdraw from the study during Part 1.

[4] For subjects not transitioning into Part 2, the date of the End of Part 1 Evaluation assessments will be the End of study. For subjects who transition to Part 2, the date of the End of Part 1 will be the date of first dose in Part 2.

[5] At the End of Part 1 evaluation, in order to allow transition to Part 2, subjects will be unblinded.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected within 20 to 24 hours after the injection of study treatment or sham procedure.

[9] At the evaluations scheduled for injection of study treatment or sham procedure, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference.
[10]Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
[11]Neurological examinations will occur between 4 to 6 hours after the injection of study treatment or sham procedure.
[12]Blood chemistry, hematology, and urinalysis panels.
[13]Samples for safety laboratory tests will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only.
[14]End of Part 1 safety laboratory tests may be performed locally in addition to centrally to accommodate the Part 2 Day 1 dosing.
[15]Refer to Table 5 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[16]Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment or sham procedure only on Day 1. Refer to Table 5 for the plasma PK sample schedule.
[17]Blood samples for PK assessment will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only. Refer to Table 5 for the plasma PK sample schedule.
[18]Overnight stay (at least 24 hours) is required after the first injection of study treatment or sham procedure. Following all subsequent injections or sham procedures, a stay of at least 6 hours at the study site is required; overnight stays are optional on these days.
[19]In addition to concomitant medications, ancillary procedures will be recorded.
[20]AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

4.2.2. Schedule of Events: Part 2

Table 3: Part 2 Schedule of Activities for Subjects Randomized to Receive ISIS 396443 in Part 1

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3]or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X[5]								
Inclusion/ Exclusion Criteria	X[5]								
Vital Signs[6]	X[7]		X[8]		X		X[8]		X
Weight	X[7]				X				X
Growth Parameters[9]	X[7]				X				X
Physical Examination	X[7]				X				X
Ventilator Use	X[7]			X	X			X	X
Neurological Examination[10]	X[7]		X[11]		X		X[11]		X
ECG	X[7]				X[12]				X[12]
Safety Laboratory Tests[13]	X[7]				X[14]				X
Immunogenicity Sample	X[7]				X[15]				X
CSF PK[16]	X[5, 7]				X				
Plasma PK[17]			X[17]		X[17]				X
Study Treatment Injection		X				X			
Telephone Contact for Safety Monitoring				X				X	
HINE Motor Milestone					X				X
Clinical Global Impression of Change					X				X

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
Con Med Recording[18]	X----------X								
Adverse Event Collection[19]	X----------X								

AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event.

[1] There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 2, 121, 240, 359, 478, 597, and 716). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[2] Subjects may continue receiving study treatment injection every 4 months beyond Year 2 until commercial availability of the product. If the study continues beyond Year 2 (i.e., beyond Day 715), then from Day 835 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the assessments for those additional timepoints to alternate between the assessments done on Day 120 and those done on Day 239. Day 120 assessments would be performed at Day 835 and Day 239 assessments would be performed at Day 954. The alternating pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 716, if the product is commercially available, or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, and CSF PK must be performed on Part 2 Day 1.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after the End of Part 1 visit, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, and CSF PK. If Part 2 Day 1 study treatment injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, or if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, ECG, CSF PK, and safety laboratory tests. Immunogenicity testing must also be repeated predose if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected 1 hour (±15 minutes) after the injection of study treatment.

[9] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.

[10] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.

[11] Neurological examinations will occur 1 hour after the injection of study treatment.

[12] ECG will be performed on Days 239, 477, and 715, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.

[13] Blood chemistry, hematology, and urinalysis panels.

[14] Samples for safety laboratory tests will be collected before the injection of study treatment on the same days as ECG, plasma PK, and immunogenicity samples.

[15] Blood samples for immunogenicity testing will be collected before the injection of study treatment on Days 239, 477, and 715.

[16]Refer to Table 6 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[17]Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 6 for the plasma PK sample schedule. Plasma PK samples will be collected predose on Days 239, 477, and 715.
[18]In addition to concomitant medications, ancillary procedures will be recorded.
[19]AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 4: Part 2 Schedule of Activities for Subjects Randomized to Receive Sham Procedure in Part 1

Study Period	Part 2 Treatment/Follow-Up																
Study Day	Day 1			Day 2[1]	Day 15 (±1 day)			Day 16[1]	Day 29 (±1 day)			Day 30[1]	Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]			Days 65, 184, 303, 422, 541, 660, 779[1]	Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X[5]																
Inclusion/Exclusion Criteria	X[5]																
Vital Signs[6]	X[7]		X[8]	X[9]	X		X[8]		X		X[8]		X		X[8]		X
Weight	X[7]			X	X				X				X				X
Growth Parameters[10]	X[7]				X				X				X				X
Physical Examination	X[7]				X				X				X				X
Ventilator Use	X[7]			X	X			X	X			X	X			X	X
Neurological Examination[11]	X[7]		X[12]	X	X		X[12]		X		X[12]		X		X[12]		X
ECG	X[7]			X							X		X[13]				X[13]
Safety Laboratory Tests[14]	X[7]												X[15]				X
Coagulation Laboratory Tests	X[5]																
Immunogenicity Sample	X[7]												X[16]				X
CSF PK[17]	X[5, 7]				X				X				X				
Plasma PK[18]			X[18]										X[18]				X
Study Treatment Injection		X				X				X				X			
Inpatient Stay[19]			X														
Telephone Contact								X				X				X	

Study Period	Part 2 Treatment/Follow-Up																
Study Day	**Day 1**			**Day 2[1]**	**Day 15 (±1 day)**			**Day 16[1]**	**Day 29 (±1 day)**			**Day 30[1]**	**Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]**			**Days 65, 184, 303, 422, 541, 660, 779[1]**	**Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]**
	Predose[5]	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		
for Safety Monitoring																	
HINE Motor Milestone													X				X
Clinical Global Impression of Change													X				X
Con Med Recording[20]	X----------																----------X
Adverse Event Collection[21]	X----------																----------X

AE = adverse event; Bi-PAP = bilevel positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event.

[1] After the injection of study treatment on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 16, 30, 65, 184, 303, 422, 541, 660, and 779). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[2] Subjects may continue receiving study treatment injection every 4 months beyond Year 2 until commercial availability of the product. If the study continues beyond Year 2 (i.e., beyond Day 778), then from Day 897 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the schedule of events for those additional timepoints to alternate between the assessments done on Day 183 and those done on Day 302. Day 302 assessments would be performed at Day 897 and Day 183 assessments would be performed at Day 1016. That pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 778, if the product is commercially available, or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, CSF PK, and coagulation laboratory tests must be performed on Part 2 Day 1 predose. Coagulation laboratory tests will be performed locally.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after the End of Part 1 visit, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, and CSF PK. If Part 2 Day 1 study treatment

injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, or if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, the following procedures must be done on Part 2 Day 1 predose: vital signs, weight, growth parameters, physical examination, ventilator use, neurological examination, ECG, CSF PK, and safety laboratory tests. Immunogenicity testing must also be repeated if Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment only on Part 2 Day 1. On subsequent study days, vital signs will be collected 1 hour after the injection of study treatment.

[9] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected on Day 2 within 20 to 24 hours after the injection of study treatment only.

[10] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.

[11] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.

[12] Neurological examinations will occur 1 hour after the injection of study treatment.

[13] ECG will be performed at Days 64, 183, 540, and 778, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.

[14] Blood chemistry, hematology, and urinalysis panels.

[15] Samples for safety laboratory tests will be collected before the injection of study treatment on the same days as ECG, plasma PK, and immunogenicity sample.

[16] Blood samples for immunogenicity testing will be collected before the injection of study treatment on Days 64, 183, 540, and 778.

[17] Refer to Table 7 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.

[18] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 7 for the plasma PK sample schedule. Plasma PK samples will be collected predose on Days 64, 183, 540, and 778.

[19] Overnight stay (at least 24 hours) is required after the first injection of study treatment. Following all subsequent injections, a stay of at least 1 hour at the study site is required; overnight stays are optional on these days.

[20] In addition to concomitant medications, ancillary procedures will be recorded.

[21] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 5 Part 1 Pharmacokinetic Sampling Schedule[1]

Treatment Period	Part 1 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	End of Part 1	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

Table 6 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive ISIS 396443 in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 120	Predose	NA	0.5
	Day 239	Predose	0.5	0.5
	Day 358	Predose	NA	0.5
	Day 477	Predose	0.5	0.5
	Day 596	Predose	NA	0.5
	Day 715	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

Table 7 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive Sham Procedure in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	Day 421	Predose	NA	0.5
	Day 540	Predose	0.5	0.5
	Day 659	Predose	NA	0.5
	Day 778	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

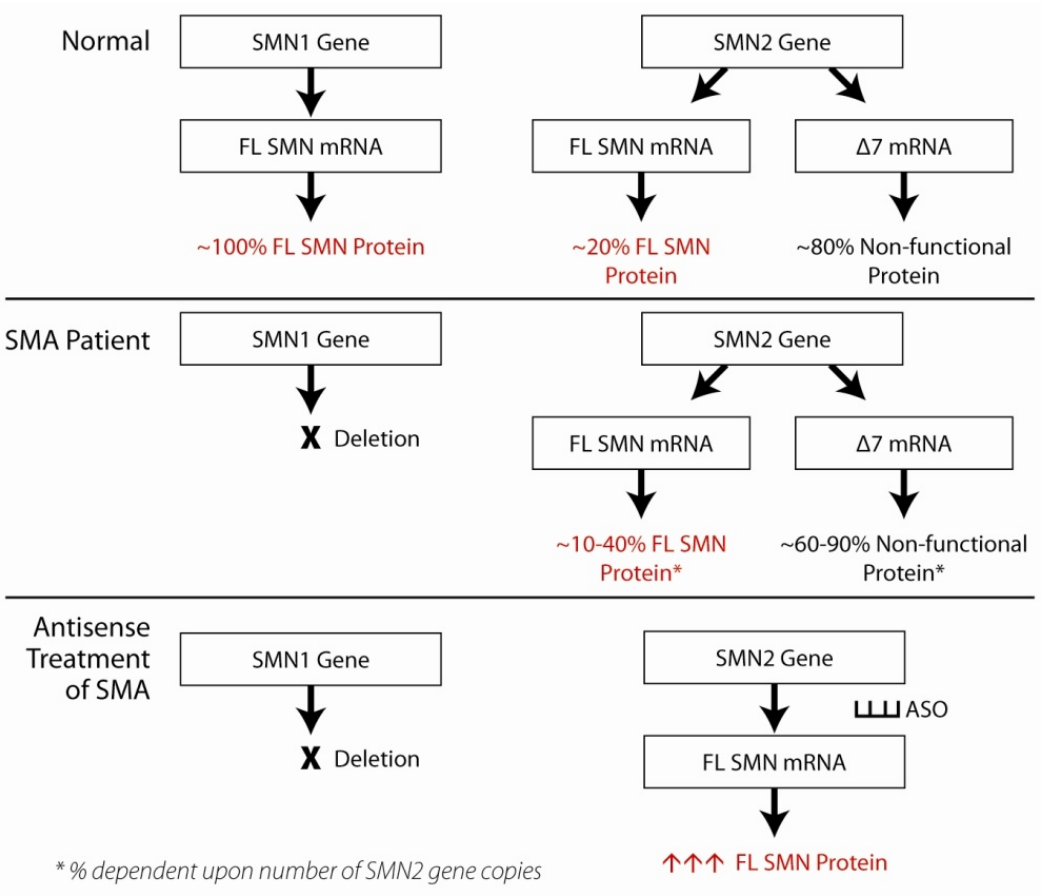
[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

5. INTRODUCTION

ISIS 396443 is a uniformly modified, 2′-*O*-(2-methoxyethyl) (2′-MOE), antisense oligonucleotide (ASO) drug in development for the treatment of spinal muscular atrophy (SMA) due to genetic defects in the survival motor neuron 1 (*SMN1*) gene.

ASOs are short synthetic strings of nucleotides designed to alter the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein. In patients with SMA, the number of survival motor neuron 2 (*SMN2*) gene copies and the resulting amount of survival motor neuron (SMN) protein are correlated with disease onset and severity. A therapeutic approach predicted to benefit patients with SMA is to increase the levels of full-length SMN2 pre-messenger ribonucleic acid (mRNA) by restoring the splicing pattern that gives rise to full-length SMN2 mRNA, thus increasing full-length SMN protein levels and SMN protein activity. ISIS 396443 is designed to bind to intron 7 of the SMN2 pre-mRNA, restoring the splicing pattern that gives rise to full-length SMN2 mRNA and thus increases full-length SMN protein levels (Figure 2).

Figure 2: Antisense Oligonucleotide Therapeutic Approach for Treatment of Spinal Muscular Atrophy



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.

5.1. Overview of 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. With an incidence of 1:6000 to 1:10,000 live births, SMA is the most common genetic cause of infant mortality, and a major cause of childhood morbidity due to weakness, in developed countries. 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 I 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 the age of 2 years. Patients with Type II SMA are able to sit but never walk unaided, with symptoms typically presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but may become severely and increasingly disabled. Patients with Type IV or adult-onset SMA have an age of onset over 18 years and have normal life expectancies.

SMA is caused by loss of SMN protein due to a homozygous deletion or mutation or compound heterozygous mutation in the *SMN1* gene on chromosome 5q11-q13. Humans have a duplication of the chromosome region where *SMN1* is found, resulting in a second copy of the gene, *SMN2*. In *SMN2*, a C to T nucleotide substitution in exon 7 results in an alternative splicing event such that the majority of transcripts produced (~90%) lack exon 7, and a defective truncated protein is produced. The remainder, SMN2 transcripts containing exon 7, produces a full-length protein product identical to the SMN1 protein, since 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 full-length SMN protein expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlate with SMA disease severity; thus, *SMN2* is a key modifier of disease phenotype [Coovert 1997; Feldkötter 2002; Lefebvre 1997; Prior 2004].

5.2. Current Therapies for Spinal Muscular Atrophy

There are currently no approved therapies for SMA. Current medical care is supportive and focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery [Wang 2007].

5.3. Profile of Previous Experience With ISIS 396443

5.3.1. Nonclinical Experience

ISIS 396443 was identified after an extensive screen of greater than 500 2′-MOE oligonucleotides in reporter gene assays, in vitro splicing assays, and SMA patient fibroblasts [Hua 2007; Hua 2008]. Data have shown that ISIS 396443 promotes a concentration-dependent increase in full-length transcripts (including exon 7) in patient fibroblast cells, achieving >90% full-length SMN2 transcripts, and forms nuclear structures called gems, known to contain SMN protein [Liu and Dreyfuss 1996]. In a mild mouse model of SMA, ISIS 396443 promoted inclusion of exon 7 in the SMN2 transgene in a variety of peripheral tissues when dosed systemically [Hua 2008] and in central nervous system (CNS) tissue, including the spinal cord,

when injected into the lateral ventricle [Hua 2010]. ISIS 396443 produced >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 CNS delivery of drug produced a dose-dependent effect on SMN2 exon 7 inclusion, SMN protein production, and survival. These mice treated with ISIS 396443 demonstrated improved weight gain; improvements in muscle morphology, muscle strength, and motor coordination; and improved morphology of the motor neuron junctions [Passini 2011]. Furthermore, ISIS 396443 was shown to distribute widely in the CNS after intrathecal administration in monkeys [Passini 2011].

The pharmacokinetics (PK) and toxicity of ISIS 396443 were assessed after a single intrathecal lumbar bolus injection (1 to 7 mg) in adult monkeys; after 14 weeks of repeated intrathecal lumbar bolus injections (0.3 mg/week to 3 mg/week or every other week) in juvenile monkeys (with a 4-week interim sacrifice); and after 53 weeks of repeated intrathecal lumbar bolus injections in juvenile monkeys. In addition, a dedicated multiple-dose PK study in adult monkeys (3-week dosing period) was performed to assess the half-life of ISIS 396443 in cerebrospinal fluid (CSF), tissues, and plasma.

In the single-dose study, following intrathecal dose administration, ISIS 396443 distributed from the CSF into the spinal cord, brain, and systemic circulation via CSF turnover. Plasma concentrations of ISIS 396443 were relatively low compared to CSF concentrations.

In the multiple-dose PK study, concentrations of ISIS 396443 in both CSF and plasma exhibited multiphasic disposition following intrathecal administration. The terminal elimination half-life of ISIS 396443 in CSF was 102 days. CSF concentrations peaked 1 hour after intrathecal injection, while plasma concentrations peaked 4 hours after the intrathecal injection. Animals were sacrificed at multiple times after intrathecal administration, and analysis demonstrated that ISIS 396443 was slowly cleared from CNS tissues with terminal elimination half-lives between various brain and spinal cord regions ranging from 74 to 275 days (median: 116 days).

In the 14-week and 53-week repeat-dose studies, concentrations of ISIS 396443 in CSF, plasma, and tissue were consistent with the pattern established in the 4-week multiple dose PK study. CSF and plasma concentrations increased in a dose-dependent manner in both studies. Consistent with previous studies, the time to reach maximum observed concentration (T_{max}) in the plasma occurred approximately 2 to 5 hours after intrathecal bolus administration. Tissue concentrations were measured for CNS tissues, and consistent values were obtained between the 14- and 53-week studies after adjusting for the difference in dosing regimens.

In both repeat-dose toxicology studies, dose-dependent increases in tissue concentrations of ISIS 396443 were seen in the brain, spinal cord, and liver. In the 53-week study, during which ISIS 396443 was administered every 6 weeks, tissue concentrations were lower compared to the 14-week study, as expected. CNS tissues had half-lives of 117 to 195 days (median: 174 days), which is consistent with the range of elimination half-lives determined from the multiple-dose PK study.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience

Completed studies in subjects with SMA

ISIS 396443 has been evaluated in 3 completed open-label studies in subjects with SMA diagnosed during childhood: ISIS 396443-CS1, ISIS 396443-CS2, and ISIS 396443-CS10.

Study ISIS 396443-CS1 was a single-ascending dose Phase 1 study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with later-onset SMA. A single dose of ISIS 396443 was administered by intrathecal injection to subjects with SMA who were 2 to 14 years of age. Four doses (1, 3, 6, and 9 mg) were evaluated sequentially. Each dose was studied in a cohort of 6 or 10 subjects. All subjects received study treatment. Twenty-eight subjects were dosed in the clinical trial, and all subjects completed dosing and follow-up visits per protocol. ISIS 396443 was well tolerated, and no safety concerns were reported when administered as a single dose up to 9 mg. Mild adverse events (AEs) of headache were the most commonly reported events. The 2 events related to ISIS 396443 (palpitations and paresthesia) were mild in severity, were not dose related, and had resolved. No serious AEs (SAEs) and no discontinuations due to AEs were reported. There were no clinically significant changes in vital signs or safety laboratory parameters related to ISIS 396443. CSF and plasma drug concentrations of ISIS 396443 were dose dependent and consistent with the nonclinical data.

Study ISIS 396443-CS2 was an open-label, multiple-ascending dose, Phase 1/2a study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with later-onset SMA. Multiple doses of ISIS 396443 were administered by intrathecal injection to subjects with SMA who were 2 to 15 years of age. Four dose levels (3, 6, 9, and 12 mg) were evaluated sequentially. Each dose level was studied in a cohort of 8 or 9 subjects, where all subjects received study treatment. The 6 subjects who participated in Cohort 1 of ISIS 396443-CS1 were eligible to enroll in ISIS 396443-CS2; 3 of these subjects enrolled in ISIS 396443-CS2 Cohort 1 and the other 3 enrolled in ISIS 396443-CS2 Cohort 2. Thirty-four subjects were enrolled, and all but 1 subject completed the study. One subject in the 12-mg ISIS 396443 dose cohort discontinued treatment early because of the Investigator's decision. The Investigator concluded that the subject and the parents could not tolerate the study procedures associated with dosing and PK draws, and thus, the subject was withdrawn. ISIS 396443 was well tolerated, and no safety concerns were reported when ISIS 396443 was administered as multiple doses up to 12 mg. Post lumbar puncture (LP) syndrome was the most commonly reported AE. None of the AEs reported during the study were considered related to ISIS 396443 or resulted in discontinuation from the study or of the study treatment. Three SAEs were reported during the study; all were assessed as unrelated to ISIS 396443. There were no clinically significant changes in vital signs, neurological or physical examination findings, or safety laboratory parameters related to ISIS 396443. There were no dose-related safety concerns.

Study ISIS 396443-CS10 was a single-dose open-label study to assess the safety and tolerability of a single intrathecal dose in subjects with later-onset SMA who participated in ISIS 396443-CS1 Cohorts 2, 3, and 4 (3, 6, or 9 mg). Eighteen subjects (4 subjects at 6-mg dose and 14 subjects at 9-mg dose) were enrolled and received study treatment. All 18 subjects completed the study.

Ongoing studies in subjects with SMA

ISIS 396443 is also being evaluated in 7ongoing studies: ISIS 396443-CS3B, ISIS 396443-CS3A, 232SM201, ISIS 396443-CS4, ISIS 396443-CS12, ISIS 396443-CS11, and 232SM202 (the present study).

Studies in subjects with SMA diagnosed during infancy

Study ISIS 396443-CS3B is an ongoing, pivotal, randomized, double-blind, sham procedure-controlled, Phase 3, multicenter study to assess the clinical efficacy and safety of ISIS 396443 in infants with SMA (onset of clinical signs and symptoms consistent with SMA at ≤6 months of age) who have 2 *SMN2* copies. Approximately 111 subjects are expected to be enrolled. Subjects are to be randomized in a 2:1 ratio to receive either a scaled equivalent 12-mg dose of ISIS 396443 or a sham procedure control, respectively.

Study ISIS 396443-CS3A is an ongoing, open-label, Phase 2 study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443. Enrollment has been completed with 21 subjects enrolled. Two loading dose levels (scaled by infant age to be equivalent to either 6 or 12 mg dose for children >2 years of age based on CSF volume) were evaluated sequentially in symptomatic infants with SMA who were between ≥21 and ≤7 months of age at screening. Loading doses were administered on Days 1, 15, and 85. Maintenance dosing commenced 24 weeks following Day 85 and at 18-week intervals thereafter.

Study 232SM201 is an open-label, multicenter, global, single-arm study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 in presymptomatic subjects with genetically diagnosed SMA. The study is being conducted in subjects ≤6 weeks of age with genetic documentation of 5q *SMA* homozygous gene deletion or mutation or compound heterozygous mutation, genetic documentation of 2 or 3 copies of the *SMN2* gene, CMAP ≥1 mV, and the absence of signs or symptoms of SMA. Up to 25 subjects are planned to be treated in the study. All subjects will receive a scaled equivalent 12-mg dose of ISIS 396443.

Studies in subjects with SMA diagnosed during childhood

Study ISIS 396443-CS4 is an ongoing, pivotal, randomized, multicenter, double-blind, sham procedure-controlled, Phase 3 study in subjects with later-onset SMA (onset of clinical signs and symptoms consistent with SMA at >6 months of age) being conducted to assess the clinical efficacy and safety of ISIS 396443. Enrollment has been completed with 126 subjects enrolled. Subjects are randomized in a 2:1 ratio to receive either a scaled equivalent 12 mg dose of ISIS 396443 or a sham procedure control, respectively.

Study ISIS 396443-CS12 is an ongoing open-label study to assess the safety, tolerability, and PK of ISIS 396443 (12 mg) administered intrathecally to subjects with later-onset SMA who previously participated in either ISIS 396443-CS2 or ISIS 396443-CS10.

Studies in subjects with SMA diagnosed during infancy or childhood

Study ISIS 396443-CS11 is an ongoing OLE study being conducted to evaluate the long-term safety, tolerability, and efficacy of ISIS 396443 administered intrathecally to subjects with SMA who previously participated in investigational studies of ISIS 396443. Up to 274 subjects are planned to be treated in the study.

5.4. Study Rationale

There is reasonably high genotype-phenotype correlation such that the *SMN2* copy number can be used to predict the severity of disease (moderate or severe) with approximately 80% to 85% accuracy [Burghes and Beattie 2009; Prior 2010; Swoboda 2005]. Evaluation of relationship between categories of functional status and number of *SMN2* copies have indicated that as *SMN2* copy number increases so does functional status [Feldkötter 2002; Swoboda 2005]. However, assessment of various outcome measures over time have indicated that there is overlap among SMA types, and values vary widely with age and gross motor functional status with an overall age dependent decline [Swoboda 2005].

5.4.1. Rationale for Part 1

The intent of Part 1 of this study is to assess safety, tolerability, and explore the utility of selected efficacy endpoints in subjects who have onset of clinical signs and symptoms that are consistent with SMA at age ≤6 months or >6 months. These subjects have either 2 or 3 *SMN2* copies and are not eligible to participate in the 2 pivotal clinical studies, ISIS 396443-CS3B and ISIS 396443-CS4. ISIS 396443-CS3B is a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of ISIS 396443 in subjects with 2 *SMN2* copies who have onset of clinical signs and symptoms of SMA at ≤6 months of age. ISIS 396443-CS4 is a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of ISIS 396443 in subjects who have onset of clinical signs and symptoms of SMA at >6 months of age. To be consistent with the study design of the 2 pivotal clinical studies and to understand the safety and tolerability of ISIS 396443 compared with natural history, the present study is designed to include sham procedure control for an unbiased assessment of safety, tolerability, and selected efficacy endpoints in the study population that is not eligible to participate in the studies ISIS 396443-CS3B or ISIS 396443-CS4. The design of the present study will also allow exploration of the safety and tolerability of a higher dose regimen in subjects who have onset of clinical signs and symptoms at >6 months of age, but who are not eligible for Study ISIS 396443-CS4.

5.4.2. Rationale for Part 2: Open-Label Extension Phase

The rationale for Part 2 of this study is to assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

5.5. Rationale for Dose and Schedule Selection

The ISIS 396443 dose and dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dosing intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving ISIS 396443 in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1, will receive maintenance doses starting on Day 183 of Part 2.

ISIS 396443 will be administered as an intrathecal injection. The volume of the injection, and thus the dose, will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower dose of drug, achieved by injecting a smaller volume that is proportional to the estimated CSF volume for age, such that the dose volume will be equivalent to 5 mL for a 2-year-old child to adult. Dosing instructions and details regarding administration will be provided in the Directions for Handling and Administration (DHA).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives and Endpoints

Part 1

The primary objective of Part 1 of this study is:

- To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline (see Section 16.1) in neurological examination outcomes

Part 2

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, ECGs, and vital signs
- Change from baseline (see Section 16.1) in neurological examination outcomes

6.2. Secondary Objectives and Endpoints

Part 1

The secondary objective of Part 1 of this study is:

- To examine the PK of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

The endpoint that relates to this objective is:

- ISIS 396443 concentrations in plasma and CSF

Part 2

The secondary objective of Part 2 of this study is:

- To examine the PK of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments

The endpoint that relates to this objective is:

- ISIS 396443 concentrations in plasma and CSF

6.3. Exploratory Objectives and Endpoints

Part 1

The exploratory objective of Part 1 of this study is:

- To explore the efficacy of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE)
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through final safety follow-up evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through final safety follow-up evaluation

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

Part 2

The exploratory objective of Part 2 of this study is:

- To explore the efficacy of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the HINE
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through Part 2 Final Follow-up Evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through Part 2 Final Follow-up Evaluation

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2 multicenter study conducted in 2 parts. The study was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 up to approximately 14 months (from the first dose until End of Part 1 Evaluation). Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an OLE phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 for approximately 24 additional months (or until availability of commercial product). In Part 1 of the study, up to 21 subjects will be randomized in a ratio of 2:1 to receive ISIS 396443 by intrathecal LP injection (n = 14) or to a sham procedure-control (n = 7). Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months. In Part 2 of the study, all subjects who participated in Part 1, who completed their End of Part 1 Evaluation assessments, and who elected to enroll in Part 2 will receive ISIS 396443 by intrathecal injection.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

See Section 4.1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

Part 1 of the study will consist of a Screening Period, Treatment Period, and post-treatment End of Part 1 Evaluation. For subjects who meet eligibility criteria and enroll in Part 1, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations.

Part 2 will consist of a Treatment Period and a post-treatment Final Follow-up Evaluation. For subjects who meet eligibility criteria and enroll in Part 2, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months (or until availability of commercial product) and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment in Part 2.

Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.

7.2.1. Screening

Subject eligibility for Part 1 of the study will be determined within 4 weeks (Day -28 to Day -1) prior to the first injection of ISIS 396443 or administration of sham procedure and will be confirmed before randomization. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period at the discretion of the Investigator. End of Part 1 Evaluation assessments will be used to confirm subjects' eligibility for Part 2.

7.2.2. Treatment

Part 1

Eligible subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of ISIS 396443 or a sham procedure. After the injection on Day 1, subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, and 302 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of study treatment or sham procedure, for a total of 6 injections or sham procedures over a dosing period of 10 months. During these 5 evaluations, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment or sham procedure. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

After completing the End of Part 1 Evaluation assessments, all eligible subjects may elect to enroll in Part 2.

Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 Evaluation assessments. All subjects enrolled in the study at the time of Sponsor termination will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Unblinding will occur in order for the subjects to transition from Part 1 to Part 2.

End of Part 1 Evaluation assessments are required to be done prior to the transition to Part 2. After performing the End of Part 1 Evaluation assessments, the subject may immediately transition to Part 2.

Part 2

Part 2 study procedures and schedules will be determined based on the subject's treatment assignment in Part 1.

Subjects who were randomized to receive ISIS 396443 in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving ISIS 396443 in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of ISIS 396443 in Part 1. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 3) and then receive their first dose of ISIS 396443 for Part 2 (next maintenance dose).

Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 (±7 days for all days) for follow-up evaluations and subsequent injections of ISIS 396443 over a dosing period of approximately 24 months (or until availability of commercial product). Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following their End of Part 1 Evaluation, in the event of early termination by the Sponsor due to emergent data from the ISIS 396443 clinical development program. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 4) and then receive their first injection of ISIS 396443 (first loading dose). Subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of ISIS 396443 over a dosing period of approximately 24 months (or until availability of commercial product). Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

For both groups of subjects, Part 2 of the study will continue for approximately 24 months (or until availability of commercial product) and in accordance with applicable laws and regulations. Subjects may continue receiving treatment every 4 months beyond Year 2 until commercial availability of the product. From Year 2 onwards, subjects will maintain evaluations for injection of study treatment every 4 months as indicated in Table 3 and Table 4.

7.2.3. Follow-Up

Subjects who enroll in Part 1 but not Part 2 will return to the study site for an End of Part 1 Evaluation approximately 4 months after the last dose of study treatment (End of Part 1 on Day 422 [±7 days]).

In the event of a decision by the Sponsor to terminate the study earlier than the end of Part 1 based on emergent data from the ISIS 396443 clinical development program, subjects who do not elect to participate in Part 2 will complete their next evaluation after Part 1 is terminated and that visit will be the End of Part 1 Evaluation.

Subjects who enroll in Part 2 will have a Part 2 Final Follow-up Evaluation approximately 4 months after the last open-label dose of ISIS 396443.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

7.3. Study Stopping Rules

For Part 1 and Part 2 of the study, the Sponsor may terminate the study at any time by informing Investigators (who will subsequently inform the corresponding ethics committees) and any other applicable regulatory agencies. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.4. End of Study

The end of the study is the last subject's completion of the last evaluation for Part 2.

7.5. Safety Monitoring and Data and Safety Monitoring Board

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor. Safety data will also be reviewed on a quarterly basis, throughout Part 1 of the study, by an independent Data and Safety Monitoring Board (DSMB; see Section 19.2).

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Genetic documentation of 5q *SMA* homozygous gene deletion, mutation, or compound heterozygote.
3. Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age and have documentation of 3 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age, >7 months of age (211 days) at screening, and have documentation of 2 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at >6 months of age, are ≤18 months of age at screening, and have documentation of 2 or 3 *SMN2* copies.
4. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either the anesthesiologist or pulmonologist).
5. Medical care, such as routine immunizations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis [palivizumab] if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA, in the opinion of the Investigator.
6. Subjects with 2 *SMN2* copies must reside within approximately 9 hours' ground-travel distance from a participating study site for the duration of the study. Residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor.
7. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

For Part 2 only:

To be eligible to participate in Part 2 of this study, candidates must meet the following eligibility criteria at the time of consent to participate in Part 2:

1. Participation in Part 1 and completion of the End of Part 1 Evaluation assessments.
2. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and to provide signed and dated informed consent on the Part 2 informed consent form

(ICF) and authorization to use confidential health information in accordance with national and local subject privacy regulations.

3. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or at the time point specified in the individual criterion listed:

1. Any previous exposure to ISIS 396443; previous dosing in this study or previous studies with ISIS 396443.
2. Signs or symptoms of SMA present at birth or within the first week after birth.
3. Ventilation for ≥16 hours per day continuously for >21 days at screening.
4. Permanent tracheostomy, implanted shunt for CSF drainage, or implanted CNS catheter at screening.
5. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments.
6. Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 months prior to screening, or hospitalization for surgery planned during the study.
7. Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG, as assessed by the Investigator, at the Screening Visit that would render the subject unsuitable for inclusion.
8. Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening. Any history of gene therapy, prior ASO treatment, or cell transplantation.
9. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures.
10. 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 assessments.
11. Subject's parent or legal guardian is not willing to continue to meet standard of care guidelines for care (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study.
12. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the subject unsuitable for enrollment.

For Part 2 only:

Candidates will be excluded from the Part 2 if they meet the following exclusion criterion at the time of consent into Part 2 of the study:

1. Any significant change in clinical status, including laboratory tests that, in the opinion of the Investigator, would make them unsuitable to participate in Part 2. The Investigator must reassess the subject's medical fitness for participation and consider any diseases that would preclude treatment.

Note that subjects who have been previously exposed to ISIS 396443 in Part 1 of the study (Exclusion criterion 1 for Part 1) may participate in Part 2.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

The subject's legally authorized representative (e.g., parent or legal guardian) must provide informed consent for Part 1 before study-specific screening tests are performed and for Part 2 before study-specific procedures are performed (see Section 17.3). When a subject's parent/guardian signs the ICF, that subject is assigned a unique subject identification number through the interactive response technology (IRT) system and is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents, within the IRT system, and on the screening log. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period, at the discretion of the Investigator.

9.2. Registration and Randomization of Subjects

In Part 1 of the study, subjects will be registered and randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Section 8.1 and Section 8.2 No subject may begin treatment until the subject is documented as registered (assigned a unique identification number) and is randomized for the study in the IRT system. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

In Part 1 of the study, using an IRT system, eligible subjects will be randomized to receive ISIS 396443:sham procedure in a 2:1 ratio. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus $\leq$6 months. Subjects who withdraw from the study may be replaced.

At the beginning of Part 2 of the study, the subject's treatment assignment will be unblinded via the IRT system. Part 2 is the OLE phase of the study in which all subjects receive ISIS 396443.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

Part 1 of the study is a randomized, double-blind, sham-procedure controlled study. The Sponsor, parents and/or legal guardians, and key study site personnel will be blinded throughout Part 1 of the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or that of the Sponsor, except the unblinded site study staff (dedicated team) and the unblinded medical monitor or clinical research associate. The DSMB may be unblinded as described in the DSMB charter.

Before Part 2 Day 1, parents and/or legal guardians, key study site personnel, and the Sponsor will be unblinded to the treatment group to which the subjects were randomized in Part 1. This will be performed according to the unblinding plan, which will be finalized prior to unblinding. Of note, in the event that the Sponsor decides to rollover subjects to Part 2 early, unblinding for key study site personnel will occur prior to the End of Part 1 Evaluation in order to facilitate bringing subjects who were randomized to receive sham in Part 1 as soon as possible and to maintain the 4-month dosing interval for subjects who were randomized to receive ISIS 396443 in Part 2. Treatment in Part 2 will be open-label, and all study subjects will receive ISIS 396443.

9.3.1. Emergency Unblinding of Treatment Assignment

In Part 1 of the study, if a subject has experienced an SAE (as defined in Section 15.1.2), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the IRT. However, prior to unblinding, the Investigator should attempt to contact the blinded Medical Monitor to discuss the emergency. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. Every reasonable attempt should be made to complete the End of Part 1 Evaluation assessments prior to unblinding, as knowledge of the treatment arm could influence subject assessment. 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, nor to personnel involved with the analysis and conduct of the study. In cases where there are ethical reasons to have a subject whose treatment assignment was unblinded for safety reasons remain in the study, the Investigator must obtain specific approval from the Sponsor and the Medical Monitor for the subject to continue in the study.

In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's (or designee) Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (Section 15.3.4).

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

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

- The subject's parent or legal guardian withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or the Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

In Part 1 of the study, subjects who discontinue treatment will continue follow-up evaluations (i.e., predose evaluations at regular study evaluations) but with no postdose safety monitoring telephone contacts (Section 4.2, Table 2) unless either consent is withdrawn (Section 10.2) or the Sponsor terminates Part 1 early, in the case of emergent data from the ISIS 396443 clinical development program. If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. At these evaluations or telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator use/bi-level positive airway pressure (Bi-PAP), and health status will be recorded. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document.

In Part 2 of the study, subjects who discontinue treatment will continue follow-up evaluations unless consent is withdrawn (Section 10.2). If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document. Follow-up evaluations for any subjects who discontinue treatment in Part 2 will continue through the end of Part 2.

10.2. Withdrawal of Subjects From Study

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

- The subject's parent or legal guardian withdraws consent.
- The subject's parent or legal guardian is unwilling or unable to comply with the protocol.
- The Sponsor terminates Part 1 early because of emergent data from the ISIS 396443 clinical development program, and the subject elects not to enroll in Part 2.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments (see Section 4.2 [Table 2]) at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination

Evaluation assessments at the time of withdrawal (see Section 4.2 [Table 3, and Table 4]). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for complete details.

11.1.1. Study Treatment

In Part 1 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of ISIS 396443 or sham procedure on Days 1, 15, 29, 64, 183, and 302 by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, the study coordinator, or outcome assessors). The study treatment administration will be performed in a dedicated room, and key study personnel and the parents will not be present during the procedure to ensure blinding.

In Part 2 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of ISIS 396443 at the days determined by their Part 1 treatment assignment as specified in Table 3 and Table 4. Treatment administration will not be blinded.

ISIS 396443 will be administered using a "spinal anesthesia" needle and a 5-mL syringe. A 22G to 25G spinal anesthesia needle is recommended based on 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. Depending on institutional guidelines, anesthesia may be used for the LP procedure or for the sham procedure, following institutional procedures. Subjects will be encouraged to lie down flat for 1 hour following injection of the study treatment, if possible. Prior to each injection, 5 mL of CSF fluid will be collected for analyses. CSF will be used for ISIS 396443 PK analyses. Upon consent, extra CSF will be stored for optional future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel) or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or other actions of ISIS 396443 with CSF constituents. CSF analyses and data presentation will be conducted in a blinded manner.

The volume of the injection, and thus, the dose, will be adjusted for the subject's age on the day of dosing, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling (Table 1). Thus, younger subjects will be given a lower dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for a 2-year-old child to adult.

11.1.2. Sham Procedure

In Part 1 of the study, subjects randomized to the sham procedure control group will undergo a sham procedure, rather than study treatment administration, on Study Days 1, 15, 29, 64, 183, and 302. Details regarding the sham procedure will be provided in the DHA. The sham procedure will be administered by dedicated study personnel who are unblinded to treatment

group; this cannot be any of the key study site personnel (i.e., the Investigator, study coordinator, or outcomes assessors). The sham procedure will be performed in a dedicated room, and key study personnel and the parent or legal guardian will not be present during the procedure to ensure blinding.

In general, the sham procedure will consist of a small needle prick on the lower back at the location where the LP injection is normally made. The needle will break the skin, but no LP injection or needle insertion will occur. The needle prick will be covered with the same bandage that is used to cover the LP injection normally, thus simulating the appearance of an LP injection. If institutional guidelines require the use of anesthesia or sedation for an LP procedure in ISIS 396443-treated subjects, then 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. The study subject will be kept in the procedure room for the same amount of time that subjects administered study treatment are kept, thus simulating the time period of the study treatment administration procedure.

Study treatment and sham kits will be packaged in a blinded fashion. Blinded kits for the sham procedure contain artificial CSF (5.0 mL solution per 6 mL vial) that will not be injected but will be used to simulate CSF samples for that subject.

11.2. Modification of Dose and/or Treatment Schedule

No adjustment of dose is permitted. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted but must be approved by the Medical Monitor.

11.3. Precautions

There are no protocol-required treatment precautions.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Screening and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

Allowed Concomitant Therapy

Throughout the study, Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

Disallowed Concomitant Therapy

Subjects are prohibited from receiving other experimental agents, including gene therapy, during the study. This includes marketed agents at experimental doses that are being tested for the treatment of SMA (e.g., albuterol/ salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea).

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or medically qualified staff. Study treatment is to be dispensed only for subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial should not be used for another subject.

12.1. Study Treatment

ISIS 396443 is formulated as an isotonic solution at 2.4 mg/mL and is provided as a 5.0-mL fill volume in a 6-mL clear glass vial. ISIS 396443 drug product contains the heptadecasodium salt of an 18-base residue phosphorothioate oligonucleotide.

ISIS 396443 active drug is manufactured by Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, drug identifier, and quantity of dosage units, lot number, and other pertinent information in accordance with local laws. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration date.

For Part 1 of the study, the study drug (ISIS 396443) and sham kits will be packaged in a blinded fashion. Blinded kits for sham procedure contain artificial CSF provided as 5.0 mL solution per 6 mL vial that will not be injected but will be used to simulate CSF samples for a subject.

For Part 2 of the study, the study drug (ISIS 396443) kits will be packaged in an open-label fashion.

12.1.1. Study Treatment Preparation

The individual preparing ISIS 396443 or artificial CSF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, do not use it. The vials in question should be saved at the study site and the problem immediately reported to the Sponsor (or designee).

12.1.2. Study Treatment Storage

Study treatment must be stored in a secure location.

ISIS 396443 is to be protected from light and stored long term at 2°C to 8°C in a locked refrigerator with limited access. For additional information on storage requirements, follow the instructions provided in the DHA.

12.1.3. Study Treatment Handling and Disposal

The Investigator must return all used and unused vials of ISIS 396443 and artificial CSF as instructed by the Sponsor (or designee).

If any used ISIS 396443 or artificial CSF supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor (or designee), by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor (or designee) must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Study Treatment Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of ISIS 396443 or artificial CSF supplied, dispensed, and subsequently destroyed or returned to the Sponsor (or designee). A written explanation must be provided for any discrepancies.

13. EFFICACY, PHARMACOKINETIC, AND IMMUNOGENICITY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all efficacy assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of ISIS 396443:

- Ventilator use
- HINE (Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

13.2. Pharmacokinetic (ISIS 396443 Concentration) Assessments

The following tests will be performed to assess the PK of ISIS 396443:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

13.3. Immunogenicity Assessments

The following test will be performed to assess the immunogenicity of ISIS 396443:

- Anti-ISIS 396443 plasma antibody concentrations

14. SAFETY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of ISIS 396443:

- Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes)
- AEs, including SAEs
- Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide)
- Weight
- Physical examinations
- Medical history
- 12-Lead ECGs
- Use of concomitant medications

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed to evaluate the safety profile of ISIS 396443:

- Blood chemistry: total protein, albumin, creatinine, cystatin C, creatine phosphokinase, blood urea nitrogen, total bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, calcium, phosphorus, chloride, sodium, potassium
- Hematology: red blood cells, hemoglobin, hematocrit, platelets, white blood cells, white blood cell differential
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject's legally authorized representative and/or main caregiver(s) must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Abnormal laboratory findings that are considered by the Investigator as not clinically significant should not be reported as AEs. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of >24 hours to a medical facility and does not qualify as an AE
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. 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 site 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 consent from the subject's parent or legal guardian to participate in the study.
- The condition requiring 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 parent's or legal guardian's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Related	There is clear evidence that the event is related to the use of the investigational drug (e.g., confirmation by positive re-challenge 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 administration of the investigational drug.
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 investigational drug 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; therefore, the Investigator believes no relationship exists between the event and the investigational drug.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
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.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor (or designee) according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

For subjects who receive study treatment, any AE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment injection or sham procedure. For subjects who never receive study treatment, no AEs need to be recorded on the applicable CRF.

15.3.2. Serious Adverse Events

For subjects who receive study treatment, any SAE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on an SAE form and on the applicable CRF, regardless of the severity of the event or its relationship to study treatment. For subjects who never receive study treatment, any SAE occurring between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment; however, the SAE does not need to be recorded on the applicable CRF.

SAEs must be reported to the safety vendor listed in the Study Reference Guide within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until their Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2). Thereafter, the event should be reported as described in the Study Reference Guide only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the safety contact as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject's parent or legal guardian has signed the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be reported as described in the Study Reference Guide, within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** as described in the Study Reference Guide regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form as

described in the Study Reference Guide.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports as described in the Study Reference Guide. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor (or designee) to be related to the study treatment administered.

The Sponsor (or designee) will report SUSARs to the appropriate regulatory authorities and to Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol; an overdose must be documented as a protocol deviation. A brief description should be provided in the deviation form, including whether the subject was symptomatic (with a list of symptoms) or asymptomatic. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be reported to the Medical Monitor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Medical Monitor even if the overdose does not result in an AE. If an overdose results in an AE, then the AE must be recorded. If an overdose results in an SAE, then the SAE form must be completed and faxed as described in the Study Reference Guide. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.2. 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 [redacted], MD, Office: [redacted], Mobile: [redacted], Fax: [redacted], [redacted] (or [redacted] medical emergency: [redacted] or [redacted]) or [redacted], MD at [redacted].

15.4.2.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator (or designee) should attempt to contact the blinded Biogen MA Medical Director or blinded [redacted] Medical Monitor to discuss the emergency within 24 hours. In these instances, the Investigator (or designee) may access the subject's treatment assignment by IRT.

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 personnel involved with the analysis and conduct of the study.

15.5. Safety Responsibilities

15.5.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to 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 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.

15.5.2. The Sponsor

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.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Part 1 and Part 2 will be analyzed separately. For Part 1, in general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category. For Part 2, no formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

For the Part 1 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 1. For the Part 2 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 2. In addition, a pooled analysis incorporating data from both Part 1 and Part 2 will be conducted to characterize the safety profile of ISIS 396443. For subjects on active treatment in Part 1, safety data from both Part 1 and Part 2 will be included in the pooled analysis and the Part 1 baseline will used for those subjects in the pooled analysis. For subjects on sham procedure in Part 1, only safety data from Part 2 will be included in the pooled analysis and the Part 2 baseline will be used for those subjects in the pooled analysis.

Concomitant medication usage for each subject will be listed for review.

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

16.2. Safety and Tolerability

Safety is the primary objective for the study. All AEs, laboratory abnormalities, ECGs, and vital signs will be evaluated for safety.

16.2.1. Analysis Population

Safety analyses will be conducted in the safety population. This safety set will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure. Treatment duration and amount of study treatment received will be summarized by treatment group.

16.2.2. Methods of Analysis

16.2.2.1. Neurological Examinations

Neurological examination findings will be listed for review, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal, and abnormal (not AE) will be summarized.

16.2.2.2. Adverse Events

All AEs will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment emergent if it was present prior to the first dose of study treatment and subsequently worsened, or was not present prior to the first dose of study treatment but subsequently appeared. The incidence of treatment-emergent AEs will be summarized overall, by severity, and by relationship to study treatment. A subject having the same AE more than once will be counted only once in the incidence for that event. The occurrence of the AE with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the AE with the strongest relationship to study treatment will be used in the calculation of incidence by relationship to study treatment.

All treatment-emergent AEs and SAEs will be summarized for each treatment group 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, SAEs, early withdrawals from study treatment and from study due to AEs will be provided.

16.2.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented. Summary statistics for actual values and change from Baseline will also be presented.

16.2.2.4. ECGs

ECG results will be presented by subject, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal clinically significant, and abnormal (not clinically significant) will be summarized.

16.2.2.5. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using study visit for each treatment group. These safety variables will also be presented over time after study treatment administration, as appropriate. Laboratory parameters will also be summarized using shift tables, as appropriate.

16.3. Efficacy

16.3.1. Analysis Population

The exploratory analysis of efficacy will be performed on the intent-to-treat population. The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

16.3.2. Methods of Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

16.4. Pharmacokinetics

16.4.1. Analysis Population

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

16.4.2. Methods of Analysis

Plasma PK parameters, as applicable, and ISIS 396443 concentrations in plasma and CSF for the PK population will be summarized using descriptive statistics and, where warranted, presented graphically.

16.5. Immunogenicity

16.5.1. Analysis Population

The analysis population for immunogenicity will include all subjects with available immunogenicity data.

16.5.2. Methods of Analysis

Results from the immunogenicity analyses for anti-ISIS 396443 plasma antibody status and titer will be summarized at the specified visits.

16.6. Interim Analyses

No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

16.7. Sample Size Considerations

Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

17. ETHICAL REQUIREMENTS

The Sponsor, [redacted] (the contract research organization [CRO] for this study), and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor (or designee) will submit documents on behalf of the investigational sites in countries other than the US.

If the Investigator makes any changes to the ICF, the Sponsor (or designee) must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor (or designee). After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor (or designee).

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor (or designee) must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

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).

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will not be collected for the purposes of data analysis during the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent, if applicable, must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent, if applicable, must also be documented in the subject's medical record.

17.4. 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, subjects' race and ethnicity will not 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. Sponsor, 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.

17.5. Compensation for Injury

The Sponsor (or designee) maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. 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).

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit conducted by the Sponsor (or designee). This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

CRFs will be not be used as source data. Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. 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 the Sponsor. Ionis is the Sponsor of the study in the United States and Biogen Idec Research Limited is the Sponsor of the study in the Rest of World. Biogen will be responsible for managing the study globally. All financial details are provided in the separate contract(s) between the institution, Investigator, and the Sponsor.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

The Sponsor may transfer any or all of its study-related responsibilities to a CRO and other third parties; however, the Sponsor retains overall accountability for these activities.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool that is developed and supported by an electronic data capture vendor and configured by Sponsor or CRO.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory will be selected by the Sponsor to analyze all hematology, blood chemistry, urine, and CSF samples collected at all study sites. Local laboratories may be used to accommodate acute or urgent needs as discussed in in the Study Reference Guide.

During the Part 1 Screening Period, a blood sample will be collected for *SMN2* copy number analysis by the central laboratory only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

19.2. Study Committees

Safety data will be reviewed on an ongoing quarterly basis throughout Part 1 of the study by an independent DSMB. The DSMB will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 396443 during the study. Based on its ongoing assessment of the safety and tolerability of ISIS 396443, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the

investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor (or designee) may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Burghes AH, Beattie CE. Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nat Rev Neurosci. 2009;10(8):597-609.

Coovert DD, Le TT, McAndrew PE, et al. The survival motor neuron protein in spinal muscular atrophy. Hum Mol Genet. 1997;6(8):1205-14.

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Matsuzawa J, Matsui M, Konishi T, et al. Age-related volumetric changes of brain gray and white matter in healthy infants and children. Cereb Cortex. 2001;11(4):335-42.

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Prior TW. Perspectives and diagnostic considerations in spinal muscular atrophy. Genet Med. 2010;12(3):145-52.

Prior TW, Swoboda KJ, Scott HD, et al. Homozygous SMN1 deletions in unaffected family members and modification of the phenotype by SMN2. Am J Med Genet A. 2004;130A(3):307-10.

Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol. 2005;57(5):704-12.

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Wirth B, Brichta L, Schrank B, et al. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. Hum Genet. 2006;119(4):422-8.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4" 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 (Print)

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
USA

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

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 232SM202

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

EUDRA CT NO **2014-003657-33**

DATE: 05 May 2016
Version 2
Final

Supersedes previous Version 1 dated 31 October 2014.

SIGNATURE OF BIOGEN MA THERAPEUTIC AREA HEAD

Neurology

Protocol 232SM202, Version 2, was approved by:

[redacted], BCh, MMSC
[redacted]
Biogen MA Inc.

6-May-2016
Date

SIGNATURE OF IONIS PHARMACEUTICALS, INC. CHIEF CLINICAL DEVELOPMENT OFFICER

Chief Clinical Development Officer

Protocol 232SM202, Version 2, was approved by:

[redacted], MBBS

5 MAY 2016

Date

Ionis Pharmaceuticals, Inc.

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1. SPONSOR INFORMATION

Ionis Pharmaceuticals, Inc. (Ionis) is the Sponsor of the study in the United States. Biogen Idec Research Limited is the Sponsor of the study in the Rest of World. Biogen Idec Research Limited (or designee) will be responsible for managing the study globally.

Biogen MA Inc. 250 Binney Street Cambridge, MA 02142 United States	Biogen Idec Research Limited Innovation House 70 Norden Road Maidenhead, Berkshire SL6 4AY United Kingdom	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 USA

Primary contact for urgent medical issues:

[redacted]: [redacted], MD
Office [redacted]
Mobile: [redacted]
Fax: [redacted]
[redacted]
[redacted] medical emergency: [redacted]
or [redacted]

Secondary contact for urgent medical issues:

Biogen MA[redacted]: [redacted], MD
Cell phone: [redacted]

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

2. LIST OF ABBREVIATIONS

2′ MOE	2′ O (2 methoxyethyl)
AE	adverse event
ASO	antisense oligonucleotide
Bi-PAP	bi-level positive airway pressure
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
GCP	Good Clinical Practice
HINE	Hammersmith Infant Neurological Examination
ICF	informed consent form
ICH	International Conference on Harmonisation
IRT	interactive response technology
LP	lumbar puncture
mRNA	messenger ribonucleic acid
OLE	open-label extension
PK	pharmacokinetic(s)
RNA	ribonucleic acid
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to reach maximum observed concentration

3. SYNOPSIS

This is a brief summary. For details, refer to the body of the protocol.

Protocol Number:	232SM202
Protocol Title:	A Phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
Version Number:	2
Name of Study Treatment:	ISIS 396443 (BIIB058)
Study Indication:	Spinal muscular atrophy (SMA)
Phase of Development:	2
Study Rationale:	The rationale of Part 1 of the study is to assess the safety and tolerability and evaluate the utility of selected exploratory efficacy endpoints in subjects with SMA treated intrathecally with ISIS 396443 who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 (the open-label extension phase) prior to completion of all Part 1 evaluations. The rationale of Part 2 of the study is to assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.
Study Objectives and Endpoints:	**Part 1** Primary objective: The primary objective of Part 1 of this study is: • To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. The primary endpoints that relate to this objective are:

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline in neurological examination outcomes

Secondary objective:

The secondary objective and endpoint of Part 1 of this study are as follows:

- To examine the pharmacokinetics (PK) of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
- ISIS 396443 concentrations in plasma and cerebrospinal fluid (CSF)

Part 2

Primary objective:

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The primary endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline in clinical laboratory parameters, ECGs, and vital signs
- Change from baseline in neurological examination outcomes

Secondary objective:

The secondary objective and endpoint of Part 2 of this study are as follows:

- To examine the PK of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments
- ISIS 396443 concentrations in plasma and CSF

Exploratory objectives and endpoints are listed in Section 6.3.

Study Design: This is a Phase 2 multicenter study conducted in 2 parts:

Part 1 was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 over a

period of approximately 14 months (from the first dose until the End of Part 1 Evaluation). Up to 21 subjects will be randomized in a ratio of 2:1 to receive ISIS 396443 by intrathecal lumbar puncture (LP) injection or a sham-procedure control. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months.

After informed consent is obtained, subjects will undergo a screening evaluation no greater than 28 days prior to administration of the first dose of study treatment. Subjects who meet the eligibility criteria will be randomized to receive ISIS 396443 or sham procedure. Subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of study treatment or sham procedure. Subjects will return to the study site on Days 15, 29, 64, 183, and 302 for follow-up evaluations and subsequent injections or sham procedures. For subjects receiving ISIS 396443 or sham procedure, a CSF sample will be taken predose on each injection day in a manner that maintains the blind.

After the study treatment dosing or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours for safety monitoring. Following all subsequent injections, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring.

Safety monitoring will occur on the day following each injection of study treatment or sham procedure. Subjects receiving the dosing or sham procedure on Days 15, 29, 64, 183, and 302 will be monitored by telephone contact on Days 16, 30, 65, 184, and 303.

In addition, subjects will also be monitored through telephone contact throughout the duration of the study.

An End of Part 1 Evaluation will occur up to 4 months after the last dose of ISIS 396443 or sham procedure, or sooner (if the Sponsor decides to terminate Part 1 early based on emergent data from the ISIS 396443 clinical development program, as described below). Subjects who terminate early from Part 1 of the study will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal.

After completing End of Part 1 Evaluation assessments according to the study schedule or sooner, if emergent data from the ISIS 396443 clinical development program necessitate the early termination of Part 1 by the Sponsor, all eligible subjects may elect to enroll in Part 2. All subjects enrolled in the study at the time that the Sponsor terminates Part 1 will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an open-label extension (OLE) phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 for approximately 24 additional months (or until availability of commercial product).

Part 2 study procedures will be determined based on the treatment assignment in Part 1.

Subjects who were randomized to receive ISIS 396443 in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving ISIS 396443 in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of ISIS 396443 in Part 1. On Part 2 Day 1, subjects will undergo predose evaluations according to the schedule of events and then receive their first dose of ISIS 396443 for Part 2 (next maintenance dose). Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 for follow-up evaluations and subsequent maintenance dose injections. All subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment. Subjects will be monitored by telephone contact on Days 2, 121, 240, 359, 478, 597, and 716.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 of the study will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine eligibility for Part 2 of the study. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following the End of Part 1 Evaluation, in the event of early termination due to emergent data from the ISIS 396443 clinical development program. On Part 2 Day 1, subjects

will undergo predose evaluations according to the schedule of events and then receive their first dose of ISIS 396443 (first loading dose). Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 for follow-up evaluations and subsequent injections. Subjects will remain at the study site for at least 24 hours on Day 1. Following all subsequent injections, all subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure.

Safety monitoring by telephone contact will occur on the day after injection of study treatment after Day 1. Subjects will be monitored by telephone contact on Days 16, 30, 65, 184, 303, 422, 541, 660, and 779.

In addition, subjects will be monitored through telephone contact throughout the duration of the study.

A Part 2 Final Follow-up Evaluation will occur approximately 4 months after the last dose in Part 2. Subjects who terminate early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

Rationale for Dose and Schedule Selection:	In Part 1, a scaled equivalent dose of 12 mg ISIS 396443 will be administered at each of the 6 doses (i.e., on Study Days 1, 15, 29, 64, 183, and 302) over a dosing period of approximately 10 months to subjects randomized to receive active treatment. In Part 2, a scaled equivalent dose of 12 mg ISIS 396443 will be administered at each dose over a dosing period of approximately 24 months (or until availability of the commercial product). The volume of the injection will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower absolute mg dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for 2 years of age to adult. The dose regimen and the dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dose intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443 to date. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible

for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving ISIS 396443 in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1 will receive maintenance doses starting on Day 183 of Part 2.

Table 1 ISIS 396443 Dose Volume To Be Injected

Age	Estimated CSF Volume (mL)	Injection Volume (mL)	Dose (mg)
0-3 months (0-90 days)	120	4	9.6
3-6 months (91-182 days)	130	4.3	10.3
6-12 months (183-365 days)	135	4.5	10.8
12-24 months (366-730 days)	140	4.7	11.3
>24 months (>730 days)	150	5.0	12.0

Source: [Matsuzawa 2001]
CSF = cerebrospinal fluid.

Study Location: Global, multicenter

Number of Planned Subjects: In Part 1, up to 21 subjects are planned (14 ISIS 396443; 7 sham procedure).

In Part 2, up to 21 subjects are planned (21 ISIS 396443).

Study Population: Part 1 of this study will be conducted in subjects who have clinical signs and symptoms of SMA at ≤6 months of age or at >6 months of age and who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

Part 2 will include only subjects who participated in Part 1 and completed their End of Part 1 Evaluation assessments. Subjects

	enrolling in Part 2 must meet the Part 2-specific criteria. Detailed eligibility criteria are described in Section 8.
Treatment Groups:	In Part 1, subjects will receive either ISIS 396443 intrathecally or sham-procedure control in a 2:1 ratio. Randomization will be balanced for the stratification factor (age of symptom onset >6 months versus ≤6 months). A single dose level of 12 mg ISIS 396443 will be scaled by age at the time of dosing for each subject. In Part 2, all subjects will receive open-label ISIS 396443. A single dose level of 12 mg ISIS 396443 will be scaled by age at the time of dosing for each subject.
Duration of Treatment and Follow-up:	For subjects who meet the eligibility criteria and enroll in Part 1 of the study, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations. For subjects who meet the eligibility criteria and enroll in Part 2 of the study, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months (or until availability of commercial product) and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment. Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.
Criteria for Evaluation:	The criteria for evaluation for Part 1 and Part 2 are as follows:
Safety:	• Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes) • AEs, including SAEs • Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide) • Weight • Physical examinations

- Medical history
- 12-Lead ECGs
- Use of concomitant medications
- Clinical laboratory tests (blood chemistry, hematology, and urinalysis)

Pharmacokinetics:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

Efficacy:

- Ventilator use
- Hammersmith Infant Neurological Examination (HINE, Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

Immunogenicity:

- Anti-ISIS 396443 plasma antibody concentrations

Statistical Methods:

Analysis Population

The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

Part 1

Safety Analysis

The analysis of safety will be performed on the safety population. The incidence of treatment-emergent AEs and SAEs will be tabulated. Changes from baseline in clinical laboratory parameters, vital signs, and ECG parameters will be summarized. Incidence of clinically relevant changes from baseline in vital signs and ECGs will be summarized. Laboratory parameters will also be summarized using shift tables, as appropriate.

PK Analysis

Summary statistics for plasma and CSF concentrations of ISIS 396443 will be provided.

Exploratory Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

Part 2

No formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

Interim Analysis: No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

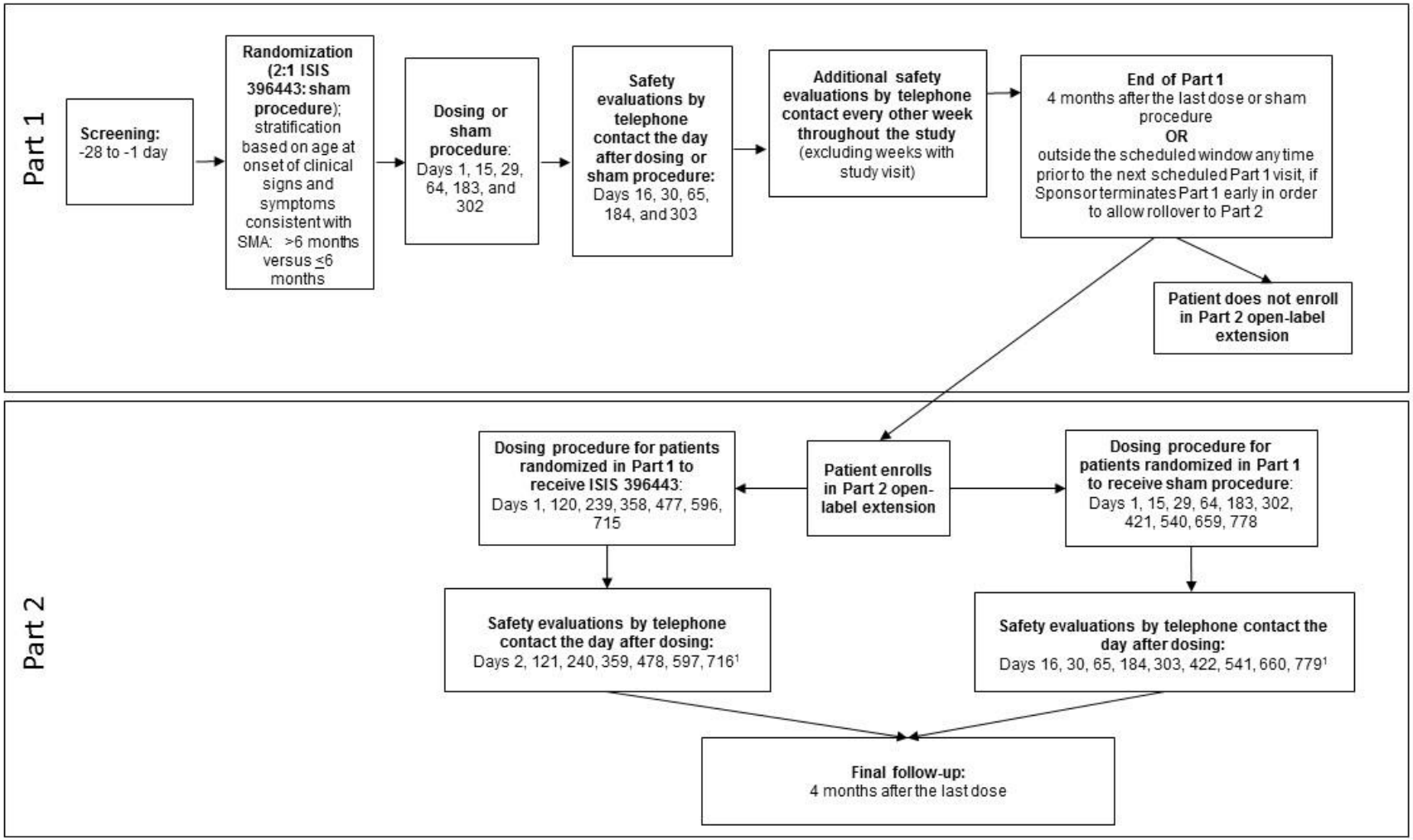
Sample Size Determination: Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy

	endpoints in the selected study population.
Study Stopping Rules:	The Sponsor may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 232SM202

4.1. Study Schematic

Figure 1: Study Schematic



[1]Study visits may continue every 4 months beyond Year 2 if commercial product is not yet available.

4.2. Schedule of Events

4.2.1. Schedule of Events: Part 1

Table 2: Part 1 Schedule of Activities

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3, 4, 5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Vital Signs[6]	X	X		4X[7]	X[8]	X		4X[7]		X		4X[7]		X		4X[7]		X
Weight	X	X			X	X				X				X				X
Growth Parameters[9]	X	X				X				X				X				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
Neurological Examination[10]	X	X		X[11]	X	X		X[11]		X		X[11]		X		X[11]		X
ECG	X				X							X						X
Safety Laboratory Tests[12]	X													X[13]				X[14]
Coagulation Laboratory Tests	X																	X[14]
Immunogenicity Sample		X												X				X
CSF PK[15]		X				X				X				X				
Plasma PK				X[16]										X[17]				X
Study Treatment			X				X				X				X			

Study Period	Screen[1]	Part 1 Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	End of Part 1[3, 4, 5]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Injection or Sham Procedure																		
Inpatient Stay[18]				X														
Telephone Contact for Safety Monitoring[2]									X				X				X	
HINE Motor Milestone		X												X				X
Clinical Global Impression of Change		X												X				X
Con Med Recording[19]	X ---------- X																	
Adverse Event Collection[20]	X ---------- X																	

AE = adverse event; Bi PAP = bi level positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

[1] A blood sample will be collected at Screening for *SMN2* copy number only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

[2] After the injection of study treatment or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. On the day following the injection of study treatment or sham procedure on Days 15, 29, 64, 183, and 302, there will be safety monitoring through telephone contact. During that telephone contact (i.e., Days 16, 30, 65, 184 and 303), changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[3] End of Part 1 is one of the following: Part 1 Final Follow-up Evaluation (Day 422 [±7 days]) according to the study schedule, early Part 1 Final Follow-up Evaluation to allow for rollover into Part 2, or Early Termination Evaluation for subjects who withdraw from the study during Part 1.

[4] For subjects not transitioning into Part 2, the date of the End of Part 1 Evaluation assessments will be the End of study. For subjects who transition to Part 2, the date of the End of Part 1 will be the date of first dose in Part 2.

, [5] At the End of Part 1 evaluation, in order to allow transition to Part 2, subjects will be unblinded.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected within 20 to 24 hours after the injection of study treatment or sham procedure.
[9] At the evaluations scheduled for injection of study treatment or sham procedure, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.
[10] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
[11] Neurological examinations will occur between 4 to 6 hours after the injection of study treatment or sham procedure.
[12] Blood chemistry, hematology, and urinalysis panels.
[13] Samples for safety laboratory tests will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only.
[14] End of Part 1 safety laboratory tests and coagulation laboratory tests to be performed at the local laboratory in parallel with the central laboratory.
[15] Refer to Table 5 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[16] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment or sham procedure only on Day 1. Refer to Table 5 for the plasma PK sample schedule.
[17] Blood samples for PK assessment will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only. Refer to Table 5 for the plasma PK sample schedule.
[18] Overnight stay (at least 24 hours) is required after the first injection of study treatment or sham procedure. Following all subsequent injections or sham procedures, a stay of at least 6 hours at the study site is required; overnight stays are optional on these days.
[19] In addition to concomitant medications, ancillary procedures will be recorded.
[20] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

4.2.2. Schedule of Events: Part 2

Table 3: Part 2 Schedule of Activities for Subjects Randomized to Receive ISIS 396443 in Part 1

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
Informed Consent	X[5]								
Inclusion/ Exclusion Criteria	X[5]								
Vital Signs[6]	X[7,12]		X[8]	X	X		X[8]		X
Weight	X[7,12]				X				X
Growth Parameters[9]	X[7,12]				X				X
Physical Examination	X[7,12]				X				X
Ventilator Use	X[7,12]			X	X			X	X
Neurological Examination[10]	X[7,12]		X[11]		X		X[11]		X
ECG	X[12]				X[13]				X
Safety Laboratory Tests[14]	X[12]				X[15]				X
Immunogenicity Sample	X[12]				X[16]				X
CSF PK[17]	X[5]				X				
Plasma PK			X[18]		X[18]				X
Study Treatment Injection		X				X			
Telephone Contact for Safety Monitoring				X				X	
HINE Motor Milestone	X[12]				X				X
Clinical Global Impression of Change	X[12]				X				X

Study Period	Part 2 Treatment/Follow-Up								
Study Day	Day 1			Day 2[1]	Days 120, 239, 358, 477, 596, 715 (±7 days)[2]			Days 121, 240, 359, 478, 597, 716[1]	Part 2 Final Follow-Up (Day 835 [±7 days])[3] or Part 2 Early Termination[4]
	Predose[5]	LP	Postdose		Predose	LP	Postdose		
Con Med Recording[19]	X----------								----------X
Adverse Event Collection[20]	X----------								----------X

AE = adverse event; Bi PAP = bi level positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event.

[1] There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 2, 121, 240, 359, 478, 597, and 716). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi PAP use, and health status will be recorded.

[2] Subjects may continue receiving study treatment injection every 4 months beyond Year 2 until commercial availability of the product. If the study continues beyond Year 2 (i.e., beyond Day 715), then from Day 835 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the assessments for those additional timepoints to alternate between the assessments done on Day 120 and those done on Day 239. Day 120 assessments would be performed at Day 835 and Day 239 assessments would be performed at Day 954. The alternating pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 716, if the product is commercially available, or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, and CSF PK must be performed on Part 2 Day 1.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] The indicated predose assessments will be repeated on Part 2 Day 1 if the study treatment injection will occur more than 24 hours after End of Part 1 Evaluation.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected 1 hour (±15 minutes) after the injection of study treatment. Note that on Part 2 Day 1, this group of patients must have a plasma PK blood sample 4 hours after injection of study treatment.

[9] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.

[10] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.

[11] Neurological examinations will occur 1 hour after the injection of study treatment.

[12] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, safety laboratory testing and ECG must be performed in addition to the indicated predose assessments. If Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, safety laboratory testing, ECG, and immunogenicity testing must be performed in addition to the indicated predose assessments.

[13] ECG will be performed on Days 239, 477, and 715, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.

[14] Blood chemistry, hematology, and urinalysis panels.

[15] Blood samples for safety laboratory tests will be collected before the injection of study treatment on Days 239, 477, and 715, and at the Part 2 Final Follow-up Evaluation on the same day as ECG, plasma PK, and immunogenicity sample.

[16] Blood samples for immunogenicity samples will be collected before the injection of study treatment on Days 239, 477, and 715, and at the Part 2 Final Follow-up Evaluation.
[17] Refer to Table 6 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[18] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 6 for the plasma PK sample schedule. Plasma PK to be performed predose on Days 239, 477, and 715.
[19] In addition to concomitant medications, ancillary procedures will be recorded.
[20] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 4: Part 2 Schedule of Activities for Subjects Randomized to Receive Sham Procedure in Part 1

Study Period	Part 2 Treatment/Follow-Up																
Study Day	**Day 1**			**Day 2[1]**	**Day 15 (±1 day)**			**Day 16[1]**	**Day 29 (±1 day)**			**Day 30[1]**	**Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]**			**Days 65, 184, 303, 422, 541, 660, 779[1]**	**Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]**
	Predose[5]	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		
Informed Consent	X[5]																
Inclusion/Exclusion Criteria	X[5]																
Vital Signs[6]	X[7, 13]		4X[8]	X[9]	X		X[8]		X		X[8]		X		X[8]		X
Weight	X[7, 13]			X	X				X				X				X
Growth Parameters[10]	X[7, 13]				X				X				X				X
Physical Examination	X[7, 13]				X				X				X				X
Ventilator Use	X[7, 13]			X	X			X	X			X	X			X	X
Neurological Examination[11]	X[7, 13]		X[12]	X	X		X[12]		X		X[12]		X		X[12]		X
ECG	X[13]			X							X		X[14]				X
Safety Laboratory Tests[15]	X[13]												X[16]				X
Coagulation Laboratory Tests	X[5 13]																
Immunogenicity Sample	X[13]												X[17]				X
CSF PK[18]	X[5]				X				X				X				
Plasma PK[19]			X[19]										X[19]				X
Study Treatment Injection		X				X				X				X			
Inpatient Stay[20]			X														
Telephone Contact for Safety Monitoring								X				X				X	

Study Period	Part 2 Treatment/Follow-Up																
Study Day	**Day 1**			**Day 2[1]**	**Day 15 (±1 day)**			**Day 16[1]**	**Day 29 (±1 day)**			**Day 30[1]**	**Days 64, 183, 302, 421, 540, 659, 778 (±7 days)[2]**			**Days 65, 184, 303, 422, 541, 660, 779[1]**	**Part 2 Final Follow-Up (Day 897 [±7 days])[3] or Part 2 Early Termination[4]**
	Predose[5]	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		
HINE Motor Milestone	X[13]												X				X
Clinical Global Impression of Change	X[13]												X				X
Con Med Recording[21]	X----------																----------X
Adverse Event Collection[22]	X----------																----------X

AE = adverse event; Bi PAP = bi level positive airway pressure; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event.

[1] After the injection of study treatment on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. There will be safety monitoring through telephone contact on the day following the injection of study treatment (i.e., Days 16, 30, 65, 184, 303, 422, 541, 660, and 779). During that telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi PAP use, and health status will be recorded.

[2] Subjects may continue receiving study treatment injection every 4 months beyond Year 2 until commercial availability of the product. If the study continues beyond Year 2 (i.e., beyond Day 778), then from Day 897 onwards, subjects will maintain evaluations for study treatment injection every 4 months with the schedule of events for those additional timepoints to alternate between the assessments done on Day 183 and those done on Day 302. Day 302 assessments would be performed at Day 897 and Day 183 assessments would be performed at Day 1016. That pattern would continue until the end of the study. Part 2 Final Follow-up Evaluation would then occur approximately 4 months after the last injection of study treatment.

[3] The Part 2 Final Follow-up Evaluation will occur 4 months after the last injection of study treatment, which will either be on Day 778, if the product is commercially available, or later, if Part 2 of the study continues beyond Year 2.

[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the Part 2 Early Termination Evaluation.

[5] Inclusion/Exclusion Criteria, Informed Consent, CSF PK, and coagulation laboratory tests must be performed on Part 2 Day 1.

[6] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each evaluation. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.

[7] The indicated predose assessments will only repeated on Part 2 Day 1 if the study treatment injection will occur more than 24 hours after End of Part 1 Evaluation.

[8] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment only on Part 2 Day 1. On subsequent study days, vital signs will be collected 1 hour after the injection of study treatment.

[9] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected on Day 2 within 20 to 24 hours after the injection of study treatment only.

[10] At the evaluations scheduled for injection of study treatment, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference. Growth parameters and weight are to be collected at the same time.
[11] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
[12] Neurological examinations will occur 1 hour after the injection of study treatment.
[13] If Part 2 Day 1 study treatment injection is delayed more than 24 hours after End of Part 1 due to an AE, SAE, or other safety concern, safety laboratory testing and ECG must be performed in addition to the indicated predose assessments. If Part 2 Day 1 study treatment injection is delayed more than 30 days after End of Part 1 for any reason, safety laboratory testing, ECG, and immunogenicity testing must be performed, in addition to the indicated predose assessments.
[14] ECG will be performed at Days 64, 183, 540, and 778, and at the Part 2 Final Follow-up Evaluation. ECG must be performed before obtaining blood samples for safety laboratory tests.
[15] Blood chemistry, hematology, and urinalysis panels.
[16] Blood samples for safety laboratory tests will be collected before the injection of study treatment on same days as ECG, plasma PK, and immunogenicity sample.
[17] Blood samples for immunogenicity testing will be collected before the injection of study treatment on Days 64, 183, 540, and 778, and at the Part 2 Final Follow-up Evaluation.
[18] Refer to Table 7 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[19] Blood samples for PK assessment will be collected 4 hours (±1 hour) after the injection of study treatment only on Day 1. Refer to Table 7 for the plasma PK sample schedule. Plasma PK will be collected predose on Days 64, 183, 540, and 778, and at the Part 2 Final Follow-up Evaluation.
[20] Overnight stay (at least 24 hours) is required after the first injection of study treatment. Following all subsequent injections, a stay of at least 1 hour at the study site is required; overnight stays are optional on these days.
[21] In addition to concomitant medications, ancillary procedures will be recorded.
[22] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 5 Part 1 Pharmacokinetic Sampling Schedule[1]

Treatment Period	Part 1 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	End of Part 1	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.

[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

Table 6 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive ISIS 396443 in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 120	Predose	NA	0.5
	Day 239	Predose	0.5	0.5
	Day 358	Predose	NA	0.5
	Day 477	Predose	0.5	0.5
	Day 596	Predose	NA	0.5
	Day 715	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

Table 7 Part 2 Pharmacokinetic Sampling Schedule for Subjects Randomized to Receive Sham Procedure in Part 1[1]

Treatment Period	Part 2 Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	Day 421	Predose	NA	0.5
	Day 540	Predose	0.5	0.5
	Day 659	Predose	NA	0.5
	Day 778	Predose	0.5	0.5
	Part 2 Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

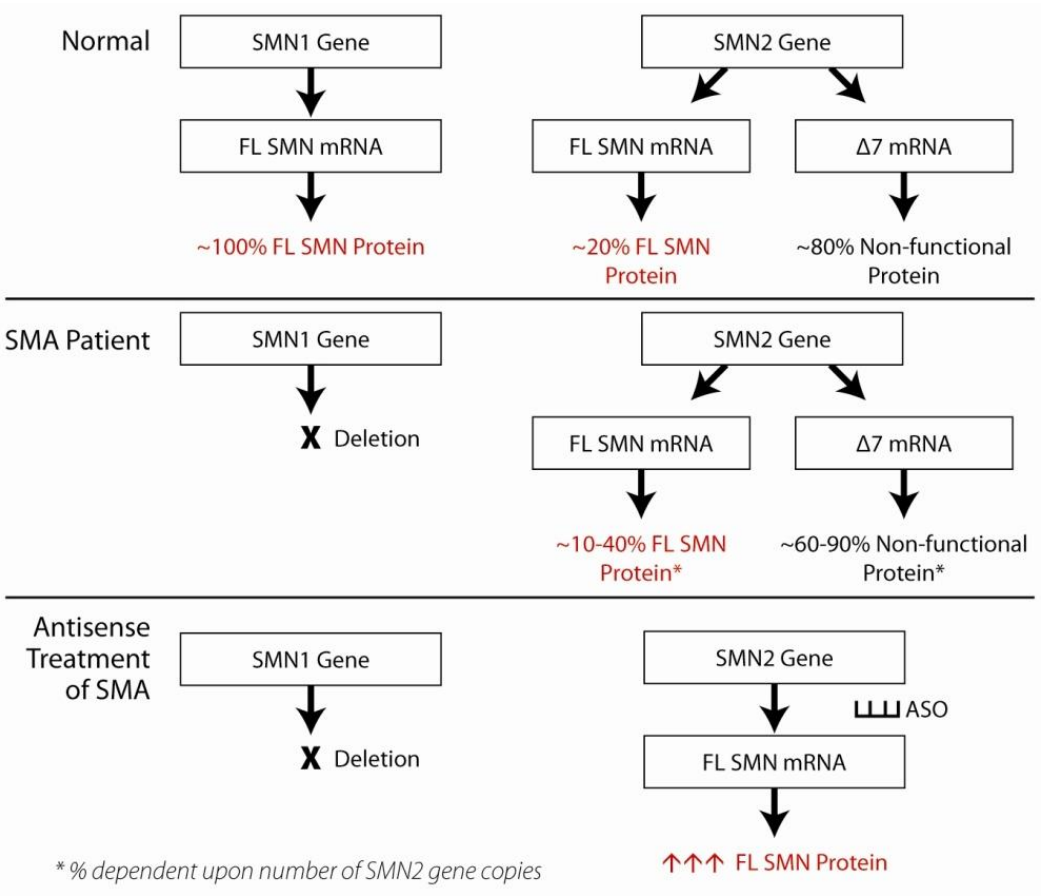
[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

5. INTRODUCTION

ISIS 396443 is a uniformly modified, 2′-*O*-(2-methoxyethyl) (2′-MOE), antisense oligonucleotide (ASO) drug in development for the treatment of spinal muscular atrophy (SMA) due to genetic defects in the survival motor neuron 1 (*SMN1*) gene.

ASOs are short synthetic strings of nucleotides designed to alter the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein. In patients with SMA, the number of survival motor neuron 2 (*SMN2*) gene copies and the resulting amount of survival motor neuron (SMN) protein are correlated with disease onset and severity. A therapeutic approach predicted to benefit patients with SMA is to increase the levels of full-length SMN2 pre-messenger ribonucleic acid (mRNA) by restoring the splicing pattern that gives rise to full-length SMN2 mRNA, thus increasing full-length SMN protein levels and SMN protein activity. ISIS 396443 is designed to bind to intron 7 of the SMN2 pre-mRNA, restoring the splicing pattern that gives rise to full-length SMN2 mRNA and thus increases full-length SMN protein levels (Figure 2).

Figure 2: Antisense Oligonucleotide Therapeutic Approach for Treatment of Spinal Muscular Atrophy



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.

5.1. Overview of 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. With an incidence of 1:6000 to 1:10,000 live births, SMA is the most common genetic cause of infant mortality, and a major cause of childhood morbidity due to weakness, in developed countries. 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 I 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 the age of 2 years. Patients with Type II SMA are able to sit but never walk unaided, with symptoms typically presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but may become severely and increasingly disabled. Patients with Type IV or adult-onset SMA have an age of onset over 18 years and have normal life expectancies.

SMA is caused by loss of SMN protein due to a homozygous deletion or mutation or compound heterozygous mutation in the *SMN1* gene on chromosome 5q11-q13. Humans have a duplication of the chromosome region where *SMN1* is found, resulting in a second copy of the gene, *SMN2*. In *SMN2*, a C to T nucleotide substitution in exon 7 results in an alternative splicing event such that the majority of transcripts produced (~90%) lack exon 7, and a defective truncated protein is produced. The remainder, SMN2 transcripts containing exon 7, produces a full-length protein product identical to the SMN1 protein, since 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 full-length SMN protein expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlate with SMA disease severity; thus, *SMN2* is a key modifier of disease phenotype [Coovert 1997; Feldkötter 2002; Lefebvre 1997; Prior 2004].

5.2. Current Therapies for Spinal Muscular Atrophy

There are currently no approved therapies for SMA. Current medical care is supportive and focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery [Wang 2007].

5.3. Profile of Previous Experience With ISIS 396443

5.3.1. Nonclinical Experience

ISIS 396443 was identified after an extensive screen of greater than 500 2′-MOE oligonucleotides in reporter gene assays, in vitro splicing assays, and SMA patient fibroblasts [Hua 2007; Hua 2008]. Data have shown that ISIS 396443 promotes a concentration-dependent increase in full-length transcripts (including exon 7) in patient fibroblast cells, achieving >90% full-length SMN2 transcripts, and forms nuclear structures called gems, known to contain SMN protein [Liu and Dreyfuss 1996]. In a mild mouse model of SMA, ISIS 396443 promoted inclusion of exon 7 in the SMN2 transgene in a variety of peripheral tissues when dosed

systemically [Hua 2008] and in central nervous system (CNS) tissue, including the spinal cord, when injected into the lateral ventricle [Hua 2010]. ISIS 396443 produced >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 CNS delivery of drug produced a dose-dependent effect on SMN2 exon 7 inclusion, SMN protein production, and survival. These mice treated with ISIS 396443 demonstrated improved weight gain; improvements in muscle morphology, muscle strength, and motor coordination; and improved morphology of the motor neuron junctions [Passini 2011]. Furthermore, ISIS 396443 was shown to distribute widely in the CNS after intrathecal administration in monkeys [Passini 2011].

The pharmacokinetics (PK) and toxicity of ISIS 396443 were assessed after a single intrathecal lumbar bolus injection (1 to 7 mg) in adult monkeys; after 14 weeks of repeated intrathecal lumbar bolus injections (0.3 mg/week to 3 mg/week or every other week) in juvenile monkeys (with a 4-week interim sacrifice); and after 53 weeks of repeated intrathecal lumbar bolus injections in juvenile monkeys. In addition, a dedicated multiple-dose PK study in adult monkeys (3-week dosing period) was performed to assess the half-life of ISIS 396443 in cerebrospinal fluid (CSF), tissues, and plasma.

In the single-dose study, following intrathecal dose administration, ISIS 396443 distributed from the CSF into the spinal cord, brain, and systemic circulation via CSF turnover. Plasma concentrations of ISIS 396443 were relatively low compared to CSF concentrations.

In the multiple-dose PK study, concentrations of ISIS 396443 in both CSF and plasma exhibited multiphasic disposition following intrathecal administration. The terminal elimination half-life of ISIS 396443 in CSF was 102 days. CSF concentrations peaked 1 hour after intrathecal injection, while plasma concentrations peaked 4 hours after the intrathecal injection. Animals were sacrificed at multiple times after intrathecal administration, and analysis demonstrated that ISIS 396443 was slowly cleared from CNS tissues with terminal elimination half-lives between various brain and spinal cord regions ranging from 74 to 275 days (median: 116 days).

In the 14-week and 53-week repeat-dose studies, concentrations of ISIS 396443 in CSF, plasma, and tissue were consistent with the pattern established in the 4-week multiple dose PK study. CSF and plasma concentrations increased in a dose-dependent manner in both studies. Consistent with previous studies, the time to reach maximum observed concentration (T_{max}) in the plasma occurred approximately 2 to 5 hours after intrathecal bolus administration. Tissue concentrations were measured for CNS tissues, and consistent values were obtained between the 14- and 53-week studies after adjusting for the difference in dosing regimens.

In both repeat-dose toxicology studies, dose-dependent increases in tissue concentrations of ISIS 396443 were seen in the brain, spinal cord, and liver. In the 53-week study, during which ISIS 396443 was administered every 6 weeks, tissue concentrations were lower compared to the 14-week study, as expected. CNS tissues had half-lives of 117 to 195 days (median: 174 days), which is consistent with the range of elimination half-lives determined from the multiple-dose PK study.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience

Completed studies in subjects with SMA

ISIS 396443 has been evaluated in 3 completed open-label studies in subjects with SMA diagnosed during childhood: ISIS 396443-CS1, ISIS 396443-CS2, and ISIS 396443-CS10.

Study ISIS 396443-CS1 was a single-ascending dose Phase 1 study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with later-onset SMA. A single dose of ISIS 396443 was administered by intrathecal injection to subjects with SMA who were 2 to 14 years of age. Four doses (1, 3, 6, and 9 mg) were evaluated sequentially. Each dose was studied in a cohort of 6 or 10 subjects. All subjects received study treatment. Twenty-eight subjects were dosed in the clinical trial, and all subjects completed dosing and follow-up visits per protocol. ISIS 396443 was well tolerated, and no safety concerns were reported when administered as a single dose up to 9 mg. Mild adverse events (AEs) of headache were the most commonly reported events. The 2 events related to ISIS 396443 (palpitations and paresthesia) were mild in severity, were not dose related, and had resolved. No serious AEs (SAEs) and no discontinuations due to AEs were reported. There were no clinically significant changes in vital signs or safety laboratory parameters related to ISIS 396443. CSF and plasma drug concentrations of ISIS 396443 were dose dependent and consistent with the nonclinical data.

Study ISIS 396443-CS2 was an open-label, multiple-ascending dose, Phase 1/2a study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with later-onset SMA. Multiple doses of ISIS 396443 were administered by intrathecal injection to subjects with SMA who were 2 to 15 years of age. Four dose levels (3, 6, 9, and 12 mg) were evaluated sequentially. Each dose level was studied in a cohort of 8 or 9 subjects, where all subjects received study treatment. The 6 subjects who participated in Cohort 1 of ISIS 396443-CS1 were eligible to enroll in ISIS 396443-CS2; 3 of these subjects enrolled in ISIS 396443-CS2 Cohort 1 and the other 3 enrolled in ISIS 396443-CS2 Cohort 2. Thirty-four subjects were enrolled, and all but 1 subject completed the study. One subject in the 12-mg ISIS 396443 dose cohort discontinued treatment early because of the Investigator's decision. The Investigator concluded that the subject and the parents could not tolerate the study procedures associated with dosing and PK draws, and thus, the subject was withdrawn. ISIS 396443 was well tolerated, and no safety concerns were reported when ISIS 396443 was administered as multiple doses up to 12 mg. Post lumbar puncture (LP) syndrome was the most commonly reported AE. None of the AEs reported during the study were considered related to ISIS 396443 or resulted in discontinuation from the study or of the study treatment. Three SAEs were reported during the study; all were assessed as unrelated to ISIS 396443. There were no clinically significant changes in vital signs, neurological or physical examination findings, or safety laboratory parameters related to ISIS 396443. There were no dose-related safety concerns.

Study ISIS 396443-CS10 was a single-dose open-label study to assess the safety and tolerability of a single intrathecal dose in subjects with later-onset SMA who participated in ISIS 396443-CS1 Cohorts 2, 3, and 4 (3, 6, or 9 mg). Eighteen subjects (4 subjects at 6-mg dose and 14 subjects at 9-mg dose) were enrolled and received study treatment. All 18 subjects completed the study.

Ongoing studies in subjects with SMA

ISIS 396443 is also being evaluated in 7ongoing studies: ISIS 396443-CS3B, ISIS 396443-CS3A, 232SM201, ISIS 396443-CS4, ISIS 396443-CS12, ISIS 396443-CS11, and 232SM202 (the present study).

Studies in subjects with SMA diagnosed during infancy

Study ISIS 396443-CS3B is an ongoing, pivotal, randomized, double-blind, sham procedure-controlled, Phase 3, multicenter study to assess the clinical efficacy and safety of ISIS 396443 in infants with SMA (onset of clinical signs and symptoms consistent with SMA at ≤6 months of age) who have 2 *SMN2* copies. Approximately 111 subjects are expected to be enrolled. Subjects are to be randomized in a 2:1 ratio to receive either a scaled equivalent 12-mg dose of ISIS 396443 or a sham procedure control, respectively.

Study ISIS 396443-CS3A is an ongoing, open-label, Phase 2 study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443. Enrollment has been completed with 21 subjects enrolled. Two loading dose levels (scaled by infant age to be equivalent to either 6 or 12 mg dose for children >2 years of age based on CSF volume) were evaluated sequentially in symptomatic infants with SMA who were between ≥21 and ≤7 months of age at screening. Loading doses were administered on Days 1, 15, and 85. Maintenance dosing commenced 24 weeks following Day 85 and at 18-week intervals thereafter.

Study 232SM201 is an open-label, multicenter, global, single-arm study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 in presymptomatic subjects with genetically diagnosed SMA. The study is being conducted in subjects ≤6 weeks of age with genetic documentation of 5q *SMA* homozygous gene deletion or mutation or compound heterozygous mutation, genetic documentation of 2 or 3 copies of the *SMN2* gene, CMAP ≥1 mV, and the absence of signs or symptoms of SMA. Up to 25 subjects are planned to be treated in the study. All subjects will receive a scaled equivalent 12-mg dose of ISIS 396443.

Studies in subjects with SMA diagnosed during childhood

Study ISIS 396443-CS4 is an ongoing, pivotal, randomized, multicenter, double-blind, sham procedure-controlled, Phase 3 study in subjects with later-onset SMA (onset of clinical signs and symptoms consistent with SMA at >6 months of age) being conducted to assess the clinical efficacy and safety of ISIS 396443. Enrollment has been completed with 126 subjects enrolled. Subjects are randomized in a 2:1 ratio to receive either a scaled equivalent 12 mg dose of ISIS 396443 or a sham procedure control, respectively.

Study ISIS 396443-CS12 is an ongoing open-label study to assess the safety, tolerability, and PK of ISIS 396443 (12 mg) administered intrathecally to subjects with later-onset SMA who previously participated in either ISIS 396443-CS2 or ISIS 396443-CS10.

Studies in subjects with SMA diagnosed during infancy or childhood

Study ISIS 396443-CS11 is an ongoing OLE study being conducted to evaluate the long-term safety, tolerability, and efficacy of ISIS 396443 administered intrathecally to subjects with SMA who previously participated in investigational studies of ISIS 396443. Up to 274 subjects are planned to be treated in the study.

5.4. Study Rationale

There is reasonably high genotype-phenotype correlation such that the *SMN2* copy number can be used to predict the severity of disease (moderate or severe) with approximately 80% to 85% accuracy [Burghes and Beattie 2009; Prior 2010; Swoboda 2005]. Evaluation of relationship between categories of functional status and number of *SMN2* copies have indicated that as *SMN2* copy number increases so does functional status [Feldkötter 2002; Swoboda 2005]. However, assessment of various outcome measures over time have indicated that there is overlap among SMA types, and values vary widely with age and gross motor functional status with an overall age dependent decline [Swoboda 2005].

5.4.1. Rationale for Part 1

The intent of Part 1 of this study is to assess safety, tolerability, and explore the utility of selected efficacy endpoints in subjects who have onset of clinical signs and symptoms that are consistent with SMA at age ≤6 months or >6 months. These subjects have either 2 or 3 *SMN2* copies and are not eligible to participate in the 2 pivotal clinical studies, ISIS 396443-CS3B and ISIS 396443-CS4. ISIS 396443-CS3B is a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of ISIS 396443 in subjects with 2 *SMN2* copies who have onset of clinical signs and symptoms of SMA at ≤6 months of age. ISIS 396443-CS4 is a randomized, double-blind, sham procedure-controlled study investigating the therapeutic benefit of ISIS 396443 in subjects who have onset of clinical signs and symptoms of SMA at >6 months of age. To be consistent with the study design of the 2 pivotal clinical studies and to understand the safety and tolerability of ISIS 396443 compared with natural history, the present study is designed to include sham procedure control for an unbiased assessment of safety, tolerability, and selected efficacy endpoints in the study population that is not eligible to participate in the studies ISIS 396443-CS3B or ISIS 396443-CS4. The design of the present study will also allow exploration of the safety and tolerability of a higher dose regimen in subjects who have onset of clinical signs and symptoms at >6 months of age, but who are not eligible for Study ISIS 396443-CS4.

5.4.2. Rationale for Part 2: Open-Label Extension Phase

The rationale for Part 2 of this study is to assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

5.5. Rationale for Dose and Schedule Selection

The ISIS 396443 dose and dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dosing intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. In Part 1, maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months. Subjects who were receiving ISIS 396443 in Part 1 will continue receiving maintenance doses in Part 2 every 4 months. Subjects who were receiving sham in Part 1, will receive maintenance doses starting on Day 183 of Part 2.

ISIS 396443 will be administered as an intrathecal injection. The volume of the injection, and thus the dose, will be adjusted based on the subject's age on the day of dosing as shown in Table 1, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower dose of drug, achieved by injecting a smaller volume that is proportional to the estimated CSF volume for age, such that the dose volume will be equivalent to 5 mL for a 2-year-old child to adult. Dosing instructions and details regarding administration will be provided in the Directions for Handling and Administration (DHA).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives and Endpoints

Part 1

The primary objective of Part 1 of this study is:

- To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline (see Section 16.1) in neurological examination outcomes

Part 2

The primary objective of Part 2 of this study is:

- To assess the long-term safety and tolerability of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Incidence of AEs and SAEs
- Change from baseline (see Section 16.1) in clinical laboratory parameters, ECGs, and vital signs
- Change from baseline (see Section 16.1) in neurological examination outcomes

6.2. Secondary Objectives and Endpoints

Part 1

The secondary objective of Part 1 of this study is:

- To examine the PK of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

The endpoint that relates to this objective is:

- ISIS 396443 concentrations in plasma and CSF

Part 2

The secondary objective of Part 2 of this study is:

- To examine the PK of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments

The endpoint that relates to this objective is:

- ISIS 396443 concentrations in plasma and CSF

6.3. Exploratory Objectives and Endpoints

Part 1

The exploratory objective of Part 1 of this study is:

- To explore the efficacy of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE)
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through final safety follow-up evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through final safety follow-up evaluation

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

Part 2

The exploratory objective of Part 2 of this study is:

- To explore the efficacy of ISIS 396443 in subjects with SMA who participated in Part 1 and completed their End of Part 1 Evaluation assessments.

The endpoints that relate to this objective are:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the HINE
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through Part 2 Final Follow-up Evaluation
- Clinical Global Impression of Change (physician and caregiver assessment) through Part 2 Final Follow-up Evaluation

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2 multicenter study conducted in 2 parts. The study was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 up to approximately 14 months (from the first dose until End of Part 1 Evaluation). Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may then be offered the opportunity to be unblinded and transition to Part 2 prior to completion of all Part 1 evaluations. Part 2 is an OLE phase that will assess long-term safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 for approximately 24 additional months (or until availability of commercial product). In Part 1 of the study, up to 21 subjects will be randomized in a ratio of 2:1 to receive ISIS 396443 by intrathecal LP injection (n = 14) or to a sham procedure-control (n = 7). Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months. In Part 2 of the study, all subjects who participated in Part 1, who completed their End of Part 1 Evaluation assessments, and who elected to enroll in Part 2 will receive ISIS 396443 by intrathecal injection.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

See Section 4.1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

Part 1 of the study will consist of a Screening Period, Treatment Period, and post-treatment End of Part 1 Evaluation. For subjects who meet eligibility criteria and enroll in Part 1, the duration of Part 1 will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and an End of Part 1 Evaluation approximately 4 months after the last dose. Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 evaluations.

Part 2 will consist of a Treatment Period and a post-treatment Final Follow-up Evaluation. For subjects who meet eligibility criteria and enroll in Part 2, the duration of Part 2 will be approximately 28 months and will include an open-label Treatment Period of approximately 24 months (or until availability of commercial product) and a Part 2 Final Follow-up Evaluation approximately 4 months after the last dose of study treatment in Part 2.

Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 43 months.

7.2.1. Screening

Subject eligibility for Part 1 of the study will be determined within 4 weeks (Day -28 to Day -1) prior to the first injection of ISIS 396443 or administration of sham procedure and will be confirmed before randomization. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period at the discretion of the Investigator. End of Part 1 Evaluation assessments will be used to confirm subjects' eligibility for Part 2.

7.2.2. Treatment

Part 1

Eligible subjects will be admitted to the study site on Part 1 Day 1, undergo predose evaluations, and then receive an LP injection of ISIS 396443 or a sham procedure. After the injection on Day 1, subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, and 302 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of study treatment or sham procedure, for a total of 6 injections or sham procedures over a dosing period of 10 months. During these 5 evaluations, all subjects will remain at the study site for at least 6 hours postdose for safety monitoring. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment or sham procedure. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

After completing the End of Part 1 Evaluation assessments, all eligible subjects may elect to enroll in Part 2.

Based on emergent data from the ISIS 396443 clinical development program, the Sponsor may decide to terminate Part 1 early, and all subjects may be offered the opportunity to transition to Part 2 prior to completion of all Part 1 Evaluation assessments. All subjects enrolled in the study at the time of Sponsor termination will be considered Part 1 completers. The next study evaluation for those subjects will serve as an End of Part 1 Evaluation, which may occur at any time prior to the next scheduled Part 1 study evaluation.

Unblinding will occur in order for the subjects to transition from Part 1 to Part 2.

End of Part 1 Evaluation assessments are required to be done prior to the transition to Part 2. After performing the End of Part 1 Evaluation assessments, the subject may immediately transition to Part 2.

Part 2

Part 2 study procedures and schedules will be determined based on the subject's treatment assignment in Part 1.

Subjects who were randomized to receive ISIS 396443 in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving ISIS 396443 in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or approximately 4 months following the last injection of ISIS 396443 in Part 1. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 3) and then receive their first dose of ISIS 396443 for Part 2 (next maintenance dose).

Subjects will return to the study site on Days 120, 239, 358, 477, 596, and 715 (±7 days for all days) for follow-up evaluations and subsequent injections of ISIS 396443 over a dosing period of approximately 24 months (or until availability of commercial product). Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

Subjects who were randomized to receive sham procedure in Part 1

End of Part 1 Evaluation assessments will be used to determine subject eligibility for Part 2 of the study. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 will occur following the End of Part 1 Evaluation or as soon as possible following their End of Part 1 Evaluation, in the event of early termination by the Sponsor due to emergent data from the ISIS 396443 clinical development program. On Part 2 Day 1, these subjects will undergo predose evaluations according to the schedule of events (Table 4) and then receive their first injection of ISIS 396443 (first loading dose). Subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 (±1 day for Days 15 and 29 and ±7 days for all other days) for follow-up evaluations and subsequent injections of ISIS 396443 over a dosing period of approximately 24 months (or until availability of commercial product). Subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit) throughout the study period.

For both groups of subjects, Part 2 of the study will continue for approximately 24 months (or until availability of commercial product) and in accordance with applicable laws and regulations. Subjects may continue receiving treatment every 4 months beyond Year 2 until commercial availability of the product. From Year 2 onwards, subjects will maintain evaluations for injection of study treatment every 4 months as indicated in Table 3 and Table 4.

7.2.3. Follow-Up

Subjects who enroll in Part 1 but not Part 2 will return to the study site for an End of Part 1 Evaluation approximately 4 months after the last dose of study treatment (End of Part 1 on Day 422 [±7 days]).

In the event of a decision by the Sponsor to terminate the study earlier than the end of Part 1 based on emergent data from the ISIS 396443 clinical development program, subjects who do not elect to participate in Part 2 will complete their next evaluation after Part 1 is terminated and that visit will be the End of Part 1 Evaluation.

Subjects who enroll in Part 2 will have a Part 2 Final Follow-up Evaluation approximately 4 months after the last open-label dose of ISIS 396443.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments at the time of withdrawal. Subjects who withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal.

7.3. Study Stopping Rules

For Part 1 and Part 2 of the study, the Sponsor may terminate the study at any time by informing Investigators (who will subsequently inform the corresponding ethics committees) and any other applicable regulatory agencies. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.4. End of Study

The end of the study is the last subject's completion of the last evaluation for Part 2.

7.5. Safety Monitoring and Data and Safety Monitoring Board

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor. Safety data will also be reviewed on a quarterly basis, throughout Part 1 of the study, by an independent Data and Safety Monitoring Board (DSMB; see Section 19.2).

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Genetic documentation of 5q *SMA* homozygous gene deletion, mutation, or compound heterozygote.
3. Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age and have documentation of 3 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age, >7 months of age (211 days) at screening, and have documentation of 2 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at >6 months of age, are ≤18 months of age at screening, and have documentation of 2 or 3 *SMN2* copies.
4. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either the anesthesiologist or pulmonologist).
5. Medical care, such as routine immunizations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis [palivizumab] if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA, in the opinion of the Investigator.
6. Subjects with 2 *SMN2* copies must reside within approximately 9 hours' ground-travel distance from a participating study site for the duration of the study. Residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor.
7. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

For Part 2 only:

To be eligible to participate in Part 2 of this study, candidates must meet the following eligibility criteria at the time of consent to participate in Part 2:

1. Participation in Part 1 and completion of the End of Part 1 Evaluation assessments.

2. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and to provide signed and dated informed consent on the Part 2 informed consent form (ICF) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
3. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or at the time point specified in the individual criterion listed:

1. Any previous exposure to ISIS 396443; previous dosing in this study or previous studies with ISIS 396443.
2. Signs or symptoms of SMA present at birth or within the first week after birth.
3. Ventilation for ≥16 hours per day continuously for >21 days at screening.
4. Permanent tracheostomy, implanted shunt for CSF drainage, or implanted CNS catheter at screening.
5. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments.
6. Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 months prior to screening, or hospitalization for surgery planned during the study.
7. Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG, as assessed by the Investigator, at the Screening Visit that would render the subject unsuitable for inclusion.
8. Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening. Any history of gene therapy, prior ASO treatment, or cell transplantation.
9. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures.
10. 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 assessments.
11. Subject's parent or legal guardian is not willing to continue to meet standard of care guidelines for care (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study.

12. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the subject unsuitable for enrollment.

For Part 2 only:

Candidates will be excluded from the Part 2 if they meet the following exclusion criterion at the time of consent into Part 2 of the study:

1. Any significant change in clinical status, including laboratory tests that, in the opinion of the Investigator, would make them unsuitable to participate in Part 2. The Investigator must reassess the subject's medical fitness for participation and consider any diseases that would preclude treatment.

Note that subjects who have been previously exposed to ISIS 396443 in Part 1 of the study (Exclusion criterion 1 for Part 1) may participate in Part 2.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

The subject's legally authorized representative (e.g., parent or legal guardian) must provide informed consent for Part 1 before study-specific screening tests are performed and for Part 2 before study-specific procedures are performed (see Section 17.3). When a subject's parent/guardian signs the ICF, that subject is assigned a unique subject identification number through the interactive response technology (IRT) system and is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents, within the IRT system, and on the screening log. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period, at the discretion of the Investigator.

9.2. Registration and Randomization of Subjects

In Part 1 of the study, subjects will be registered and randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Section 8.1 and Section 8.2 No subject may begin treatment until the subject is documented as registered (assigned a unique identification number) and is randomized for the study in the IRT system. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

In Part 1 of the study, using an IRT system, eligible subjects will be randomized to receive ISIS 396443:sham procedure in a 2:1 ratio. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus $\leq$6 months. Subjects who withdraw from the study may be replaced.

At the beginning of Part 2 of the study, the subject's treatment assignment will be unblinded via the IRT system. Part 2 is the OLE phase of the study in which all subjects receive ISIS 396443.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

Part 1 of the study is a randomized, double-blind, sham-procedure controlled study. The Sponsor, parents and/or legal guardians, and key study site personnel will be blinded throughout Part 1 of the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or that of the Sponsor, except the unblinded site study staff (dedicated team) and the unblinded medical monitor or clinical research associate. The DSMB may be unblinded as described in the DSMB charter.

Before Part 2 Day 1, parents and/or legal guardians, key study site personnel, and the Sponsor will be unblinded to the treatment group to which the subjects were randomized in Part 1. This will be performed according to the unblinding plan, which will be finalized prior to unblinding. Of note, in the event that the Sponsor decides to rollover subjects to Part 2 early, unblinding for key study site personnel will occur prior to the End of Part 1 Evaluation in order to facilitate bringing subjects who were randomized to receive sham in Part 1 as soon as possible and to maintain the 4-month dosing interval for subjects who were randomized to receive ISIS 396443 in Part 2. Treatment in Part 2 will be open-label, and all study subjects will receive ISIS 396443.

9.3.1. Emergency Unblinding of Treatment Assignment

In Part 1 of the study, if a subject has experienced an SAE (as defined in Section 15.1.2), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the IRT. However, prior to unblinding, the Investigator should attempt to contact the blinded Medical Monitor to discuss the emergency. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. Every reasonable attempt should be made to complete the End of Part 1 Evaluation assessments prior to unblinding, as knowledge of the treatment arm could influence subject assessment. 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, nor to personnel involved with the analysis and conduct of the study. In cases where there are ethical reasons to have a subject whose treatment assignment was unblinded for safety reasons remain in the study, the Investigator must obtain specific approval from the Sponsor and the Medical Monitor for the subject to continue in the study.

In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's (or designee) Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (Section 15.3.4).

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

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

- The subject's parent or legal guardian withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or the Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

In Part 1 of the study, subjects who discontinue treatment will continue follow-up evaluations (i.e., predose evaluations at regular study evaluations) but with no postdose safety monitoring telephone contacts (Section 4.2, Table 2) unless either consent is withdrawn (Section 10.2) or the Sponsor terminates Part 1 early, in the case of emergent data from the ISIS 396443 clinical development program. If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. At these evaluations or telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator use/bi-level positive airway pressure (Bi-PAP), and health status will be recorded. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document.

In Part 2 of the study, subjects who discontinue treatment will continue follow-up evaluations unless consent is withdrawn (Section 10.2). If a subject is unable to come for study evaluations, the minimum requirement for follow up will be telephone calls on a monthly basis. The methods used to continue follow up (i.e., site evaluations or telephone calls to the subject's parent, guardian, or caregiver) should be documented in the source document. Follow-up evaluations for any subjects who discontinue treatment in Part 2 will continue through the end of Part 2.

10.2. Withdrawal of Subjects From Study

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

- The subject's parent or legal guardian withdraws consent.
- The subject's parent or legal guardian is unwilling or unable to comply with the protocol.
- The Sponsor terminates Part 1 early because of emergent data from the ISIS 396443 clinical development program, and the subject elects not to enroll in Part 2.

Subjects who withdraw early from Part 1 will be encouraged to complete the End of Part 1 Evaluation assessments (see Section 4.2 [Table 2) at the time of withdrawal. Subjects who

withdraw early from Part 2 will be encouraged to complete the Part 2 Early Termination Evaluation assessments at the time of withdrawal (see Section 4.2 [Table 3, and Table 4]). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for complete details.

11.1.1. Study Treatment

In Part 1 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of ISIS 396443 or sham procedure on Days 1, 15, 29, 64, 183, and 302 by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, the study coordinator, or outcome assessors). The study treatment administration will be performed in a dedicated room, and key study personnel and the parents will not be present during the procedure to ensure blinding.

In Part 2 of the study, each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of ISIS 396443 at the days determined by their Part 1 treatment assignment as specified in Table 3 and Table 4. Treatment administration will not be blinded.

ISIS 396443 will be administered using a "spinal anesthesia" needle and a 5-mL syringe. A 22G to 25G spinal anesthesia needle is recommended based on 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. Depending on institutional guidelines, anesthesia may be used for the LP procedure or for the sham procedure, following institutional procedures. Subjects will be encouraged to lie down flat for 1 hour following injection of the study treatment, if possible. Prior to each injection, 5 mL of CSF fluid will be collected for analyses. CSF will be used for ISIS 396443 PK analyses. Upon consent, extra CSF will be stored for optional future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel) or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or other actions of ISIS 396443 with CSF constituents. CSF analyses and data presentation will be conducted in a blinded manner.

The volume of the injection, and thus, the dose, will be adjusted for the subject's age on the day of dosing, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling (Table 1). Thus, younger subjects will be given a lower dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for a 2-year-old child to adult.

11.1.2. Sham Procedure

In Part 1 of the study, subjects randomized to the sham procedure control group will undergo a sham procedure, rather than study treatment administration, on Study Days 1, 15, 29, 64, 183,

and 302. Details regarding the sham procedure will be provided in the DHA. The sham procedure will be administered by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, study coordinator, or outcomes assessors). The sham procedure will be performed in a dedicated room, and key study personnel and the parent or legal guardian will not be present during the procedure to ensure blinding.

In general, the sham procedure will consist of a small needle prick on the lower back at the location where the LP injection is normally made. The needle will break the skin, but no LP injection or needle insertion will occur. The needle prick will be covered with the same bandage that is used to cover the LP injection normally, thus simulating the appearance of an LP injection. If institutional guidelines require the use of anesthesia or sedation for an LP procedure in ISIS 396443-treated subjects, then 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. The study subject will be kept in the procedure room for the same amount of time that subjects administered study treatment are kept, thus simulating the time period of the study treatment administration procedure.

Study treatment and sham kits will be packaged in a blinded fashion. Blinded kits for the sham procedure contain artificial CSF (5.0 mL solution per 6 mL vial) that will not be injected but will be used to simulate CSF samples for that subject.

11.2. Modification of Dose and/or Treatment Schedule

No adjustment of dose is permitted. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted but must be approved by the Medical Monitor.

11.3. Precautions

There are no protocol-required treatment precautions.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Screening and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

Allowed Concomitant Therapy

Throughout the study, Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

Disallowed Concomitant Therapy

Subjects are prohibited from receiving other experimental agents, including gene therapy, during the study. This includes marketed agents at experimental doses that are being tested for the treatment of SMA (e.g., albuterol/ salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea).

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and the Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2).

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or medically qualified staff. Study treatment is to be dispensed only for subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial should not be used for another subject.

12.1. Study Treatment

ISIS 396443 is formulated as an isotonic solution at 2.4 mg/mL and is provided as a 5.0-mL fill volume in a 6-mL clear glass vial. ISIS 396443 drug product contains the heptadecasodium salt of an 18-base residue phosphorothioate oligonucleotide.

ISIS 396443 active drug is manufactured by Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, drug identifier, and quantity of dosage units, lot number, and other pertinent information in accordance with local laws. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration date.

For Part 1 of the study, the study drug (ISIS 396443) and sham kits will be packaged in a blinded fashion. Blinded kits for sham procedure contain artificial CSF provided as 5.0 mL solution per 6 mL vial that will not be injected but will be used to simulate CSF samples for a subject.

For Part 2 of the study, the study drug (ISIS 396443) kits will be packaged in an open-label fashion.

12.1.1. Study Treatment Preparation

The individual preparing ISIS 396443 or artificial CSF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, do not use it. The vials in question should be saved at the study site and the problem immediately reported to the Sponsor (or designee).

12.1.2. Study Treatment Storage

Study treatment must be stored in a secure location.

ISIS 396443 is to be protected from light and stored long term at 2°C to 8°C in a locked refrigerator with limited access. For additional information on storage requirements, follow the instructions provided in the DHA.

12.1.3. Study Treatment Handling and Disposal

The Investigator must return all used and unused vials of ISIS 396443 and artificial CSF as instructed by the Sponsor (or designee).

If any used ISIS 396443 or artificial CSF supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor (or designee), by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor (or designee) must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Study Treatment Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of ISIS 396443 or artificial CSF supplied, dispensed, and subsequently destroyed or returned to the Sponsor (or designee). A written explanation must be provided for any discrepancies.

13. EFFICACY, PHARMACOKINETIC, AND IMMUNOGENICITY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all efficacy assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of ISIS 396443:

- Ventilator use
- HINE (Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

13.2. Pharmacokinetic (ISIS 396443 Concentration) Assessments

The following tests will be performed to assess the PK of ISIS 396443:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

13.3. Immunogenicity Assessments

The following test will be performed to assess the immunogenicity of ISIS 396443:

- Anti-ISIS 396443 plasma antibody concentrations

14. SAFETY ASSESSMENTS

See Section 4.2 (Table 2, Table 3, and Table 4) for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of ISIS 396443:

- Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes)
- AEs, including SAEs
- Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide)
- Weight
- Physical examinations
- Medical history
- 12-Lead ECGs
- Use of concomitant medications

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed to evaluate the safety profile of ISIS 396443:

- Blood chemistry: total protein, albumin, creatinine, cystatin C, creatine phosphokinase, blood urea nitrogen, total bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, calcium, phosphorus, chloride, sodium, potassium
- Hematology: red blood cells, hemoglobin, hematocrit, platelets, white blood cells, white blood cell differential
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject's legally authorized representative and/or main caregiver(s) must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Abnormal laboratory findings that are considered by the Investigator as not clinically significant should not be reported as AEs. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of >24 hours to a medical facility and does not qualify as an AE
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. 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 site 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 consent from the subject's parent or legal guardian to participate in the study.
- The condition requiring 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 parent's or legal guardian's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Related	There is clear evidence that the event is related to the use of the investigational drug (e.g., confirmation by positive re-challenge 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 administration of the investigational drug.
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 investigational drug 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; therefore, the Investigator believes no relationship exists between the event and the investigational drug.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
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.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor (or designee) according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

For subjects who receive study treatment, any AE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment injection or sham procedure. For subjects who never receive study treatment, no AEs need to be recorded on the applicable CRF.

15.3.2. Serious Adverse Events

For subjects who receive study treatment, any SAE experienced between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) will be recorded on an SAE form and on the applicable CRF, regardless of the severity of the event or its relationship to study treatment. For subjects who never receive study treatment, any SAE occurring between the time of signing the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment; however, the SAE does not need to be recorded on the applicable CRF.

SAEs must be reported to the safety vendor listed in the Study Reference Guide within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until their Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2). Thereafter, the event should be reported as described in the Study Reference Guide only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the safety contact as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject's parent or legal guardian has signed the ICF and Part 2 Final Follow-up Evaluation/Telephone Call (or End of Part 1 Evaluation, if the subject does not enroll in Part 2) must be reported as described in the Study Reference Guide, within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** as described in the Study Reference Guide regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form as described in the Study Reference Guide.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports as described in the Study Reference Guide. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor (or designee) to be related to the study treatment administered.

The Sponsor (or designee) will report SUSARs to the appropriate regulatory authorities and to Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol; an overdose must be documented as a protocol deviation. A brief description should be provided in the deviation form, including whether the subject was symptomatic (with a list of symptoms) or asymptomatic. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be reported to the Medical Monitor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Medical Monitor even if the overdose does not result in an AE. If an overdose results in an AE, then the AE must be recorded. If an overdose results in an SAE, then the SAE form must be completed and faxed as described in the Study Reference Guide. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.2. 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 [redacted], MD, Office: [redacted], Mobile: [redacted], Fax: [redacted], [redacted] (or [redacted] medical emergency: [redacted] or [redacted]) or [redacted], MD at [redacted].

15.4.2.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator (or designee) should attempt to contact the blinded Biogen MA Medical Director or blinded [redacted] Medical Monitor to discuss the emergency

within 24 hours. In these instances, the Investigator (or designee) may access the subject's treatment assignment by IRT.

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 personnel involved with the analysis and conduct of the study.

15.5. Safety Responsibilities

15.5.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to 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 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.

15.5.2. The Sponsor

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.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Part 1 and Part 2 will be analyzed separately. For Part 1, in general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category. For Part 2, no formal statistical analyses will be performed. Descriptive statistics will be presented for safety and efficacy data collected.

For the Part 1 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 1. For the Part 2 analysis, baseline is defined as the last nonmissing assessment prior to the first dose of study treatment in Part 2. In addition, a pooled analysis incorporating data from both Part 1 and Part 2 will be conducted to characterize the safety profile of ISIS 396443. For subjects on active treatment in Part 1, safety data from both Part 1 and Part 2 will be included in the pooled analysis and the Part 1 baseline will used for those subjects in the pooled analysis. For subjects on sham procedure in Part 1, only safety data from Part 2 will be included in the pooled analysis and the Part 2 baseline will be used for those subjects in the pooled analysis.

Concomitant medication usage for each subject will be listed for review.

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

16.2. Safety and Tolerability

Safety is the primary objective for the study. All AEs, laboratory abnormalities, ECGs, and vital signs will be evaluated for safety.

16.2.1. Analysis Population

Safety analyses will be conducted in the safety population. This safety set will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure. Treatment duration and amount of study treatment received will be summarized by treatment group.

16.2.2. Methods of Analysis

16.2.2.1. Neurological Examinations

Neurological examination findings will be listed for review, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with

shifts from baseline normal to each of the categorical values denoting normal, abnormal, and abnormal (not AE) will be summarized.

16.2.2.2. Adverse Events

All AEs will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment emergent if it was present prior to the first dose of study treatment and subsequently worsened, or was not present prior to the first dose of study treatment but subsequently appeared. The incidence of treatment-emergent AEs will be summarized overall, by severity, and by relationship to study treatment. A subject having the same AE more than once will be counted only once in the incidence for that event. The occurrence of the AE with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the AE with the strongest relationship to study treatment will be used in the calculation of incidence by relationship to study treatment.

All treatment-emergent AEs and SAEs will be summarized for each treatment group 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, SAEs, early withdrawals from study treatment and from study due to AEs will be provided.

16.2.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented. Summary statistics for actual values and change from Baseline will also be presented.

16.2.2.4. ECGs

ECG results will be presented by subject, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal clinically significant, and abnormal (not clinically significant) will be summarized.

16.2.2.5. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using study visit for each treatment group. These safety variables will also be presented over time after study treatment administration, as appropriate. Laboratory parameters will also be summarized using shift tables, as appropriate.

16.3. Efficacy

16.3.1. Analysis Population

The exploratory analysis of efficacy will be performed on the intent-to-treat population. The intent-to-treat population is defined as all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

16.3.2. Methods of Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

16.4. Pharmacokinetics

16.4.1. Analysis Population

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

16.4.2. Methods of Analysis

Plasma PK parameters, as applicable, and ISIS 396443 concentrations in plasma and CSF for the PK population will be summarized using descriptive statistics and, where warranted, presented graphically.

16.5. Immunogenicity

16.5.1. Analysis Population

The analysis population for immunogenicity will include all subjects with available immunogenicity data.

16.5.2. Methods of Analysis

Results from the immunogenicity analyses for anti-ISIS 396443 plasma antibody status and titer will be summarized at the specified visits.

16.6. Interim Analyses

No formal interim analyses are planned. However, if the Sponsor decides to terminate Part 1 early, data prior to the unblinding of the first subject in Part 1 may be archived; no analyses are planned to be conducted based on the archived data. Full analysis of Part 1 data will be done following database lock at the end of Part 1.

16.7. Sample Size Considerations

Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

17. ETHICAL REQUIREMENTS

The Sponsor, [redacted] (the contract research organization [CRO] for this study), and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor (or designee) will submit documents on behalf of the investigational sites in countries other than the US.

If the Investigator makes any changes to the ICF, the Sponsor (or designee) must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor (or designee). After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor (or designee).

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor (or designee) must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

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).

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will not be collected for the purposes of data analysis during the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent, if applicable, must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent, if applicable, must also be documented in the subject's medical record.

17.4. 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, subjects' race and ethnicity will not 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. Sponsor, 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.

17.5. Compensation for Injury

The Sponsor (or designee) maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. 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).

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit conducted by the Sponsor (or designee). This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

CRFs will be not be used as source data. Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. 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 the Sponsor. Ionis is the Sponsor of the study in the United States and Biogen Idec Research Limited is the Sponsor of the study in the Rest of World. Biogen will be responsible for managing the study globally. All financial details are provided in the separate contract(s) between the institution, Investigator, and the Sponsor.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

The Sponsor may transfer any or all of its study-related responsibilities to a CRO and other third parties; however, the Sponsor retains overall accountability for these activities.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool that is developed and supported by an electronic data capture vendor and configured by Sponsor or CRO.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory will be selected by the Sponsor to analyze all hematology, blood chemistry, urine, and CSF samples collected at all study sites. Local laboratories may be used to accommodate acute or urgent needs as discussed in in the Study Reference Guide.

During the Part 1 Screening Period, a blood sample will be collected for *SMN2* copy number analysis by the central laboratory only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

19.2. Study Committees

Safety data will be reviewed on an ongoing quarterly basis throughout Part 1 of the study by an independent DSMB. The DSMB will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 396443 during the study. Based on its ongoing assessment of the safety and tolerability of ISIS 396443, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor (or designee) may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4" 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 (Print)

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
USA

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 232SM202

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

EUDRA CT NO **2014-003657-33**

DATE: 31 October 2014
Version 1
FINAL

SIGNATURE OF BIOGEN IDEC CLINICAL TRIAL REVIEW BOARD CHAIR

Protocol 232SM202, Version 1, was approved by:

[redacted]

03-Nov-2014

[redacted], MD

Date

[redacted]

Biogen Idec MA Inc.

SIGNATURE OF BIOGEN IDEC THERAPEUTIC AREA HEAD

Neurology

Protocol 232SM202, Version 1, was approved by:

[redacted]

06 NOV 2014

[redacted], MD

Date

[redacted]

Biogen Idec MA Inc.

SIGNATURE OF ISIS PHARMACEUTICALS, INC. CHIEF MEDICAL OFFICER

Protocol 232SM202, Version 1, was approved by:

[redacted], MD

10/31/14
Date

Isis Pharmaceuticals, Inc.

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1. SPONSOR INFORMATION

Isis Pharmaceuticals, Inc. (Isis) is the Sponsor of the study in the United States. Biogen Idec Inc. (Biogen Idec) is the Sponsor of the study in the Rest of World. Biogen Idec (or designee) will be responsible for managing the study globally.

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142
USA

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
USA

Biogen Idec Australia Pty Ltd
Suite 1, Level 5
123 Epping Road
North Ryde, NSW 2113
Australia

Primary contact for urgent medical issues:

[redacted]: [redacted], MD
Cell phone: [redacted]
[redacted] medical emergency: [redacted]
or [redacted]

Secondary contact for urgent medical issues:

Biogen Idec [redacted]: [redacted], MD, MPH
Cell phone: [redacted]

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

2. LIST OF ABBREVIATIONS

2′-MOE	2′-O-(2-methoxyethyl)
AE	adverse event
ASO	antisense oligonucleotide
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
GCP	Good Clinical Practice
HINE	Hammersmith Infant Neurological Examination
ICF	informed consent form
ICH	International Conference on Harmonisation
IRT	interactive response technology
LP	lumbar puncture
mRNA	messenger ribonucleic acid
PK	pharmacokinetic(s)
RNA	ribonucleic acid
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SUSAR	suspected unexpected serious adverse reaction

3. SYNOPSIS

This is a brief summary. For details, refer to the body of the protocol.

Protocol Number:	232SM202
Protocol Title:	A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4
Version Number:	1
Name of Study Treatment:	ISIS 396443 (BIIB058)
Study Indication:	Spinal muscular atrophy (SMA)
Phase of Development:	2
Rationale for the Study:	The rationale is to assess the safety and tolerability and evaluate the utility of selected exploratory efficacy endpoints in subjects with SMA treated intrathecally with ISIS 396443 who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4.
Study Objectives and Endpoints:	**Objectives** Primary objective: • To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 Secondary objective: • To examine the pharmacokinetics (PK) of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 Exploratory objective: • To explore the efficacy of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

Endpoints

Primary endpoints:

The primary safety and tolerability endpoints of this study are as follows:

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline in neurological examination outcomes

Secondary endpoint:

The secondary endpoint is as follows:

- ISIS 396443 concentrations in plasma and cerebrospinal fluid (CSF)

Exploratory endpoints:

The exploratory efficacy endpoints of this study are as follows:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE)
- Change from baseline in growth parameters through final safety follow-up visit
- Clinical Global Impression of Change (physician and caregiver assessment) through final safety follow-up visit

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

Study Design:

This randomized, double-blind, sham-procedure controlled study will assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 over a period of 14 months (from the first dose until the last safety follow-up visit). Up to 21 subjects will be randomized in a ratio of 2:1 to receive ISIS 396443 by intrathecal lumbar puncture (LP) injection or a sham-procedure control. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus $\leq$6 months.

After informed consent is obtained, subjects will undergo a screening evaluation no greater than 28 days prior to administration of the first dose. Subjects who meet the eligibility criteria will be randomized to study treatment. Subjects will be admitted to the study site on Study Day 1, undergo predose evaluations, and then receive an LP injection of

study treatment or sham procedure. Subjects will return to the study site on Days 15, 29, 64, 183, and 302 for follow-up evaluations and subsequent injections or sham procedures. For subjects receiving ISIS396443, a CSF sample will be taken predose on each injection day in a manner that maintains the blind.

After the dosing or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours for safety monitoring. Following all subsequent injections, the subjects will remain at the study site for at least 6 hours after the procedure for safety monitoring.

Safety monitoring will occur on the day following each injection of study treatment or sham procedure. Subjects receiving the dosing or sham procedure on Days 15, 29, 64, 183, and 302 will be monitored by telephone contact on Days 16, 30, 65, 184, and 303.

In addition, subjects will also be monitored through telephone contact throughout the duration of the study.

A final follow-up evaluation will occur approximately 4 months after the last dose or sham procedure. Subjects who terminate early from the study will be encouraged to complete the early termination study procedures and assessments at the time of withdrawal. After treatment and the final follow-up evaluation, all eligible subjects may elect to enroll in an open-label treatment extension study, pending study approval by the ethics committees and the appropriate regulatory authorities. This will be done without unblinding the subject's treatment group.

Rationale for Dose and Schedule Selection:

A scaled equivalent dose of 12 mg, ISIS 396443 will be administered at each of the 6 doses (i.e., on Study Days 1, 15, 29, 64, 183, and 302) over a dosing period of approximately 10 months.

The volume of the injection will be adjusted based on the subject’s age on the day of dosing as shown in Table 1, such that each subject will receive a 12 mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower absolute mg dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for 2 years of age to adult.

The dose regimen and the dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dose intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443 to date. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue

concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by LP. The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. Maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months.

Table 1 ISIS 396443 Dose Volume To Be Injected

Age	Estimated CSF Volume (mL)	Injection Volume (mL)	Dose (mg)
0-3 months (0-90 days)	120	4	9.6
3-6 months (91-182 days)	130	4.3	10.3
6-12 months (183-365 days)	135	4.5	10.8
12-24 months (366-730 days)	140	4.7	11.3
>24 months (>730 days)	150	5.0	12.0

Study Location:	Global, multicenter
Number of Planned Subjects:	Up to 21 subjects are planned (14 ISIS 396443; 7 sham procedure)
Study Population:	This study will be conducted in subjects who have clinical signs and symptoms of SMA at ≤6 months of age or at >6 months of age and who are not eligible for the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4. Detailed criteria are described in Section 8.
Treatment Groups:	Subjects will receive either ISIS 396443 or sham-procedure control intrathecally in a 2:1 ratio. Randomization will be balanced for the stratification factor (age of symptom onset >6 months versus ≤6 months). A single dose level of 12 mg ISIS 396443 will be scaled by age at the time of dosing for each subject.
Duration of Treatment and Follow-up:	For subjects who meet the eligibility criteria and enroll in the study, the study duration will be approximately 15 months (450 days) and will include a Screening Period of no greater than 28 days, a 302-day Treatment Period, and a final follow-up evaluation approximately 4 months after the last dose. Subjects who terminate early from the study will be encouraged to complete the early termination study procedures and assessments at the time of withdrawal.
Criteria for Evaluation:	The criteria for evaluation are as follows:
Safety:	• Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes) • AEs, including SAEs • Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide) • Weight • Physical examinations • Medical history • 12-Lead ECGs

- Use of concomitant medications
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)

Pharmacokinetics:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

Efficacy:

- Ventilator use
- HINE (Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

Immunogenicity:

- Anti-ISIS 396443 plasma antibody concentrations

Statistical Methods:

Analysis Population

The intent-to-treat population is defined as all subjects who are randomized, receive at least 1 dose of study treatment or sham procedure, and have at least 1 postbaseline evaluation.

The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure.

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

Safety Analysis

The analysis of safety will be performed on the safety population. The incidence of treatment-emergent AEs and SAEs will be tabulated. Changes from baseline in clinical laboratory parameters, vital signs, and ECG parameters will be summarized. Incidence of clinically relevant changes from baseline in vital signs and ECGs will be summarized. Laboratory parameters will also be summarized using shift tables.

PK Analysis

Summary statistics for plasma and CSF concentrations of ISIS 396443 will be provided.

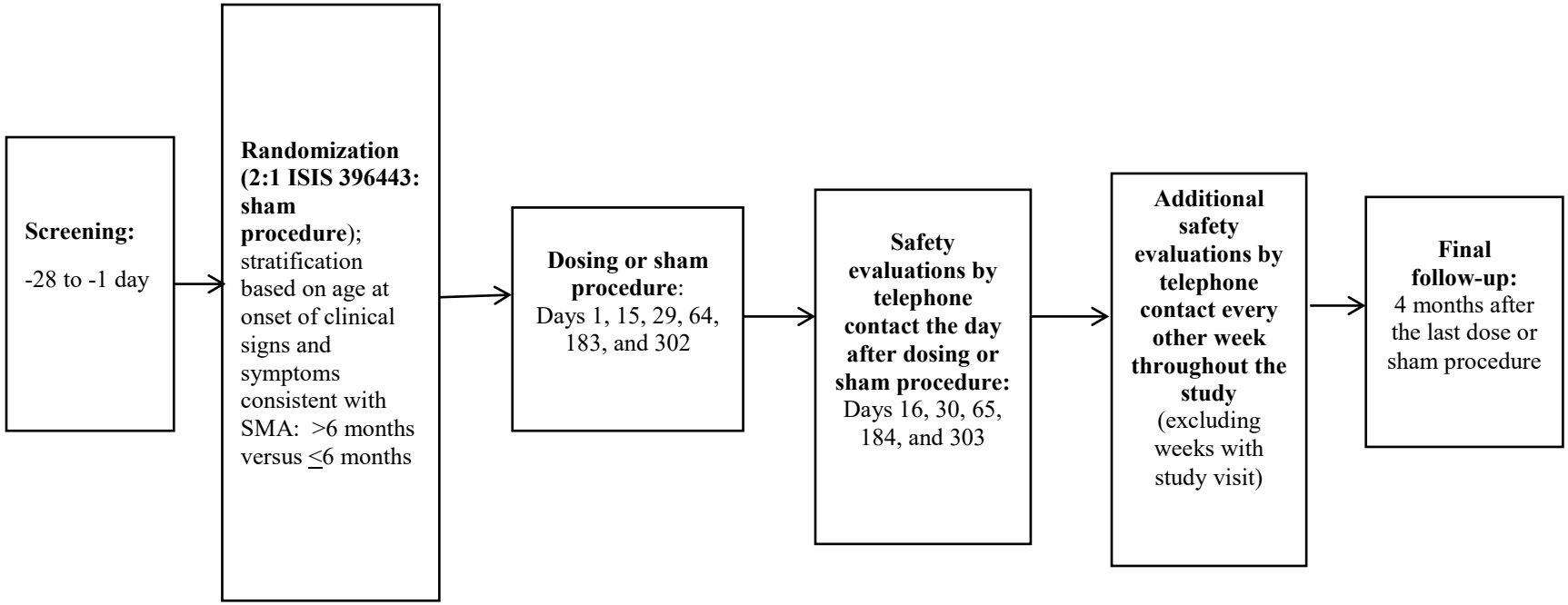
Exploratory Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the

	proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.
Interim Analysis:	No interim analyses will be conducted.
Sample Size Determination:	Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.
Study Stopping Rules:	The Sponsor may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 232SM202

4.1. Study Schematic



4.2. Schedule of Events

Note: After the first injection of study treatment or sham procedure, subjects will be monitored by phone every other week (excluding weeks in which there is a study visit) throughout the study. At telephone contact, changes in concomitant medications and AEs will be recorded, as well as information on the subject's daily ventilator/bi-level positive airway pressure (Bi-PAP) use, and health status.

Table 2: Schedule of Activities

Study Period	**Screen**[1]	**Treatment/Follow-Up**																
Study Day	**Days -28 to -1**	**Day 1**			**Day 2**[2]	**Day 15 (±1 day)**			**Day 16**[2]	**Day 29 (±1 day)**			**Day 30**[2]	**Days 64, 183, 302 (±7 days)**			**Days 65, 184, 303**[2]	**Final Follow-Up (Day 422 [±7 days])**[3] **or Early Termination**[4]
		Predose	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Vital Signs[5]	X	X		4X[6]	X[7]	X		X		X		4X[6]		X		4X[6]		X
Weight	X	X			X	X				X				X				X
Growth Parameters[8]	X	X				X				X				X				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
Neurological Examination[9]	X	X		X[10]	X	X		X[10]		X		X[10]		X		X[10]		X
ECG	X				X							X						X
Safety Laboratory Tests[11]	X													X[12]				X
Coagulation Laboratory Tests	X																	

Study Period	Screen[1]	Treatment/Follow-Up																
Study Day	Days -28 to -1	Day 1			Day 2[2]	Day 15 (±1 day)			Day 16[2]	Day 29 (±1 day)			Day 30[2]	Days 64, 183, 302 (±7 days)			Days 65, 184, 303[2]	Final Follow-Up (Day 422 [±7 days])[3] or Early Termination[4]
		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		Predose	LP	Postdose		
Immunogenicity Sample		X												X				X
CSF PK[13]		X				X				X				X				
Plasma PK				X[14]										X[15]				X
Study Treatment Injection or Sham Procedure			X				X				X				X			
Inpatient Stay[16]				X														
Telephone Contact for Safety Monitoring[2]									X				X				X	
HINE Motor Milestone		X												X				X
Clinical Global Impression of Change		X												X				X
Con Med Recording[17]	X ---------- X																	
Adverse Event Collection[18]	X ---------- X																	

AE = adverse event; Con Med = concomitant medication; CSF = cerebrospinal fluid; ECG = electrocardiogram; LP = lumbar puncture; PK = pharmacokinetic(s); SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

[1] A blood sample will be collected at Screening for *SMN2* copy number only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

[2] After the injection of study treatment or sham procedure on Day 1, subjects will remain at the study site for at least 24 hours (Day 2) for safety monitoring. On the day following the injection of study treatment or sham procedure on Days 15, 29, 64, 183, and 302, there will be safety monitoring through telephone contact. During that telephone contact (i.e., Days 16, 30, 65, 184 and 303), changes in concomitant medications and AEs, information on the subject's daily ventilator/Bi-PAP use, and health status will be recorded.

[3] The final follow-up visit will occur 4 months (Day 422 [±7 days]) after the last injection of study treatment or sham procedure.
[4] Subjects who terminate early will be encouraged to complete the safety evaluations scheduled for the final follow-up visit.
[5] Vital signs include resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide. Pulse oximetry and transcutaneous carbon dioxide will be measured predose at each visit. For subjects who are not receiving noninvasive ventilation, pulse oximetry will be measured overnight once a week at home.
[6] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected at 4 timepoints: 1, 2, 4, and 6 hours (all ±15 minutes) after the injection of study treatment or sham procedure.
[7] Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry) will be collected within 20-24 hours after the injection of study treatment or sham procedure.
[8] At the visits scheduled for injection of study treatment or sham procedure, subjects will be assessed for the following growth parameters: body length, head circumference, chest circumference, and arm circumference.
[9] Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes.
[10] Neurological examinations will occur between 4 to 6 hours after the injection of study treatment or sham procedure.
[11] Serum chemistry, hematology, and urinalysis panels.
[12] Samples for safety laboratory tests will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only.
[13] Refer to Table 3 for CSF PK sample schedule. The CSF samples will be analyzed for ISIS 396443 concentrations. The remaining CSF sample will be stored for optional future biomarker analyses.
[14] Blood samples for PK assessment will be collected 4 hours (±1 h) after the injection of study treatment or sham procedure only on Day 1. Refer to Table 3 for the plasma PK sample schedule.
[15] Blood samples for PK assessment will be collected before the injection of study treatment or sham procedure on Days 64 and 183 only. Refer to Table 3 for the plasma PK sample schedule.
[16] Overnight stay (at least 24 hours) is required after the first injection of study treatment or sham procedure. Following all subsequent injections or sham procedures, a stay of at least 6 hours at the study site is required; overnight stays are optional on these days.
[17] In addition to concomitant medications, ancillary procedures will be recorded.
[18] AEs and SAEs will be collected in the case report form from the time of signing of the informed consent form as described in Section 15.3.1 and Section 15.3.2.

Table 3 Pharmacokinetic Sampling Schedule[1]

Treatment Period	Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[2]
Multiple Dose: LP Injection	Day 1	Predose	NA	0.5
		4 h (±1 h) postdose	0.5	NA
	Day 15	Predose	NA	0.5
	Day 29	Predose	NA	0.5
	Day 64	Predose	0.5	0.5
	Day 183	Predose	0.5	0.5
	Day 302	Predose	NA	0.5
	Final Follow-Up	NA	0.5	NA

CSF = cerebrospinal fluid; h = hour; min = minutes; LP = lumbar puncture; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); SMA = spinal muscular atrophy.

[1] Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.

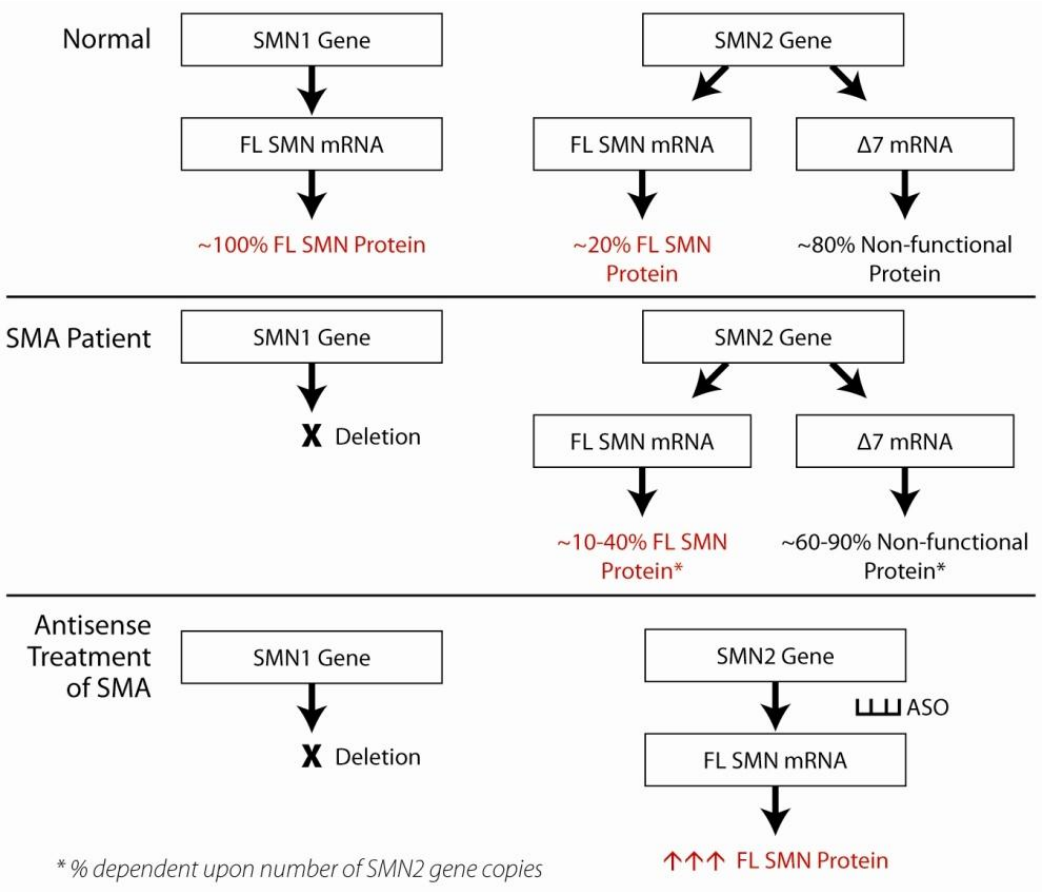
[2] Upon consent, the collected CSF samples from the study subjects will be stored for future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel), for profiling of study drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and immunogenicity assessments (including assay development and validation purposes), or for assessing other actions of ISIS 396443 with plasma and CSF constituents.

5. INTRODUCTION

ISIS 396443 is a uniformly modified, 2′-*O*-(2-methoxyethyl) (2′-MOE), antisense oligonucleotide (ASO) drug in development for the treatment of spinal muscular atrophy (SMA) due to genetic defects in the survival motor neuron 1 (*SMN1*) gene.

ASOs are short synthetic strings of nucleotides designed to alter the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein. In patients with SMA, the number of survival motor neuron 2 (*SMN2*) gene copies and the resulting amount of survival motor neuron (SMN) protein are correlated with disease onset and severity. A therapeutic approach predicted to benefit patients with SMA is to increase the levels of full-length SMN2 pre-messenger ribonucleic acid (mRNA) by restoring the splicing pattern that gives rise to full-length SMN2 mRNA, thus increasing full-length SMN protein levels and SMN protein activity. ISIS 396443 is designed to bind to intron 7 of the SMN2 pre-mRNA, restoring the splicing pattern that gives rise to full-length SMN2 mRNA and thus increases full-length SMN protein levels (Figure 1).

Figure 1: Antisense Oligonucleotide Therapeutic Approach for Treatment of Spinal Muscular Atrophy



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.

Overview of 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. With an incidence of 1:6000 to 1:10,000 live births, SMA is the most common genetic cause of infant mortality, and a major cause of childhood morbidity due to weakness, in developed countries. 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 I 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 the age of 2 years. Patients with Type II SMA are able to sit but never walk unaided, with symptoms typically presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but may become severely and increasingly disabled. Patients with Type IV or adult-onset SMA have an age of onset over 18 years and have normal life expectancies.

SMA is caused by loss of SMN protein due to a homozygous deletion or mutation or compound heterozygous mutation in the *SMN1* gene on chromosome 5q11-q13. Humans have a duplication of the chromosome region where *SMN1* is found, resulting in a second copy of the gene, *SMN2*. In *SMN2*, a C to T nucleotide substitution in exon 7 results in an alternative splicing event such that the majority of transcripts produced (~90%) lack exon 7, and a defective truncated protein is produced. The remainder, SMN2 transcripts containing exon 7, produces a full-length protein product identical to the SMN1 protein, since the C to T substitution is silent. Humans have a variable copy number of the *SMN2* gene (0 to 8 copies). The number of *SMN2* copies and the resulting amount of full-length SMN protein expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlate with SMA disease severity; thus, *SMN2* is a key modifier of disease phenotype [Coovert 1997], [Lefebvre 1997], [Feldkötter 2002], [Prior 2004].

Current Therapies for Spinal Muscular Atrophy

There are currently no approved therapies for SMA. Current medical care is supportive and focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery [Wang 2007].

5.1. Profile of Previous Experience With ISIS 396443

Nonclinical Experience

ISIS 396443 was identified after an extensive screen of greater than 500 2′-MOE oligonucleotides in reporter gene assays, in vitro splicing assays, and SMA patient fibroblasts [Hua 2007], [Hua 2008]. Data have shown that ISIS 396443 promotes a concentration-dependent increase in full-length transcripts (including exon 7) in patient fibroblast cells, achieving >90% full-length SMN2 transcripts, and forms nuclear structures called gems, known to contain SMN protein [Liu and Dreyfuss 1996]. In a mild mouse model of SMA, ISIS 396443 promoted inclusion of exon 7 in the SMN2 transgene in a variety of peripheral tissues when dosed systemically [Hua 2008] and in central nervous system (CNS) tissue, including the spinal cord, when injected into the lateral ventricle [Hua 2010]. ISIS 396443 produced >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 CNS delivery of drug produced a dose-dependent effect on SMN2 exon 7 inclusion, SMN protein production, and survival. These mice treated with ISIS 396443 demonstrated improved weight gain; improvements in muscle morphology, muscle strength, and motor coordination; and improved morphology of the motor neuron junctions [Passini 2011]. Furthermore, ISIS 396443 was shown to distribute widely in the CNS after intrathecal administration in monkeys [Passini 2011].

The pharmacokinetics (PK) and toxicity of ISIS 396443 were assessed after a single intrathecal lumbar bolus injection (1 to 7 mg) in adult monkeys, after 14 weeks (with a 4-week interim sacrifice) of repeated intrathecal lumbar bolus injections (0.3 to 3 mg/week or every other week) in juvenile monkeys, and after 53 weeks of repeated intrathecal lumbar bolus injections in juvenile monkeys. In addition, a dedicated PK study in adult monkeys was performed to assess the half-life of ISIS 396443 in cerebrospinal fluid (CSF), tissues, and plasma.

See the Investigator's Brochure for detailed information on nonclinical studies.

Clinical Experience

ISIS 396443 has been evaluated in 2 completed open-label studies: ISIS 396443-CS1 and ISIS 396443-CS10.

ISIS 396443-CS1 is a single-ascending-dose, phase 1 study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with SMA. A single dose of ISIS 396443 was administered by intrathecal injection to subjects with SMA who were 2 to 14 years of age. Four doses (1, 3, 6, and 9 mg) were evaluated sequentially. Each dose was studied in a cohort of 6 or 10 subjects, where all subjects received study treatment. In this study, all subjects completed dosing and follow-up visits per protocol. Overall, ISIS 396443 was well tolerated, and no safety concerns were identified up to the 9-mg dose. No serious adverse events (SAEs) or dose-limiting toxicities were reported in ISIS 396443-CS1. Adverse events (AEs) were mild or moderate in severity, and there was no relationship with ISIS 396443 dose. In addition, no ISIS 396443-related adverse changes in neurological examinations were reported despite intensive monitoring during the immediate postdosing period. CSF and plasma drug concentrations observed were generally consistent with predictions made from nonclinical monkey studies.

ISIS 396443-CS10 was a single-dose, phase 1 redosing study to assess the safety, tolerability, and PK of ISIS 396443 in subjects with SMA who previously participated in Cohorts 2, 3, and 4 of ISIS 396443-CS1.

ISIS 396443 is also being evaluated in 5 ongoing studies: ISIS 396443-CS2, ISIS 396443-CS12, ISIS 396443-CS3A, ISIS 396443-CS3B, and ISIS 396443-CS4.

ISIS 396443-CS2 is an open-label, multiple-ascending-dose, phase 1/2a study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with SMA. Multiple doses of ISIS 396443, ranging from 3 to 12 mg, are being administered by intrathecal injection to 2- to 15-year-old subjects with SMA.

ISIS 396443-CS12 is an open-label, multiple-dose, phase 1 study to assess the safety and tolerability of a single intrathecal dose of ISIS 396443 (12 mg) in subjects with SMA who previously participated in either ISIS 396443-CS2 or ISIS 396443-CS10.

ISIS 396443-CS3A is an open-label, multiple-dose, phase 2 study designed to assess the safety, tolerability, and PK of ISIS 396443 in subjects with infantile-onset SMA. Multiple doses of ISIS 396443 are being administered by intrathecal injection to symptomatic infants with SMA ≤7 months of age. Two doses (6- and 12-mg dose equivalent scaled by CSF volume) are being evaluated sequentially.

ISIS 396443-CS3B is a randomized, double-blind, sham-procedure controlled, phase 3 study to assess the clinical efficacy and safety of ISIS 396443 in subjects with infantile-onset SMA (onset of clinical signs and symptoms consistent with SMA at ≤6 months of age) who have 2 *SMN2* copies. A dose level of 12 mg ISIS 396443 (scaled to equivalent dose by age) or sham procedure will be administered at each of 6 doses over a dosing period of 10 months.

ISIS 396443-CS4, is a randomized, double-blind, sham-procedure controlled, phase 3 study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in subjects with later-onset (onset of clinical signs and symptoms consistent with SMA at >6 months of age). A dose of 12 mg ISIS 396443 or sham procedure will be administered at each of 4 doses over 15 months to 2-to 12 year old subjects with SMA.

5.2. Study Rationale

There is reasonably high genotype-phenotype correlation such that the *SMN2* copy number can be used to predict the severity of disease (moderate or severe) with approximately 80% to 85% accuracy [Burghes and Beattie 2009; Prior 2010; Swoboda 2005]. Evaluation of relationship between categories of functional status and number of *SMN2* copies have indicated that as *SMN2* copy number increases so does functional status [Feldkötter 2002; Swoboda 2005]. However, assessment of various outcome measures over time have indicated that there is overlap among SMA types, and values vary widely with age and gross motor functional status with an overall age dependent decline [Swoboda 2005].

The intent of this study is to assess safety, tolerability, and explore the utility of selected efficacy endpoints in subjects who have onset of clinical signs and symptoms that are consistent with SMA at age ≤6 months or >6 months. These subjects have either 2 or 3 *SMN2* copies and are not eligible to participate in the 2 pivotal clinical studies, ISIS 396443-CS3B and ISIS 396443-CS4. ISIS 396443-CS3B is a randomized, double-blind, sham-procedure controlled study investigating the therapeutic benefit of ISIS 396443 in subjects with 2 *SMN2* copies who have onset of clinical signs and symptoms of SMA at ≤6 months of age. ISIS 396443-CS4 is a randomized, double-blind, sham-procedure controlled study investigating the therapeutic benefit of ISIS 396443 in subjects who have onset of clinical and signs and symptoms of SMA at >6 months of age. To be consistent with the study design of the 2 pivotal clinical studies and to understand the safety and tolerability of ISIS 396443 compared with natural history, the present study is designed to include sham-procedure control for an unbiased assessment of safety, tolerability, and selected efficacy endpoints in the study population that is not eligible to participate in the studies ISIS 396443 CS3B or ISIS 396443 CS4. The design of the present

study will also allow exploration of the safety and tolerability of a higher dose regimen in subjects who have onset of clinical signs and symptoms at >6 months of age, but who are not eligible for Study ISIS 396443-CS4.

5.3. Rationale for Dose and Schedule Selection

The ISIS 396443 dose and dose interval for this study were selected based on nonclinical toxicology and PK observations from monkey studies using single-dose and repeat-dosing intrathecal administration, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of ISIS 396443. Based on pharmacology and PK results in SMA transgenic mice, it is estimated that a target spinal cord tissue concentration between 1 and 10 µg/g will produce 50% to 90% SMN2 exon 7 inclusion. Nonclinical studies in juvenile monkeys receiving intrathecal doses of ISIS 396443 showed a resulting gradient of distribution of 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 selected for this multiple-dose clinical study (equivalent to 12 mg of ISIS 396443) 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) after the first dose. The loading dose interval (i.e., doses on Days 1, 15, 29, and 64) was selected based on the nonclinical PK and pharmacology data in order to achieve and maintain ISIS 396443 spinal cord tissue levels that are predicted to be above or within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical tissue concentration), while at the same time considering subject safety and convenience for repeated intrathecal injections by lumbar puncture (LP). The higher number of loading doses would allow for the evaluation of safety and tolerability and preliminary exploratory efficacy endpoints in a broader population of subjects with SMA, including those who have onset of clinical signs and symptoms at >6 months of age but who are not eligible for Study ISIS 396443-CS4. The maintenance dose interval (once every 4 months) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) and was selected to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range. Maintenance doses will be given on Day 183 and Day 302, for a total of 6 doses over approximately 10 months.

ISIS 396443 will be administered as an intrathecal injection. The volume of the injection, and thus the dose, will be adjusted based on the subject's age on the day of dosing as shown in Table 4 , such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling. Thus, younger subjects will be given a lower dose of drug, achieved by injecting a smaller volume that is proportional to the estimated CSF volume for age, such that the dose volume will be equivalent to 5 mL for a 2-year-old child to adult. Dosing instructions and details regarding administration will be provided in the Directions for Handling and Administration (DHA).

Table 4 ISIS 396443 Dose Volume To Be Injected

Age	Estimated CSF Volume (mL)	Injection Volume (mL)	Dose (mg)
0-3 months (0-90 days)	120	4	9.6
3-6 months (91-182 days)	130	4.3	10.3
6-12 months (183-365 days)	135	4.5	10.8
12-24 months (366-730 days)	140	4.7	11.3
>24 months (>730 days)	150	5.0	12.0

Source: [Matsuzawa 2001]
CSF = cerebrospinal fluid.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of the study is:

- To assess the safety and tolerability of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

6.1.2. Secondary Objectives

The secondary objective of this study is:

- To examine the PK of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

6.1.3. Exploratory Objectives

The exploratory objective of this study is:

- To explore the efficacy of ISIS 396443 in subjects with SMA who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4

6.2. Endpoints

6.2.1. Primary Endpoint

The primary safety and tolerability endpoints of this study are as follows:

- Incidence of AEs and SAEs
- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs
- Change from baseline in neurological examination outcomes

6.2.2. Secondary Endpoints

The secondary endpoint of this study is as follows:

- ISIS 396443 concentrations in plasma and CSF

6.2.3. Exploratory Endpoints

The exploratory efficacy endpoints of this study are as follows:

- Change from baseline in ventilator use
- Attainment of motor milestones assessed by Section 2 of the Hammersmith Infant Neurological Examination (HINE)
- Change from baseline in growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio) through final safety follow-up visit
- Clinical Global Impression of Change (physician and caregiver assessment) through final safety follow-up visit

The exploratory immunogenicity endpoint is as follows:

- Plasma antibodies to ISIS 396443

7. STUDY DESIGN

7.1. Study Overview

This phase 2, multicenter, randomized, double-blind, sham-procedure controlled study will assess the safety and tolerability and explore the efficacy of intrathecally administered ISIS 396443 over 14 months (from the first dose until the last safety follow-up visit). Up to 21 subjects will be randomized in a ratio of 2:1 to receive ISIS 396443 by intrathecal (LP injection (n=14) or to a sham-procedure control (n=7). Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months.

If a subject terminates early from the study, they will be encouraged to complete safety assessments as per the final follow-up visit.

See Section 4.1 (Table 2) for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

The study period will consist of a Screening Period, Treatment Period, and post-treatment follow-up evaluation.

7.2.1. Screening

Subject eligibility for the study will be determined within 4 weeks (Day -28 to Day -1) prior to the administration of the first dose or sham procedure and will be confirmed before randomization. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period, at the discretion of the Investigator.

7.2.2. Treatment

Eligible subjects will be admitted to the study site on Study Day 1, undergo predose evaluations, and then receive an LP injection of ISIS 396443 or a sham procedure. After the injection on Day 1, subjects will remain at the study site for at least 24 hours after the procedure for safety monitoring.

Subjects will return to the study site on Days 15, 29, 64, 183, and 302 for follow-up evaluations and subsequent injections of study treatment or sham procedure, for a total of 6 injections or sham procedures over a dosing period of 10 months. During these 5 visits, subjects will remain at the study site for at least 6 hours after the procedure for safety monitoring. An overnight stay is optional, at the discretion of the Investigator. Safety monitoring by telephone contact will occur on the day after injection of study treatment or sham procedure. In addition, the study site will monitor the subject's condition through telephone contact every other week (excluding weeks with study visit), throughout the study period.

A CSF sample for PK analysis and for optional future analyses of biomarkers will be taken before the injection of study treatment or sham procedure on Days 1, 15, 29, 64, 183, and 302 in a manner that protects the blind.

7.2.3. Follow-Up

Subjects will return to the study site for a final follow-up evaluation approximately 4 months (Final Study Visit on Day 422 [±7 days]) after the last dose of study treatment.

Following treatment and the final follow-up evaluation, all eligible subjects may elect to enroll in an open-label treatment extension study, pending study approval by the ethics committees and the appropriate regulatory authorities. This will be done without unblinding the subject's treatment group.

Subjects who prematurely withdraw from the study are to complete the early termination study procedures and assessments at the time of withdrawal.

7.3. Study Stopping Rules

The sponsor may terminate the study at any time by informing Investigators (who will subsequently inform the corresponding ethics committees), and any other applicable regulatory

agencies. Investigators will be notified by the Sponsor if the study is placed on hold, completed, or closed.

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.4. End of Study

The end of study is last subject, last visit.

7.5. Safety Monitoring and Data and Safety Monitoring Board

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor. Safety data will also be reviewed on an ongoing basis by an independent Data and Safety Monitoring Board ([DSMB]; see Section 19.2).

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability of parent(s) or legal guardian(s) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Genetic documentation of 5q *SMA* homozygous gene deletion, mutation, or compound heterozygote.
3. Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age and have documentation of 3 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age, >7 months of age (211 days) at screening, and have documentation of 2 *SMN2* copies.

   OR

   Onset of clinical signs and symptoms consistent with SMA at >6 months of age, are ≤18 months of age at screening, and have documentation of 2 or 3 *SMN2* copies.

4. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either the anesthesiologist or pulmonologist).
5. Medical care, such as routine immunizations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis [palivizumab] if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA, in the opinion of the Investigator.
6. Subjects with 2 *SMN2* copies must reside within approximately 9 hours' ground-travel distance from a participating study site for the duration of the study. Residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor.
7. Able to complete all study procedures, measurements, and visits, and parent or legal guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or at the time point specified in the individual criterion listed:

1. Any previous exposure to ISIS 396443; previous dosing in this study or previous studies with ISIS 396443.
2. Signs or symptoms of SMA present at birth or within the first week after birth.
3. Ventilation for ≥16 hours per day continuously for >21 days at screening.
4. Permanent tracheostomy, implanted shunt for CSF drainage, or implanted CNS catheter at screening.
5. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments.
6. Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 months prior to screening, or hospitalization for surgery planned during the study.
7. Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG, as assessed by the Investigator, at the Screening Visit that would render the subject unsuitable for inclusion.
8. Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening. Any history of gene therapy, prior ASO treatment, or cell transplantation.
9. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or

cachexia, severe anemia) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures.

10. 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 assessments.
11. Subject's parent or legal guardian is not willing to continue to meet standard of care guidelines for care (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study.
12. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for enrollment.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

The subject's legally authorized representative (e.g., parent or legal guardian) must provide informed consent before any study-specific screening tests are performed (see Section 17.3). When a subject's parent/guardian signs the informed consent form (ICF), that subject is assigned a unique subject identification number through the interactive response technology (IRT) system and is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents, within the IRT system, and on the screening log. If a subject initially fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening Period, at the discretion of the Investigator.

9.2. Registration and Randomization of Subjects

Subjects will be registered and randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment until the subject is documented as registered (assigned a unique identification number) and is randomized for the study in the IRT system. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Using an IRT system, eligible subjects will be randomized to receive ISIS 396443: sham procedure in a 2:1 ratio. Randomization will be stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus ≤6 months. Subjects who withdraw from the study may be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This is a randomized, double-blind, sham-procedure controlled study. The sponsor, parents and/or legal guardians, and key study site personnel will be blinded throughout the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or that of the Sponsor, except the unblinded site study staff (dedicated team) and the unblinded medical monitor or clinical research associate. The DSMB may be unblinded as described in the DSMB charter.

9.3.1. Unblinding of Treatment Assignment

If a subject has experienced an SAE (as defined in Section 15.1.2), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the IRT. However, prior to unblinding, the Investigator should attempt to contact the blinded Medical Monitor to discuss the emergency. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. Every reasonable attempt should be made to complete the final follow-up visit (approximately 4 months after the last dose of study treatment) early termination procedures and assessments prior to unblinding, as knowledge of the treatment arm could influence subject assessment. 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, nor to personnel involved with the analysis and conduct of the study. In cases where there are ethical reasons to have a subject whose treatment assignment was unblinded for safety reasons remain in the study, the Investigator must obtain specific approval from the Sponsor and the Medical Monitor for the subject to continue in the study.

In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's (or designee) Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (Section 15.3.4).

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

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

- The subject's parent or legal guardian withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

Subjects who discontinue treatment will continue follow-up (i.e., predose evaluations at regular study visits [Days 15, 29, 64, 183, and 302] but with no postdose safety monitoring telephone contacts [Days 16, 30, 65, 184, and 303]) unless consent is withdrawn. If a subject is unable to come for study visits, the minimum requirement for follow-up will be telephone calls on a monthly basis. At these visits or telephone contact, changes in concomitant medications and AEs, information on the subject's daily ventilator use/ bi-level positive airway pressure (Bi-PAP), and health status will be recorded. The methods used to continue follow-up (i.e., site visits or telephone calls to the subject's parent or guardian or caregiver) should be documented in the source document.

10.2. Withdrawal of Subjects From Study

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

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

Subjects who prematurely withdraw from the study are to complete the early termination study procedures and observations at the time of withdrawal (see Section 4.2 [Table 2]). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for complete details.

11.1.1. Study Treatment

Each subject will receive a single intrathecal bolus (1 to 3 minutes) LP injection of ISIS 396443 or sham procedure on Days 1, 15, 29, 64, 183, and 302 by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, the study coordinator, or outcome assessors). The study treatment administration will be performed in a dedicated room, and key study personnel and the parents will not be present during the procedure to ensure blinding.

ISIS 396443 will be administered using a "spinal anesthesia" needle and a 5-mL syringe. A 22G to 25G spinal anesthesia needle is recommended based on 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. Depending on institutional guidelines, anesthesia may be used for the LP procedure or for the sham procedure, following institutional procedures. Subjects will be encouraged to lie down flat for 1 hour following injection of the study treatment, if possible. Prior to each injection, 5 mL of CSF fluid will be collected for analyses. CSF will be used for

ISIS 396443 PK analyses. Upon consent, extra CSF will be stored for optional future investigation of possible biomarkers of SMA disease (e.g., CSF mRNA, CSF protein, CSF microRNA panel) or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or other actions of ISIS 396443 with CSF constituents. CSF analyses and data presentation will be conducted in a blinded manner.

The volume of the injection, and thus, the dose, will be adjusted for the subject's age on the day of dosing, such that each subject will receive a 12-mg scaled equivalent dose based on CSF volume scaling (Table 4). Thus, younger subjects will be given a lower dose of study treatment, achieved by injecting a smaller volume that is proportional to estimated CSF volume for age, such that dose volume will be equivalent to 5 mL for a 2-year-old child to adult.

11.1.2. Sham Procedure

Subjects randomized to the sham-procedure control group will undergo a sham procedure, rather than study treatment administration, on Study Days 1, 15, 29, 64, 183, and 302. Details regarding the sham procedure will be provided in the DHA. The sham procedure will be administered by dedicated study personnel who are unblinded to treatment group; this cannot be any of the key study site personnel (i.e., the Investigator, study coordinator, or outcomes assessors). The sham procedure will be performed in a dedicated room, and key study personnel and the parent or legal guardian will not be present during the procedure to ensure blinding.

In general, the sham procedure will consist of a small needle prick on the lower back at the location where the LP injection is normally made. The needle will break the skin, but no LP injection or needle insertion will occur. The needle prick will be covered with the same bandage that is used to cover the LP injection normally, thus simulating the appearance of an LP injection. If institutional guidelines require the use of anesthesia or sedation for an LP procedure in ISIS 396443-treated subjects, then 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. The study subject will be kept in the procedure room for the same amount of time that subjects administered study treatment are kept, thus simulating the time period of the study treatment administration procedure.

Study treatment and sham kits will be packaged in a blinded fashion. Blinded kits for the sham procedure contain artificial CSF (5.0 mL solution per 6 mL vial) that will not be injected but will be used to simulate CSF samples for that subject.

11.2. Modification of Dose and/or Treatment Schedule

No adjustment of dose is permitted. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted but must be approved by the Medical Monitor.

11.3. Precautions

There are no protocol-required treatment precautions.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Screening and Final Study Visit/Telephone Call.

Allowed Concomitant Therapy

Throughout the study, Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

Disallowed Concomitant Therapy

Subjects are prohibited from receiving other experimental agents, including gene therapy, during the study. This includes marketed agents at experimental doses that are being tested for the treatment of SMA (albuterol/ salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.).

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and Final Study Visit/Telephone Call.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or medically qualified staff. Study treatment is to be dispensed only for subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial should not be used for another subject.

12.1. Study Treatment

ISIS 396443 is formulated as an isotonic solution at 2.4 mg/mL and is provided as a 5.0-mL fill volume in a 6-mL clear glass vial. ISIS 396443 drug product contains the heptadecasodium salt of an 18-base residue phosphorothioate oligonucleotide.

ISIS 396443 active drug is manufactured by Isis Pharmaceuticals, Inc., Carlsbad, CA, USA.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, drug identifier, and quantity of dosage units, lot number, and other pertinent information in accordance with local laws. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration date.

The study drug (ISIS 396443) and sham kits will be packaged in a blinded fashion. Blinded kits for sham procedure contain artificial CSF provided as 5.0 mL solution per 6 mL vial that will not be injected but will be used to simulate CSF samples for a subject.

12.1.1. Study Treatment Preparation

The individual preparing ISIS 396443 or artificial CSF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, do not use it. The vials in question should be saved at the study site and the problem immediately reported to the Sponsor (or designee).

12.1.2. Study Treatment Storage

Study treatment must be stored in a secure location.

ISIS 396443 is to be protected from light and stored long term at 2°C to 8°C in a locked refrigerator with limited access. For additional information on storage requirements, follow the instructions provided in the DHA.

12.1.3. Study Treatment Handling and Disposal

The Investigator must return all used and unused vials of ISIS 396443 and artificial CSF as instructed by the Sponsor (or designee).

If any used ISIS 396443 or artificial CSF supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor (or designee), by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor (or designee) must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Study Treatment Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of ISIS 396443 or artificial CSF supplied, dispensed, and subsequently destroyed or returned to the Sponsor (or designee). A written explanation must be provided for any discrepancies.

13. EFFICACY, PHARMACOKINETIC, AND IMMUNOGENICITYASSESSMENTS

See Section 4.2 (Table 2) for the timing of all assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of ISIS 396443:

- Ventilator use
- HINE (Section 2)
- Growth parameters (body length, head circumference, chest circumference, arm circumference, weight for age, weight for length, and head to chest circumference ratio)
- Clinical Global Impression of Change (physician and caregiver assessment)

13.2. Pharmacokinetic (ISIS 396443 Concentration) Assessments

The following tests will be performed to assess the PK of ISIS 396443:

- Plasma ISIS 396443 concentrations
- CSF ISIS 396443 concentrations

13.3. Immunogenicity Assessments

The following test will be performed to assess the immunogenicity of ISIS 396443:

- Anti-ISIS 396443 plasma antibody concentrations

14. SAFETY ASSESSMENTS

See Section 4.2 (Table 2) for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of ISIS 396443:

- Neurological examinations (assessment of mental status, level of consciousness, sensory motor function, cranial nerve function, and reflexes)
- AEs, including SAEs
- Vital signs (resting systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, pulse oximetry, and transcutaneous carbon dioxide)
- Weight
- Physical examinations
- Medical history
- 12-Lead ECGs
- Use of concomitant medications

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed to evaluate the safety profile of ISIS 396443:

- Blood chemistry: total protein, albumin, creatinine, cystatin C, creatine phosphokinase, blood urea nitrogen, total bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, calcium, phosphorus, chloride, sodium, potassium
- Hematology: red blood cells, hemoglobin, hematocrit, platelets, white blood cells, white blood cell differential
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject's legally authorized representative and/or main caregiver(s) must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Abnormal laboratory findings that are considered by the Investigator as not clinically significant should not be reported as AEs. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of >24 hours to a medical facility and does not qualify as an AE
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. 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 site 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 consent from the subject's parent or legal guardian to participate in the study.
- The condition requiring 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 parent's or legal guardian's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Related	There is clear evidence that the event is related to the use of the investigational drug (e.g., confirmation by positive re-challenge 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 administration of the investigational drug.
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 investigational drug 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; therefore, the Investigator believes no relationship exists between the event and the investigational drug.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
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.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor (or designee) according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

For subjects who receive study treatment, any AE experienced between the time of signing the ICF and Final Study Visit/Telephone Call is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. For subjects who never receive study treatment, no AEs need to be recorded on the applicable CRF.

An AE that is ongoing when the subject completes or discontinues the study should be followed by the Investigator, if possible, until the event has resolved or stabilized.

15.3.2. Serious Adverse Events

For subjects who receive study treatment, any SAE experienced between the time of signing the ICF and Final Study Visit/Telephone Call is to be recorded on an SAE form and on the applicable CRF, regardless of the severity of the event or its relationship to study treatment. For subjects who never receive study treatment, any SAE occurring between the time of signing the ICF and Final Study Visit/Telephone Call must be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment; however, the SAE does not need to be recorded on the applicable CRF.

SAEs must be reported to [redacted] Safety (Fax: [redacted]; email: [redacted]) within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until their Final Study Visit/Telephone Call. Thereafter, the event should be reported to [redacted] Safety only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify [redacted] Safety within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject's parent or legal guardian has signed the ICF and Final Study Visit/Telephone Call must be reported to [redacted] Safety, which is the designee for Biogen Idec SABR, within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] Safety regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form to the following: [redacted] Safety (fax to [redacted]; email to [redacted]).

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted] Safety. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or Sponsor (or designee) to be related to the study treatment administered.

The Sponsor (or designee) will report SUSARs to the appropriate regulatory authorities and to Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol; an overdose must be documented as a protocol deviation. A brief description should be provided in the deviation form, including whether the subject was symptomatic (with a list of symptoms) or asymptomatic. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be reported to the Medical Monitor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Medical Monitor even if the overdose does not result in an AE. If an overdose results in an AE, then the AE must be recorded. If an overdose results in an SAE, then the SAE form must be completed and faxed to [redacted] Safety. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.2. 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 [redacted] at [redacted] (or [redacted] medical emergency: [redacted] or [redacted]) or [redacted] at [redacted].

15.4.2.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator (or designee) should attempt to contact the blinded Biogen Idec Medical Director or blinded [redacted] Medical Monitor to discuss the emergency within 24 hours. In these instances, the Investigator (or designee) may access the subject's treatment assignment by IRT.

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 personnel involved with the analysis and conduct of the study.

15.5. Safety Responsibilities

15.5.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to 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 to [redacted] Safety 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 to [redacted] Safety within 24 hours of the study site staff becoming aware of new information.
- Ensure 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.

15.5.2. The Sponsor

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.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

In general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category.

Baseline is defined as the average of 2 assessments taken during the screening/baseline period. The baseline for other assessments is defined as the last nonmissing assessment prior to the first dose of study treatment.

Concomitant medication usage for each subject will be listed for review.

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

16.2. Safety and Tolerability

Safety is the primary objective for the study. All AEs, laboratory abnormalities, ECGs, and vital signs will be evaluated for safety.

16.2.1. Analysis Population

Safety analyses will be conducted in the safety population. This safety set will include all subjects who are randomized and receive at least 1 dose of study treatment or sham procedure. Treatment duration and amount of study treatment received will be summarized by treatment group.

16.2.2. Methods of Analysis

16.2.2.1. Neurological Examinations

Neurological examination findings will be listed for review, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal, and abnormal (not AE) will be summarized.

16.2.2.2. Adverse Events

All AEs will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment emergent if it was present prior to the first dose of study treatment and subsequently worsened, or was not present prior to the first dose of study treatment but subsequently appeared. The incidence of treatment-emergent AEs will be summarized overall,

by severity, and by relationship to study treatment. A subject having the same AE more than once will be counted only once in the incidence for that event. The occurrence of the AE with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the AE with the strongest relationship to study treatment will be used in the calculation of incidence by relationship to study treatment.

All treatment-emergent AEs and SAEs will be summarized for each treatment group 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, SAEs, early withdrawals from study treatment and from study due to AEs will be provided.

16.2.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented. Summary statistics for actual values and change from Baseline will also be presented.

16.2.2.4. ECGs

ECG results will be presented by subject, and as appropriate, results will be summarized descriptively for each treatment group. The number and percentage of subjects with shifts from baseline normal to each of the categorical values denoting normal, abnormal clinically significant, and abnormal (not clinically significant) will be summarized.

16.2.2.5. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using study visit for each treatment group. These safety variables will also be presented over time after study treatment administration, as appropriate.

16.3. Efficacy

16.3.1. Analysis Population

The exploratory analysis of efficacy will be performed on the intent-to-treat population. The intent-to-treat population is defined as all subjects who are randomized, receive at least 1 dose of study treatment or sham procedure, and have at least 1 postbaseline evaluation.

16.3.2. Methods of Analysis

For continuous endpoints, the mean change from baseline will be estimated with 95% confidence limits. For categorical outcomes, the proportion of subjects attaining a specified category will be estimated. Selected endpoints may be pooled across subsets as appropriate.

16.4. Pharmacokinetics

16.4.1. Analysis Population

The PK population will include all subjects who are randomized and have at least 1 evaluable postdose or postsham-procedure PK sample.

16.4.2. Methods of Analysis

Plasma PK parameters, as applicable, and ISIS 396443 concentrations in plasma and CSF for the PK population will be summarized using descriptive statistics and, where warranted, presented graphically.

16.5. Immunogenicity

16.5.1. Analysis Population

The analysis population for immunogenicity will include all subjects with available immunogenicity data.

16.5.2. Methods of Analysis

Results from the immunogenicity analyses for anti-ISIS 396443 plasma antibody status and titer will be summarized at the specified visits.

16.6. Interim Analyses

No formal interim analyses will be conducted.

16.7. Sample Size Considerations

Since this study is exploratory, sample size determination will not be based on power consideration. The sample size considered for this study will allow exploration of safety, tolerability, and selected efficacy endpoints in the selected study population.

17. ETHICAL REQUIREMENTS

The Sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor (or designee) will submit documents on behalf of the investigational sites in countries other than the United States.

If the Investigator makes any changes to the ICF, the Sponsor (or designee) must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor (or designee). After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor (or designee).

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor (or designee) must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

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).

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject's legally authorized representative (e.g., parent or legal guardian) in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject's legally

authorized representative. The subject's legally authorized representative must be given sufficient time to consider whether the subject will participate in the study.

A copy of the signed and dated ICF must be given to the subject's legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. The Sponsor, its partner(s) and designee(s), 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.

17.5. Compensation for Injury

The Sponsor (or designee) maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor or its partners) with the subject's legally authorized representative before the subject's legally authorized representative makes a decision for the subject to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit conducted by the Sponsor (or designee). This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen Idec is funding the study. Isis is the Sponsor of the study in the United States and Biogen Idec is the Sponsor of the study in the Rest of World. Biogen Idec (or designee) will be responsible for managing the study globally. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen Idec.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

The Sponsor may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, the Sponsor retains overall accountability for these activities.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool that is supported by a vendor and configured by the Sponsor or CRO.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory will be selected by the Sponsor to analyze all hematology, blood chemistry, urine, and CSF samples collected at all study sites. Local laboratories may be used to accommodate acute or urgent needs as discussed in in the Study Reference Manual.

During the Screening Period, a blood sample will be collected for *SMN2* copy number analysis by the central laboratory only from those subjects without genetic documentation of *SMN2* copy number. For all other subjects, a blood sample will be collected at any time during the study for analysis of *SMN2* copy number by the central laboratory.

19.2. Study Committees

Safety data will be reviewed on an ongoing basis by an independent DSMB. The DSMB will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 396443 during the study. Based on its ongoing assessment of the safety and tolerability of ISIS 396443, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor (or designee) may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4" 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 (Print)