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

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

PROTOCOL NUMBER: 232SM203

PHASE OF DEVELOPMENT: 2/3

PROTOCOL TITLE: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy

EUDRA CT NUMBER: 2019-002663-10

IND NUMBER: 110011

DATE: 05 August 2020

Version 4

FINAL

Supersedes previous Version 3 dated 05 June 2020.

SPONSOR INFORMATION

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

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

Biogen Japan Ltd.
Nihonbashi 1-chome
Mitsui Building 14F
4-1 Nihonbashi 1-chome
Chuo-ku, Tokyo
103-0027 Japan

Biogen Australia PTY Ltd.
Suite 1, Level 3
123 Epping Road
North Ryde, NSW 2113
Australia

For urgent medical issues in which the study Medical Director should be contacted, refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, Biogen retains overall accountability for these activities.

SPONSOR SIGNATURE PAGE

Protocol 232SM203 was approved by:

Toby Ferguson, MD, PhD
Vice President, Head of Neuromuscular Development Unit
Biogen

10 August 2020
Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy	
Protocol Number:	232SM203	
Version Number:	4	
Name of Study Treatment:	Research Name:	BIIB058
	Generic Name:	Nusinersen
	Trade Name:	Spinraza
Study Phase:	2/3	
Study Indication:	Spinal muscular atrophy (SMA)	
Study Rationale:	Efficacy and safety results across the nusinersen clinical development program have demonstrated an overall positive benefit-risk profile of nusinersen across a broad range of SMA phenotypes and patient populations. Nusinersen is approved in the United States, Europe, and other countries and regions for the treatment of SMA in pediatric and adult patients at a recommended dosage of 12 mg administered in 3 loading doses at 14-day intervals, a fourth loading dose 30 days after the third dose, and maintenance doses every 4 months thereafter. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses indicate that nusinersen drug exposure higher than that achieved with 12 mg in patients with SMA may produce an even greater benefit in motor function. Additionally, PK modeling and simulations identified dosing regimens that achieve higher drug exposure more rapidly. Therefore, this study is being conducted to investigate the efficacy, safety, tolerability, and PK of a 50/28-mg dose of nusinersen (50-mg loading dose; 28-mg maintenance dose) and a dosing regimen targeted to achieve higher drug exposure more rapidly. This study will be conducted in participants with genetically confirmed SMA.	
Rationale for Dose and Schedule Selection:	The clinical PK, safety, and efficacy of nusinersen have been evaluated in a number of patient populations (infantile-onset [SMA symptom onset ≤ 6 months (≤ 180 days) of age], later-onset [SMA symptom onset > 6 months (> 180 days) of age], and	

presymptomatic). The approved dosing regimen of nusinersen is 12 mg administered in 4 loading doses during a 2-month period followed by maintenance doses every 4 months thereafter. In the original development program, 2 different dosing regimens (4 loading doses followed by maintenance doses every 4 months and 3 loading doses followed by maintenance doses every 6 months) were evaluated in sham-controlled studies. Results from these studies, the population PK and exposure-response modeling, and the nonhuman primate safety studies were used as the basis for selecting dosing regimens in this study.

An exploratory exposure-response analysis performed in participants with infantile-onset SMA (Study CS3A, n = 20, age 38 days to 8 months) showed a statistically significant positive correlation between nusinersen cerebrospinal fluid (CSF) exposure and motor function (e.g., Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND] scores). Additional analyses in the same patient population from Studies CS3A and CS3B (n = 80, age 30 days to 8 months) showed that the near-steady-state CSF exposure (approximately 10 ng/mL) closely approximated the model-predicted concentration at 50% of the maximum observed biological effect (EC_{50}) using CHOP INTEND (change from baseline) as the primary efficacy endpoint. These results suggest that additional clinical efficacy may be possible with increased nusinersen central nervous system (CNS) exposure. Under the assumption of PK linearity, increasing the nusinersen dose to 24 mg, with a dosing frequency of 4 loading doses followed by maintenance doses administered every 4 months, should effectively increase the CSF trough concentration (C_{trough}) at steady state to approximately 20 ng/mL. This concentration is comparable to the predicted concentration at 90% of the maximum observed biological effect (EC_{90}) from the infantile-onset SMA population. This assumption is supported by nusinersen toxicokinetic results in nonhuman primates, which showed nearly dose-proportional PK in the plasma and CNS tissues (target site of action) up to 15 mg (human equivalent dose of 150 mg). It is important to highlight that the maximum response from the existing clinical data is limited because 12 mg was the highest dose administered in humans, and the majority of the dataset are within the CSF C_{trough} range of 5 to 15 ng/mL; therefore, extrapolation of the efficacy response above 20 ng/mL is not recommended. The PK/PD relationship has thus far been demonstrated primarily in the infantile-onset SMA population. However, the same positive PK/PD relationship is expected across SMA types and patient age groups because they share the same disease mechanism. This is supported by the preliminary correlation

analysis from Study 232SM202, which showed a positive relationship between CSF C_{trough} and total motor milestones scores in patients with infantile- and later-onset SMA who received 12 mg of nusinersen as 4 loading doses followed by maintenance doses every 4 months.

Using 20 ng/mL as the clinical CSF C_{trough} target concentration and the predicted CSF PK profiles from 24 mg of nusinersen (4 loading doses followed by maintenance doses every 4 months) as the reference dosing regimen, simulations were performed to evaluate additional dosing scenarios with higher doses and reduced loading-dose frequency. Additional evaluation of the maintenance dosing frequency was not performed because previous modeling showed that a dosing frequency of every 4 months best maintained the CSF concentration achieved at steady state. Assuming PK linearity, PK simulations were performed in both infantile- and later-onset SMA populations after 2 years of treatment using a population PK model developed from patients across the age range of ≤ 6 months to 18 years old. Relative to the reference dosing regimen, both 28 mg administered as 3 loading doses (biweekly) and 50 mg administered as 2 loading doses (biweekly), each followed by maintenance doses of 28 mg every 4 months, were identified to achieve the desired CSF C_{trough} (approximately 20 ng/mL) more rapidly. Nusinersen 28 mg administered as 3 loading doses (biweekly) had a comparable predicted CSF maximum concentration (C_{max}) to the reference dosing regimen, whereas the 50-mg dosing regimen surpassed the predicted C_{max} from the reference dosing regimen. Toxicology studies in nonhuman primates evaluating the nonhuman primate equivalent of the 28- and 50-mg doses have been conducted and support the safety of these doses in a clinical study. Therefore, the 28-mg dose (administered as 3 loading doses at biweekly intervals), 50-mg dose (administered as 2 loading doses at biweekly intervals), and 28-mg maintenance dose were recommended for additional clinical evaluation.

The single bolus in Part C is supported by PK simulations showing that a titration dosing regimen of a single loading dose (50 mg) followed by maintenance doses of 28 mg every 4 months thereafter achieved and maintained the higher CSF C_{trough} target concentration (approximately 20 ng/mL) in the representative populations for later-onset and infantile-onset SMA, respectively. The predicted exposures of the proposed titration dosing regimens are covered by the levels demonstrated to be safe in nonhuman primates.

Study Objectives and Endpoints

Part B Primary Objective	**Primary Endpoint**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA, as measured by change in CHOP INTEND total score	Infantile-Onset SMA • Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the joint-rank test
Part B Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	Infantile-Onset SMA • Proportion of Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone responders at Day 302 • Change from baseline to Day 302 in HINE Section 2 motor milestones total score accounting for mortality/dropout using the joint-rank test • Time to death or permanent ventilation (tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in the absence of an acute reversible event [Appendix A]) • Time to death (overall survival) Later-Onset SMA • Change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) score • Change from baseline in Revised Upper Limb Module (RULM) score • Total number of new World Health Organization (WHO) motor milestones • Change from baseline in Assessment of

	Caregiver Experience with Neuromuscular Disease (ACEND) • Change from baseline in Pediatric Quality of Life Inventory™ (PedsQL)
To examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA	• Incidence of adverse events (AEs), including serious adverse events (SAEs) • Shifts from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs • Change in growth parameters • Shifts from baseline in coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and international normalized ratio [INR]) • Change in urine total protein • Change from baseline in neurological examination outcomes • The proportion of participants with a postbaseline platelet count below the lower limit of normal on at least 2 consecutive measurements • The proportion of participants with a postbaseline corrected QT interval using Fridericia's formula (QTcF) of > 500 msec and an increase from baseline to any postbaseline timepoint in QTcF of > 60 msec
To examine the effect of nusinersen administered intrathecally at higher doses compared to the currently approved dose in participants with SMA	• Number and duration of hospitalizations • Clinical Global Impression of Change (CGIC) [physician, caregiver] at Day 302 • Number of serious respiratory events

	• Proportion of time on ventilation (infantile-onset SMA population) • Ventilator use • Change in the Parent Assessment of Swallowing Ability (PASA) scale
Parts A and C Primary Objective To examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA	**Primary Endpoints** • Incidence of AEs, including SAEs • Shifts from baseline in clinical laboratory parameters, ECGs, and vital signs • Change in growth parameters • Shifts from baseline in coagulation parameters (aPTT, PT, and INR) • Change in urine total protein • Change from baseline in neurological examination outcomes • The proportion of participants with a postbaseline platelet count below the lower limit of normal on at least 2 consecutive measurements • The proportion of participants with a postbaseline QTcF of > 500 msec and an increase from baseline to any postbaseline timepoint in QTcF of > 60 msec
Parts A and C Secondary Objectives To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	**Secondary Endpoints** Parts A and C: • Change from baseline in HFMSE score • Change from baseline in RULM score • Total number of new WHO motor milestones

	• Change from baseline in ACEND • Change from baseline in PedsQL Part C only: • Change from baseline in CHOP INTEND • Change from baseline in HINE Section 2 motor milestones
To examine the effect of nusinersen administered intrathecally at higher doses to participants with SMA	Parts A and C: • Number and duration of hospitalizations • CGIC (physician, caregiver) at Day 302 • Number of serious respiratory events • Ventilator use • Change in the PASA scale (Part A only)

Exploratory objectives and endpoints are listed in Section 4.

Study Design:

This is a 3-part (Parts A, B, and C) study in which participants will be followed for approximately 10 to 13 months after the first dose of study treatment. Following the completion of this study, all eligible participants may elect to enroll in a separate long-term extension study, pending study approval by ethics committees and the appropriate regulatory authorities. In regards to participants rolling over from Part B, this will be done without unblinding the participant's treatment group.

Part A is an open-label safety evaluation. Six participants with later-onset SMA who are 2 to ≤ 15 years of age, inclusive, at the signing of informed consent will receive 3 loading doses of 28 mg of nusinersen on Days 1, 15, and 29, followed by 2 maintenance doses of 28 mg on Days 149 and 269. Participants will remain at the clinic for at least 24 hours after each dose. A sentinel dosing approach will be used, in which the first participant will be enrolled and dosed with 28 mg of nusinersen. Following the availability of 72 hours of safety data after the first loading dose in the first participant, data for this participant will be reviewed by the Investigator and the Sponsor before the next 5 participants are enrolled. Only 1 participant can receive their first dose of study

treatment on a given day.

After 6 participants have completed the loading period (i.e., when the last participant has available safety data through the Day 64 visit), an independent data monitoring committee (IDMC) will review the available safety data to recommend whether Part B can be initiated. If deemed necessary by the Sponsor, additional participants may be enrolled in Part A to ensure sufficient data are available for the safety evaluation prior to enrollment of participants in Part B. Details regarding the IDMC review of data may be found in the IDMC charter. Meanwhile, participants in Part A will proceed to maintenance dosing without interruption. Note that the IDMC can recommend to stop the study based on the safety findings.

Part B will consist of a pivotal, double-blind, active-controlled treatment period with either 2 or 4 loading doses of nusinersen (for the 50/28-mg and Control Groups, respectively) administered intrathecally followed by maintenance doses approximately every 4 months thereafter. Up to 126 participants with infantile- or later-onset SMA will be randomized in a 1:2 ratio to receive either the currently approved dosing regimen of 4 loading doses of 12 mg of nusinersen administered intrathecally (Days 1, 15, 29, and 64) followed by 2 maintenance doses of 12 mg on Days 183 and 279 (Control Group) or 2 loading doses of 50 mg of nusinersen administered intrathecally (Days 1 and 15) followed by 2 maintenance doses of 28 mg on Days 135 and 279 (50/28-mg Group). In order to maintain blinding, 1 sham procedure will be administered in the Control Group on Day 135 and 3 sham procedures will be administered in the 50/28-mg Group on Days 29, 64, and 183 to ensure the same dosing visit schedule as the Control Group. Participants will remain at the clinic for at least 24 hours after each study treatment administration or sham procedure.

Once the fifteenth participant in Part B has been enrolled and administered the first dose of study treatment, no new participants will be dosed in Part B until after an IDMC review. The IDMC will review unblinded data from the first 15 participants in Part B who have completed the Day 29 visit (in order to achieve 6 or more participants who have received 50 mg in the 50/28-mg Group, while maintaining the blind for the rest of the study team). This review will include safety data through the Day 29 visit at a minimum and all available individual CSF and plasma nusinersen concentration data for these participants, including the Day 15 samples at a minimum. Dosing of the remaining participants in Part B and dosing in Part C will occur only after this review has completed,

provided that no safety concerns are identified. Note that the IDMC can recommend to stop the study based on the safety findings.

In Part C, approximately 20 participants will be enrolled. Participants of any age or SMA status who have already initiated treatment with nusinersen and have been receiving the approved dose of 12 mg for at least 1 year prior to entry in this study are eligible. An attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants ≥ 18 years of age must be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in Part C after consultation with the Medical Monitor. Participants will receive a single bolus dose of 50 mg (which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241. Participants in Part C will remain at the clinic for at least 24 hours after the first (bolus) dose for the purpose of completing study assessments.

Study Location: Approximately 65 sites globally are planned.

Study Population: This study will be conducted in participants who meet the following criteria:

- Parts A, B, and C:
  - Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote)
- Part A:
  - Participants with later-onset SMA, aged 2 to ≤ 15 years, inclusive, at the time of informed consent
- Part B:
  - Participants with infantile-onset SMA, aged > 1 week to ≤ 7 months (≤ 210 days) at the time of informed consent
  - Participants with later-onset SMA, aged 2 to < 10 years at the time of informed consent
- Part C:
  - Males and females of any age (individuals ≥ 18 years

of age at Screening must be ambulatory)

– Have been receiving treatment with nusinersen for at least 1 year prior to entry in this study

Detailed criteria are described in Section 6.

Number of Planned Participants: Including all 3 parts (A, B, and C), approximately 152 participants may be enrolled.

Treatment Groups:

- Part A: Six participants with later-onset SMA will receive 3 loading doses of 28 mg of nusinersen administered intrathecally on Days 1, 15, and 29. Maintenance doses of 28 mg of nusinersen will be administered on Days 149 and 269.
- Part B:
  - Control Group: A total of 42 participants (34 with infantile-onset SMA and 8 with later-onset SMA) will receive 4 loading doses of 12 mg of nusinersen administered intrathecally (Days 1, 15, 29, and 64), followed by maintenance doses of 12 mg on Days 183 and 279 (and a sham procedure on Day 135).
  - 50/28-mg Group: A total of 84 participants (68 with infantile-onset SMA and 16 with later-onset SMA) will receive 2 loading doses of 50 mg of nusinersen administered intrathecally (Days 1 and 15) and 2 sham procedures on Days 29 and 64, followed by maintenance doses of 28 mg on Days 135 and 279 (and a sham procedure on Day 183).
- Part C: Approximately 20 participants who have already been receiving treatment with nusinersen for at least 1 year prior to entry in this study will receive a single bolus dose of 50 mg of nusinersen administered intrathecally on Day 1 in this study (which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg), followed by 2 maintenance doses of 28 mg of nusinersen on Days 121 and 241.

Sample Size Determination: A total sample size of approximately 152 participants is planned for this study, with a possibility of stopping recruitment based on the interim analysis (Table 8). The justification for the sample size for

the infantile-onset SMA population in Part B is detailed below. The sample sizes for the remaining groups are not based on statistical considerations.

A minimum of 6 participants with later-onset SMA will be enrolled in Part A to characterize the safety, tolerability, and PK profile of a 28/28 mg dose of nusinersen (28-mg loading dose; 28-mg maintenance dose). A total of 24 participants with later-onset SMA will be randomized to the Control Group and 50/28-mg Group in Part B in a ratio of 1:2; this will allow the exploration of the safety, tolerability, PK profile, and efficacy of a 50/28 mg dose of nusinersen in this population. A total of approximately 20 participants will be enrolled in Part C to characterize the safety, tolerability, and PK profile of a 50/28-mg dose of nusinersen in participants transitioning from maintenance dosing at the currently approved dose of 12 mg of nusinersen.

For the infantile-onset SMA population in Part B, a sample size of up to 68 participants in the 50/28-mg Group will provide at least approximately 99% power to detect an improvement of 24 points on CHOP INTEND and 23% survival rate benefit (compared to that observed in Study CS3B participants receiving sham control) at Day 183 based on the joint-rank test at a 2-sided significance level of 0.05. This power calculation is based on simulations using data generated from a joint model of survival and functional change. The model used a difference of 24 points for the Day 183 change from baseline in CHOP INTEND total score (50/28-mg Group – Study CS3B Sham Control Group) and a population standard deviation of 8.8 for change from baseline.

For Part B, the randomization will be stratified as follows:

- For participants with infantile-onset SMA by disease duration: ≤ 12 weeks and > 12 weeks (time from age at symptom onset to age at informed consent)
- For participants with later-onset SMA by age at informed consent: < 6 years and ≥ 6 years

Visit Schedule:

Participants will have up to 10 visits during the study. The number of visits for each part is as follows:

- Part A: 8 to 9 visits
- Part B: 9 to 10 visits
- Part C: 5 to 6 visits

Visits during Days 1, 15, and 29 of the loading period of Parts A and B, and Day 1 of the loading period of Part C should be performed ±1 day from the nominal visit day. Visits during Day 64 of the loading period of Parts A and B and the maintenance period of Parts A, B, and C should be performed ±7 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the date of first dose).

Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1, Table 2, and Table 3).

Duration of Study Participation:

Study duration for each participant will be as follows:

Part A: approximately 323 to 410 days

- Screening: 21 days
- Loading period: 64 days
- Maintenance period: 205 days
- Follow-up: 33 to 120 days

Part B: approximately 323 to 420 days

- Screening: 21 days
- Loading period: 64 days
- Maintenance period: 215 days
- Follow-up: 23 to 120 days

Part C: approximately 323 to 382 days

- Screening: 21 days

- Loading period: 1 day
- Maintenance period: 240 days
- Follow-up: 61 to 120 days

Benefit-Risk Analysis: Nusinersen (Spinraza) has a positive benefit-risk profile, with more than 3 years of postmarketing experience and more than 10,000 patients treated. The safety profile to date does not preclude study of higher doses in any population.

Anticipating a potential enhancement of benefit with the dosing regimens proposed for Study 232SM203, substantiated by PK/PD modeling described in Section 3.1.2, the safety of the loading period for Study 232SM203 is supported by a nonclinical study conducted in monkeys (Study P058-17-05), with the dosing regimen matching with the most rigorous loading in Study 232SM203 (3 loading doses administered at 2-week intervals). The no-observed-adverse-effect level (NOAEL) for Study P058-17-05 was determined to be 15 mg (human equivalent dose of 150 mg), the high dose of the study, supported by the observation of non-adverse findings limited to dose-dependent/transient neurological clinical signs and histopathological findings in the brain and lymph nodes. This NOAEL provides a safety margin of at least 4.5-fold for the loading doses (based on cumulative doses during the loading period).

The safety of long-term exposure during the Study 232SM203 maintenance period is supported by a 53-week monkey study (Study 396443-AS06). This study implemented a more frequent dosing regimen than what is planned for Study 232SM203, 13 total doses during the 53-week duration, with the first 5 doses given once every week during the first 29 days, followed by an additional 8 doses given once every 6 weeks. Based on the 3 dose levels (0.3, 1, and 4 mg per dose) used in the study, for a duration of 53 weeks, the monkeys received a cumulative nusinersen dose of 3.9, 13, and 52 mg, respectively, at each dose level. Factoring in a CSF volume scale of 10 between humans and monkeys, the annual cumulative doses in monkeys from this study ranged from 3.0- to 7.2-fold (loading doses) and 6.2- to 14.4-fold (maintenance doses) higher than those planned for Study 232SM203. The major findings in monkeys were the histopathological changes in the hippocampus, which consisted of neuronal vacuolation and rare necrotic cells and cell debris at the 2 highest doses (1 and 4 mg). The overall no-observed-effect level (NOEL) for the study was 0.3 mg, driven by findings limited to the hippocampus, while no effects in any

other tissues were observed up to the high dose (4 mg) on a comprehensive histopathology evaluation. PK scaling was used to estimate the nusinersen tissue concentration in patients with SMA during maintenance treatment at 28 mg from tissue concentrations measured in patients with SMA treated with 12 mg of nusinersen (scaled from the tissue concentrations measured during autopsy of participants from Study CS3A). Tissue concentrations measured in monkeys from the 53-week toxicology study at the NOEL (0.3 mg for the hippocampus and 4 mg for all other tissues evaluated) were compared to the estimated tissue concentrations in patients with SMA. Based on these data, the exposure-based safety margin is at least 1.1-fold.

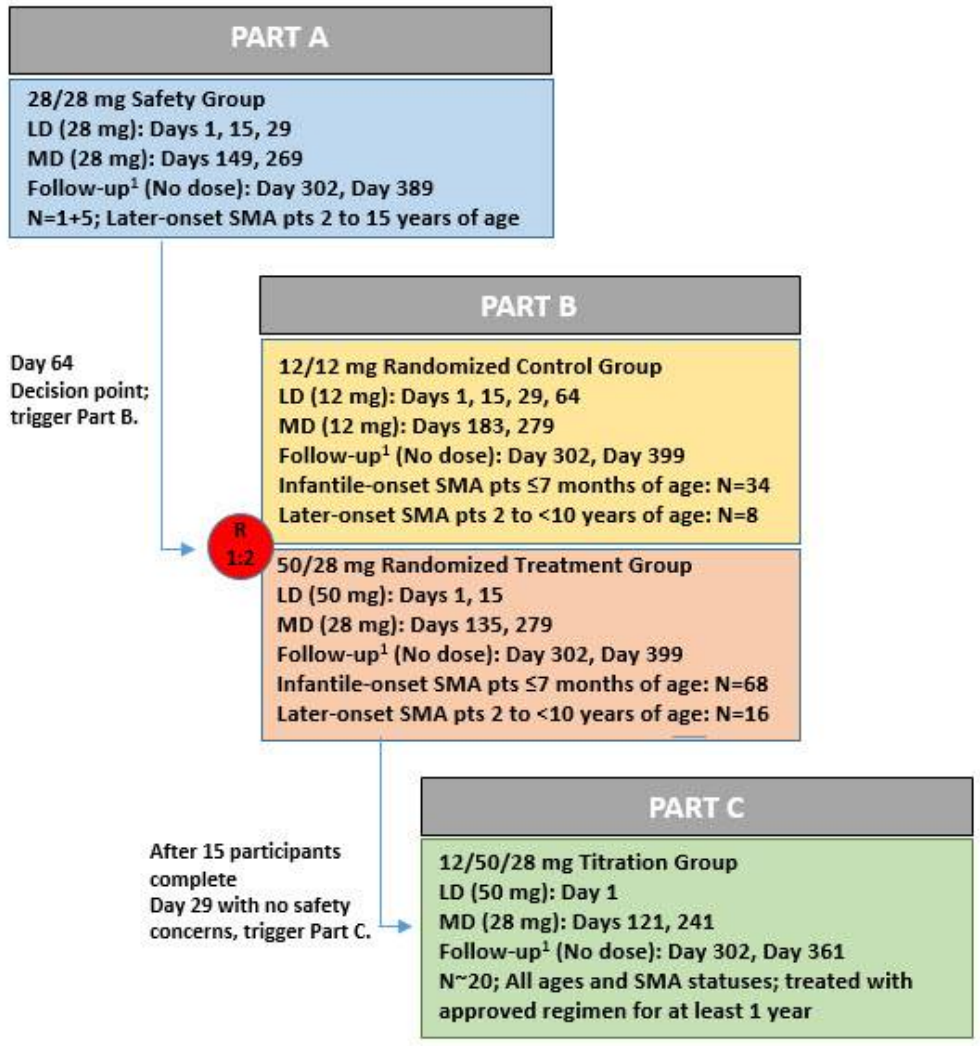
The potential risks related to participation in this study are justified by the anticipated benefit to participants.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of nusinersen is provided in the Investigator's Brochure and informed consent form. A high-level summary of the benefits and risks known during study design is provided here.

1.2. Study Design Schematic

A schematic of the study design is shown in Figure 1.

Figure 1: Study Schematic



1 + 5 = Sentinel dosing of the first participant in Part A will be followed by a review of the safety data before the remaining 5 participants in Part A are dosed; 28/28 = 28-mg loading doses and 28-mg maintenance doses; 12/12 = 12-mg loading doses and 12-mg maintenance doses; 50/28 = 50-mg loading doses and 28-mg maintenance doses; 12/50/28 = 12-mg loading doses and initial maintenance doses followed by a single 50-mg dose and subsequent 28-mg maintenance doses; LD = loading dose; MD = maintenance dose; N = number of participants; pts = participants; R = randomization; SMA = spinal muscular atrophy

Infantile-onset: SMA symptom onset ≤ 6 months (≤ 180 days) of age

Later-onset: SMA symptom onset > 6 months (> 180 days) of age

[1] Participants who meet criteria for contraception use (see Section 11.5) have a Day 302 visit and Day 389, Day 399, or Day 361 visit for Part A, Part B, or Part C, respectively. Male participants who meet this criteria may complete this visit via a telephone interview. Female participants who meet this criteria will return to the site for this visit. Participants who do not meet criteria for contraception use will have their last visit on Day 302.

1.3. Schedule of Activities

Study assessments conducted at each visit are listed in Table 1, Table 2, and Table 3.

Table 1: Schedule of Activities for Part A

	Screening Visit[1]	Treatment								Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day)**			**D64 (±7 days)**	**D149 (±7 days), D269 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D389 (+14 days)**
		Predose	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**			
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Local Urine/Serum Pregnancy Test for Females of Childbearing Potential[3]	X	X				X				X	X
Medical (including SMA) History	X										
SMA Genetic Testing[4]	X										
X-ray Examination (with the participant supine, not in a supported sitting position)[5]	X										
LP Opening Pressure			X				X				
Study Treatment Injection[6]			X				X				
Inpatient Stay (at least 24 hours)				X				X			
Vital Signs and Pulse Oximetry[7]		X		X[8]		X		X[8]		X	
Weight	X	X				X				X	

	Screening Visit[1]	Treatment								Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day)**			**D64 (±7 days)**	**D149 (±7 days), D269 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D389 (+14 days)**
		Predose	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**			
Growth Parameters (including height/ulnar length)	X	X				X[9]				X	
Physical Examination[10]	X	X				X				X	
Neurological Examination[11]	X	X		X	X	X		X		X	
ECG[12]		X		X	X			X		X	
Safety Laboratory Tests[13]	X	X			X	X				X	
Local Coagulation Laboratory Tests[14]	X	X				X					
Safety Follow-Up Telephone Contact				X[15]					X		
Immunogenicity[16]		X				X[9]				X	
CSF PK		X				X					
Plasma PK[17]		X		X		X[9]				X	
CSF Local Lab Sample (cell count, protein, and glucose)		X				X					
CSF Biomarker		X				X					
Plasma Biomarker		X				X				X	

	Screening Visit[1]	Treatment								Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day)**			**D64 (±7 days)**	**D149 (±7 days), D269 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D389 (+14 days)**
		Predose	**LP**	**Postdose**		**Predose**	**LP**	**Postdose**			
Efficacy Assessments[18] (HFMSE, RULM, WHO Motor Milestones, 6MWT, and 10MWR[19])	X[20]	X[21]			X[9]	X[9]				X	
CGIC[22]		X			X	X				X	
PedsQL and ACEND[23]		X				X				X	
Dysphagia Assessment (PASA)	X				X	X				X	
Ventilator Use[24]	X	X			X	X			X	X	
AE Recording	X----------X										
SAE Recording	X----------X										
Concomitant Therapy and Procedures Recording	X----------X										

6MWT = 6-Minute Walk Test; 10MWR = 10-Meter Walk/Run Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EOS = end of study; ET = early termination; HFMSE = Hammersmith Functional Motor Scale – Expanded; ICF = informed consent form; LP = lumbar puncture; PASA = Parent Assessment of Swallowing Ability; PedsQL = Pediatric Quality of Life Inventory™; PK = pharmacokinetic; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization

[1] If the Screening visit occurs within 7 days before Day 1, screening assessments can be used for Day 1 predose assessments. During the Screening period, participants who have an out-of-range result that is not clinically significant can be retested 1 time only at the discretion of the Investigator. The Screening period may be extended for up to 10 days for individuals who cannot complete the Day 1 visit within 21 days of signing the ICF, as long as they continue to meet other eligibility criteria.

[2] Participants who meet criteria for contraception use (see Section 11.5) have a Day 302 and a Day 389 visit. Male participants who meet this criteria may complete this visit via a telephone interview. Female participants who meet this criteria will return to the site to complete this assessment. Participants who do not meet criteria for contraception use will have their last visit on Day 302. Day 389 will take place at least 120 days after the final dose.

[3] A serum pregnancy test will be performed locally in female participants of childbearing potential in the event of a positive or equivocal urine pregnancy test result.

[4] A blood sample will be collected at Screening for *SMN2* copy number for those participants without acceptable historical genetic documentation of *SMN2* copy number. For all other participants, a blood sample will be collected during the study (preferably before or on Day 149) for analysis of both *SMN1* copy number and deletion/mutation and *SMN2* copy number by the central laboratory.

[5] Eligibility based on scoliosis severity at Screening will be determined by local analysis of the X-ray results. The results of the central X-ray read will be documented and used for subsequent data analyses. For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.

[6] Spinal ultrasound, fluoroscopy, or similar techniques may be used for the LP procedure, if deemed necessary, but are not required. Anesthesia (local or general) and/or sedation may be used for the LP procedure, at the discretion of the Investigator and/or study center.

[7] Vital signs will include temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry.

[8] Vital signs will be collected at 1, 2, 4, 6, and 8 hours (±15 minutes) postdose and 24 hours (±2 hours) postdose.

[9] These assessments may be performed up to 7 days prior to dosing/study visit.

[10] Videotaping of physical examinations is optional.

[11] On dosing visits, a neurological examination will be performed predose, at 3 and 6 hours (±15 minutes) postdose, and at 24 hours (±2 hours) postdose, or when anesthesia/sedation (if used) has worn off. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[12] ECGs will be performed predose, at 5 hours (±1 hour) postdose, and at 24 hours (±2 hours) postdose on Days 1, 15, and 29; at the Day 64 visit; at 5 hours (±1 hour) postdose on Days 149 and 269; and at Day 302/ET. Predose ECGs should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing. If a postdose ECG result is abnormal and clinically significant, a repeat ECG should be performed within 2 hours.

[13] Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. These assessments may be performed up to 7 days prior to dosing/study visit, if necessary. Urine total protein will be analyzed by local laboratory only (Appendix B). Predose clinical safety laboratory assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[14] Coagulation testing will be conducted locally at Screening and predose (within 7 days prior to dosing) at each dosing visit; results must be reviewed prior to dosing. Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[15] A safety follow-up telephone call will be made 2 weeks (±3 days) after the Day 29 dose.

[16] Immunogenicity samples will be collected predose on Day 1, predose at all maintenance dosing visits, and at Day 302/ET. Predose immunogenicity assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[17] Plasma PK samples will be collected predose at all dosing visits. In addition, postdose plasma PK samples will be collected at 2, 4, 8, and 24 hours (±2 hours) after the Day 1 dose and on Day 29 at 4 hours (±30 minutes) postdose.

[18] Videotaping of all motor milestone and motor function assessments is optional.

[19] When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments. The 10MWR and 6MWT will be performed in participants who are ambulatory. For the purposes of this protocol, "ambulatory" will be defined as any participant who has achieved independent walking (see Section 9.1.5 and Section 9.1.6, respectively). For participants who are ambulatory at any point during the study per the WHO criteria, the 10MWR test will be performed and continue to be performed through the end of the study, regardless of subsequent changes in ambulatory status. The 6MWT will be performed only in participants ≥ 3.5 years of age at the discretion of the Investigator (at enrollment and through the end of the study).

[20]Two baseline assessments are required for HFMSE and RULM. At least 1 assessment must be conducted during the Screening period. The second assessment may be conducted either during the Screening period or at Day 1 predose. If both baseline assessments are conducted during the Screening period, the assessments do not need to be repeated on Day 1.
[21]During the loading period, the efficacy assessments will be performed on Day 29 predose only. The Day 29 efficacy assessments may be performed up to 3 days prior to dosing, if necessary.
[22]CGIC will be collected on Days 29, 64, and 149 (predose), and Day 302.
[23]Assessments will be performed on Day 1, Day 149, and at Day 302/ET.
[24]Ventilator use will be collected at every study visit (see Section 9.1.10).

Table 2: Schedule of Activities for Part B

	Screening Visit[1]	Treatment							Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day), D64 (±7 days)**			**D135 (±7 days), D183 (±7 days), D279 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D399 (+14 days)**
		Predose	**LP/ SP**	**Postdose**	**Predose**	**LP/ SP**	**Postdose**			
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Local Urine/Serum Pregnancy Test for Females of Childbearing Potential[3]	X	X			X				X	X
Medical (including SMA) History	X									
SMA Genetic Testing[4]	X									
X-ray Examination for Participants With Later-Onset SMA (with the participant in a sitting or supported sitting position)[5]	X									
Randomization (Day 1 only)		X								
LP Opening Pressure[6]			X			X				
Study Treatment Injection/Sham Procedure[7]			X			X				
Inpatient Stay (at least 24 hours)				X			X			
Vital Signs and Pulse Oximetry[8]	X	X		X[9]	X		X[9]		X	
Weight	X	X			X				X	
Growth Parameters (including height/length/ulnar length, and head/chest/arm circumference)[10]	X	X			X[11]				X	

	Screening Visit[1]	Treatment							Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day), D64 (±7 days)**			**D135 (±7 days), D183 (±7 days), D279 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D399 (+14 days)**
		Predose	**LP/ SP**	**Postdose**	**Predose**	**LP/ SP**	**Postdose**			
Physical Examination[12]	X	X			X				X	
Neurological Examination[13]	X	X		X	X		X		X	
ECG[14]		X		X			X		X	
Safety Laboratory Tests[15]	X	X			X				X	
Local Coagulation Laboratory Tests[16]	X	X			X					
Safety Follow-Up Telephone Contact				X[17]				X		
Immunogenicity[18]		X			X[11]				X	
CSF PK		X			X					
Plasma PK[19]		X		X	X[11]				X	
CSF Local Lab Sample (cell count, protein, and glucose)[6]		X			X					
CSF Biomarker		X			X					
Plasma Biomarker		X			X				X	
Efficacy Assessments[20] for Participants With Infantile-Onset SMA (CHOP INTEND and HINE Section 2 Motor Milestones)	X[21]	X[22]			X[11]				X	
Efficacy Assessments[20] for Participants With Later-Onset SMA (HFMSE, RULM, WHO Motor Milestones, 6MWT, and 10MWR[23])	X[21]	X[22]			X[11]				X	

	Screening Visit[1]	Treatment							Follow-Up[2] EOS	
Assessments	**D-21 to D-1**	**D1, D15 (±1 day), D29 (±1 day), D64 (±7 days)**			**D135 (±7 days), D183 (±7 days), D279 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D399 (+14 days)**
		Predose	**LP/ SP**	**Postdose**	**Predose**	**LP/ SP**	**Postdose**			
CGIC[24]		X			X				X	
PedsQL and ACEND[25]		X			X				X	
Dysphagia Assessment (PASA)	X	X[26]			X[26]				X	
Ventilator Use[27]	X	X			X			X	X	
Ventilator Use Diary (for Participants with Infantile-Onset SMA)	X----------X									
AE Recording	X----------X									
SAE Recording	X----------X									
Concomitant Therapy and Procedures Recording	X----------X									

6MWT = 6-Minute Walk Test; 10MWR = 10-Meter Walk/Run Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; CGIC = Clinical Global Impression of Change; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EOS = end of study; ET = early termination; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; ICF = informed consent form; LP = lumbar puncture; PASA = Parent Assessment of Swallowing Ability; PedsQL = Pediatric Quality of Life Inventory™; PK = pharmacokinetic; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; SP = sham procedure; WHO = World Health Organization

[1] If the Screening visit occurs within 7 days before Day 1, screening assessments can be used for Day 1 predose assessments. During the Screening period, participants who have an out-of-range result that is not clinically significant can be retested 1 time only at the discretion of the Investigator. The Screening period may be extended for up to 10 days for individuals who cannot complete the Day 1 visit within 21 days of signing the ICF, as long as they continue to meet other eligibility criteria.

[2] Participants who meet criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 399 visit. Male participants who meet this criteria may complete this visit via a telephone interview. Female participants who meet this criteria will return to the site to complete this assessment. Participants who do not meet criteria for contraception use will have their last visit on Day 302. Day 399 will take place at least 120 days after the final dose.

[3] A serum pregnancy test will be performed locally in female participants of childbearing potential in the event of a positive or equivocal urine pregnancy test result.

[4] A blood sample will be collected at Screening for *SMN2* copy number for those participants without acceptable historical genetic documentation of *SMN2* copy number. For all other participants, a blood sample will be collected during the study (preferably before or on Day 135) for analysis of both *SMN1* copy number and deletion/mutation and *SMN2* copy number by the central laboratory.

[5] Eligibility based on scoliosis severity at Screening will be determined by local analysis of the X-ray results. Results of the central X-ray read will be documented and used for subsequent data analyses. For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.

[6] Only measure LP opening pressure and assess CSF local lab sample on Days 1, 15, and 279 to avoid potential unblinding.

[7] Spinal ultrasound, fluoroscopy, or similar techniques may be used for the LP procedure, if deemed necessary, but are not required. Local anesthesia and/or sedation may be used for the LP procedure in participants with infantile-onset SMA, and anesthesia (local or general) and/or sedation may be used for the LP procedure in participants with later-onset SMA, at the discretion of the Investigator and/or study center. If anesthesia and/or sedation is used for the LP procedure for an individual participant, in order to maintain the blind, that participant will receive equivalent anesthesia and/or sedation (according to institutional procedures) for all of the sham procedures and LP injections. For participants with infantile-onset SMA, LP injections/sham procedures may not occur within 72 hours after an immunization.

[8] Vital signs will include temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry.

[9] Vital signs will be collected at 1, 2, 4, 6, and 8 hours (±15 minutes) postdose and at 24 hours (±2 hours) postdose.

[10] Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height/ulnar length will be measured in participations with later-onset SMA.

[11] These assessments may be performed up to 7 days prior to dosing.

[12] Videotaping of physical examinations is optional.

[13] HINE Sections 1 and 3 will be administered to participants with infantile-onset SMA, and a neurological examination will be performed in participants with later-onset SMA. On dosing visits, a neurological examination will be performed predose, at 3 and 6 hours (±15 minutes) postdose, and at 24 hours (±2 hours) postdose, or when anesthesia/sedation (if used) has worn off. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[14] ECGs will be performed predose, at 5 hours (±1 hour) postdose, and at 24 hours (±2 hours) postdose on Days 1, 15, 29, and 64; at 5 hours (±1 hour) postdose on Days 135, 183, and 279; and at Day 302/ET. Predose ECGs should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing. If a postdose ECG result is abnormal and clinically significant, a repeat ECG should be performed within 2 hours later.

[15] Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. These assessments may be performed up to 7 days prior to dosing/study visit, if necessary. Urine total protein will be analyzed by local laboratory only (Appendix B). Predose clinical safety laboratory assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[16] Coagulation testing will be conducted locally at Screening and predose (within 7 days prior to dosing) at each dosing visit; results must be reviewed prior to dosing. Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[17] A safety follow-up telephone call will be made 2 weeks (±3 days) after the Day 29 dose for the first 20 participants.

[18] Immunogenicity samples will be collected predose on Day 1, predose at all maintenance dosing visits, and at Day 302/ET. Predose immunogenicity assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[19] Plasma PK samples will be collected predose on Days 1, 15, and 64, and at all maintenance dosing visits. In addition, postdose plasma PK samples will be collected at 2, 4, 8, and 24 hours (±2 hours) after the Day 1 dose and on Day 15 at 4 hours (±30 minutes) postdose.

[20] Videotaping of all motor milestone and motor function assessments is optional.

[21]Two baseline assessments are required for CHOP INTEND, HFMSE, and RULM. At least 1 assessment must be conducted during the Screening period. The second assessment may be conducted either during the Screening period or at Day 1 predose. If both baseline assessments are conducted during the Screening period, the assessments do not need to be repeated on Day 1.

[22]During the loading period, the efficacy assessments will be performed on Days 29 and 64 predose only. The Day 29 efficacy assessments may be performed up to 3 days prior to dosing, if necessary. The Day 64 efficacy assessments may be performed up to 7 days prior to dosing, if necessary.

[23]When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments. The 10MWR and 6MWT will be performed in participants with later-onset SMA who are ambulatory. For the purposes of this protocol, "ambulatory" will be defined as any participant who has achieved independent walking (see Section 9.1.5 and Section 9.1.6, respectively). For participants who are ambulatory at any point during the study per the WHO criteria, the 10MWR test will be performed and continue to be performed through the end of the study, regardless of subsequent changes in ambulatory status. The 6MWT will be performed only in participants ≥ 3.5 years of age who are ambulatory at the discretion of the Investigator (at enrollment through the end of the study).

[24]CGIC will be assessed on Days 29, 64, and 183 (predose), and Day 302.

[25]PedsQL and ACEND will be assessed only in participants with later-onset SMA. Assessments will be performed on Day 1, Day 183, and at Day 302/ET.

[26]PASA will be assessed only on Days 64 and 183.

[27]Ventilator use will be collected at every study visit (see Section 9.1.10).

Table 3: Schedule of Activities for Part C

	Screening Visit[1]	Treatment							Follow-up[2] EOS	
Assessments	**D-21 to D-1**	**D1[3]**			**D121 (±7 days), D241 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D361 (+14 days)**
		Predose	**LP**	**Postdose**	**Predose**	**LP**	**Postdose**			
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Local Urine/Serum Pregnancy Test for Females of Childbearing Potential[4]	X	X			X				X	X
Medical (including SMA) History	X									
SMA Genetic Testing[5]	X									
X-ray Examination for Participants with Later-Onset SMA (with the participant in a sitting or supported sitting position)[6]	X									
LP Opening Pressure			X			X				
Study Treatment Injection[7]			X			X				
Inpatient Stay (at least 24 hours)				X						
Vital Signs and Pulse Oximetry[8]		X		X[9]	X		X[9]		X	
Weight		X			X				X	
Growth Parameters (including height/length/ulnar length, and head/chest/arm circumference)[10]		X			X[11]				X	
Physical Examination[12]		X			X				X	

	Screening Visit[1]	**Treatment**							**Follow-up**[2] **EOS**	
Assessments	**D-21 to D-1**	**D1**[3]			**D121 (±7 days), D241 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D361 (+14 days)**
		Predose	**LP**	**Postdose**	**Predose**	**LP**	**Postdose**			
Neurological Examination[13]	X	X		X	X		X		X	
ECG[14]		X		X			X		X	
Safety Laboratory Tests[15]	X	X			X				X	
Local Coagulation Laboratory Tests[16]	X	X			X					
Safety Follow-Up Telephone Contact				X[17]				X		
Immunogenicity[18]		X			X[11]				X	
CSF PK		X			X					
Plasma PK[19]		X		X	X[11]				X	
CSF Local Lab Sample (cell count, protein, and glucose)		X			X					
CSF Biomarker		X			X					
Plasma Biomarker		X			X				X	
Efficacy Assessments Based on Clinical Status[20] (CHOP INTEND, HINE Section 2 Motor Milestones, HFMSE, RULM, WHO Motor Milestones, 6MWT, and 10MWR[21])	X[22]				X[11]				X	
CGIC					X				X	
PedsQL and ACEND[23]		X			X				X	

	Screening Visit[1]	Treatment							Follow-up[2] EOS	
Assessments	**D-21 to D-1**	**D1[3]**			**D121 (±7 days), D241 (±7 days)**			**2 to 14 Days After Each Maintenance Dose**	**D302/ET (±7 days)**	**D361 (+14 days)**
		Predose	**LP**	**Postdose**	**Predose**	**LP**	**Postdose**			
Ventilator Use[24]	X	X			X			X	X	
AE Recording	X----------X									
SAE Recording	X----------X									
Concomitant Therapy and Procedures Recording	X----------X									

6MWT = 6-Minute Walk Test; 10MWR = 10-Meter Walk/Run Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; CGIC = Clinical Global Impression of Change; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EOS = end of study; ET = early termination; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; ICF = informed consent form; LP = lumbar puncture; PedsQL = Pediatric Quality of Life Inventory™; PK = pharmacokinetic; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization

[1] If the Screening visit occurs within 7 days before Day 1, screening assessments can be used for Day 1 predose assessments. During the Screening period, participants who have an out-of-range result that is not clinically significant can be retested 1 time only at the discretion of the Investigator. The Screening period may be extended for up to 10 days for individuals who cannot complete the Day 1 visit within 21 days of signing the ICF, as long as they continue to meet other eligibility criteria.

[2] Participants who meet criteria for contraception use (see Section 11.5) have a Day 302 and a Day 361 visit. Male participants who meet this criteria may complete this visit via a telephone interview. Female participants who meet this criteria will return to the site to complete this assessment. Participants who do not meet criteria for contraception use will have their last visit on Day 302. Day 361 will take place at least 120 days after the final dose.

[3] Day 1 should be 4 months ± 14 days after the participant's most recent nusinersen maintenance dose of 12 mg.

[4] A serum pregnancy test will be performed locally in female participants of childbearing potential in the event of a positive or equivocal urine pregnancy test result.

[5] A blood sample will be collected at Screening for *SMN2* copy number for those participants without acceptable historical genetic documentation of *SMN2* copy number. For all other participants, a blood sample will be collected during the study (preferably before or on Day 121) for analysis of both *SMN1* copy number and deletion/mutation and *SMN2* copy number by the central laboratory.

[6] Up to 5 participants with severe scoliosis and/or severe contractures will be enrolled. Scoliosis severity at Screening will be determined by local analysis of the X-ray results. Results of the central X-ray read will be documented and used for subsequent data analyses. For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.

[7] Spinal ultrasound, fluoroscopy, or similar techniques may be used for the LP procedure, if deemed necessary, but is not required. Local anesthesia and/or sedation may be used for the LP procedure in participants < 2 years of age, and anesthesia (local or general) and/or sedation may be used for the LP procedure in participants ≥ 2 years of age, at the discretion of the Investigator and/or study center. LP injections may not occur within 72 hours after an immunization.
[8] Vital signs will include temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry.
[9] Vital signs will be collected at 1, 2, 4, 6, and 8 hours (±15 minutes) postdose and at 24 hours (±2 hours) postdose.
[10] Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height/ulnar length will be measured in participants with later-onset SMA.
[11] These assessments may be performed up to 7 days prior to dosing.
[12] Videotaping of physical examinations is optional.
[13] HINE Sections 1 and 3 will be administered to participants < 2 years of age at the time of informed consent, and a neurological examination will be performed in participants ≥ 2 years of age at the time of informed consent. On dosing visits, a neurological examination will be performed predose, at 3 and 6 hours (±15 minutes) postdose, and at 24 hours (±2 hours) postdose, or when anesthesia/sedation (if used) has worn off. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.
[14] ECGs will be performed predose, at 5 hours (±1 hour) postdose, and at 24 hours (±2 hours) postdose on Day 1; at 5 hours (±1 hour) postdose on Days 121 and 241; and at Day 302/ET. Predose ECGs should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing. If a postdose ECG result is abnormal and clinically significant, a repeat ECG should be performed within 2 hours.
[15] Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. These assessments may be performed up to 7 days prior to dosing/study visit, if necessary. Urine total protein will be analyzed by local laboratory only (Appendix B). Predose clinical safety laboratory assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.
[16] Coagulation testing will be conducted locally at Screening and predose (within 7 days prior to dosing) at each dosing visit; results must be reviewed prior to dosing. Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.
[17] A safety follow-up telephone call will be made 2 weeks (±3 days) after the Day 1 bolus dose.
[18] Immunogenicity samples will be collected predose on Day 1, predose on Day 241, and at Day 302/ET. Predose immunogenicity assessments should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.
[19] Plasma PK samples will be collected predose at all dosing visits. In addition, postdose plasma PK samples will be collected 2, 4, 8, and 24 hours (±2 hours) after the Day 1 dose.
[20] The Investigator will select the appropriate efficacy assessments based on criteria in Section 9.1. Videotaping of all motor milestone and motor function assessments is optional.
[21] When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments. The10MWR and 6MWT will be performed in participants who are ambulatory. For the purposes of this protocol, "ambulatory" will be defined as any participant who has achieved independent walking (see Section 9.1.5 and Section 9.1.6, respectively). For participants who are ambulatory at any point during the study per the WHO criteria, the 10MWR test will be performed and continue to be performed through the end of the study, regardless of subsequent changes in ambulatory status. The 6MWT will be performed only in participants ≥ 3.5 years of age at the discretion of the Investigator (at enrollment and through the end of the study).
[22] Two baseline assessments are required for CHOP INTEND, HFMSE, and RULM. At least 1 assessment must be conducted during the Screening period. The second assessment may be conducted either during the Screening period or at Day 1 predose. If both baseline assessments are conducted during the Screening period, the assessments do not need to be repeated on Day 1.
[23] PedsQL and ACEND will be assessed only in participants ≥ 2 years of age at Screening. Assessments will be performed on Day 1, Day 241, and at Day 302/ET.

[24]Ventilator use will be collected at every study visit (see Section 9.1.10).

2. LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
10MWR	10-Meter Walk/Run Test
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
CGIC	Clinical Global Impression of Change
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C_{trough}	trough concentration
DHA	Directions for Handling and Administration
EAC	endpoint adjudication committee
EC_{50}	concentration at 50% of the maximum observed biological effect
EC_{90}	concentration at 90% of the maximum observed biological effect
ECG	electrocardiogram
GCP	Good Clinical Practice
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IRT	interactive response technology
ITT	Intent-to-Treat
LP	lumbar puncture
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PASA	Parent Assessment of Swallowing Ability
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory™
PK	pharmacokinetic(s)
pNF-H	phosphorylated neurofilament heavy chain
QoL	quality-of-life
QTcF	corrected QT interval using Fridericia's formula
RSV	respiratory syncytial virus
RULM	Revised Upper Limb Module
SAE	serious adverse event

SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron-1
SMN2	survival motor neuron-2
SUSAR	suspected unexpected serious adverse reaction
US	United States
WHO	World Health Organization

3. INTRODUCTION

Nusinersen is an antisense oligonucleotide administered intrathecally via lumbar puncture (LP); it increases survival motor neuron (SMN) protein expression and significantly improves motor function in patients with spinal muscular atrophy (SMA). Nusinersen was approved for the treatment of SMA under the tradename Spinraza™ in the United States (US), European Union, and 15 other countries. The population for this study includes participants with infantile-onset and later-onset SMA.

3.1. Study Rationale

Efficacy and safety results across the nusinersen clinical development program have demonstrated an overall positive benefit-risk profile of nusinersen across a broad range of SMA phenotypes and patient populations. Nusinersen is approved in the US, Europe, and other countries and regions for the treatment of SMA in pediatric and adult patients at a recommended dosage of 12 mg administered in 3 loading doses at 14-day intervals, a fourth loading dose 30 days after the third dose, and maintenance doses every 4 months thereafter. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses indicate that nusinersen drug exposure higher than that achieved with 12 mg in patients with SMA may produce an even greater benefit in motor function. Additionally, PK modeling and simulations identified dosing regimens that achieve higher drug exposure more rapidly. Therefore, this study is being conducted to investigate the efficacy, safety, tolerability, and PK of a 50/28-mg dose of nusinersen (50-mg loading dose/28-mg maintenance dose) and a dosing regimen targeted to achieve higher drug exposure more rapidly. This study will be conducted in participants with genetically confirmed SMA.

Part A of the study will evaluate the safety of a higher loading dose and maintenance dosing regimen (28-mg loading/28-mg maintenance) than the approved regimen (12-mg loading/12-mg maintenance) prior to exposing participants to the target high dosing regimen (50-mg loading/28-mg maintenance) in the pivotal portion of the study.

In Part B, in order to evaluate the proposed high dosing regimen, an active-controlled design is being used, with participants randomized either to the investigational dosing regimen (50-mg loading/28-mg maintenance) or to the currently approved dosing regimen (12-mg loading/12-mg maintenance). In order to reduce the number of participants enrolled in Part B of this study, historical data from the existing data set for Study CS3B, a Phase 3 efficacy and safety study of nusinersen in participants with infantile-onset SMA, will be borrowed to augment the control arm (see Section 12.4 for details). Enrollment in Part B will begin after 6 participants in Part A have completed the loading period (i.e., when the last participant reaches the Day 64 visit) and after an independent data monitoring committee (IDMC) has reviewed the available safety data to recommend whether Part B can be initiated. If deemed necessary by the Sponsor, additional participants may be enrolled in Part A to ensure sufficient data are available for the safety evaluation prior to enrollment of participants in Part B. Details regarding the IDMC review of data may be found in the IDMC charter. Note that the IDMC can recommend to stop the study based on the safety findings.

Part C of the study will allow safety evaluation of transitioning participants who are on the currently approved dose of nusinersen (12-mg maintenance for at least 1 year after the initiation of treatment) to the proposed high dosing regimen via the administration of a single bolus of 50 mg of nusinersen (which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg), with maintenance dosing at 28 mg thereafter. Enrollment in Part C will be staggered with that in Part B such that at least 29 days of safety follow-up for at least 15 participants in Part B will be available, with no safety concerns identified by the IDMC, before the first participants will be enrolled in Part C. Note that the IDMC can recommend to stop the study based on the safety findings.

3.1.1. Rationale for Study Population

Part A will be conducted in participants with later-onset SMA who are 2 to ≤ 15 years of age, inclusive, for the purpose of evaluating adverse events (AEs).

Part B will include participants with both infantile-onset SMA (≤ 7 months of age) and later-onset SMA (2 to < 10 years of age). The infantile-onset SMA population was selected as the main population to evaluate efficacy based on the following considerations:

- The results of PK modeling and simulations showed that an improvement in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), which is administered in participants with infantile-onset SMA, may be possible with a higher dose.

- Data from Studies CS3B and CS4 show that improvement in efficacy occurs more quickly in younger participants with shorter disease duration.

Therefore, the infantile-onset SMA population may be more sensitive to a higher dose, and thus efficacy in Part B can be assessed at an earlier timepoint compared to participants with later-onset SMA. In addition, the choice of the infantile-onset SMA population allows the opportunity to leverage data from Study CS3B, which used the approved dose of 12 mg, as does the Control Group in this study.

Part C will enroll participants of all ages with SMA who have been receiving nusinersen treatment for at least 1 year prior to entry in this study. This part is designed to evaluate the safety of transitioning participants from the currently approved dosing regimen to the high dosing regimen in a representative patient population.

3.1.2. Rationale for Dosing Regimen

The clinical PK, safety, and efficacy of nusinersen have been evaluated in a number of patient populations (infantile-onset [SMA symptom onset ≤ 6 months (≤ 180 days) of age], later-onset [SMA symptom onset > 6 months (> 180 days) of age], and presymptomatic). The approved dosing regimen of nusinersen is 12 mg administered in 3 loading doses at 14-day intervals, a fourth loading dose 30 days after the third dose, and maintenance doses every 4 months thereafter. In the original development program, 2 different dosing regimens (4 loading doses

followed by maintenance doses every 4 months and 3 loading doses followed by maintenance doses every 6 months) were evaluated in sham-controlled studies. Results from these studies, population PK and exposure-response modeling, and nonhuman primate safety studies were used as the basis for selecting dosing regimens in this study.

An exploratory exposure-response analysis performed in participants with infantile-onset SMA (Study CS3A, n = 20, age 38 days to 8 months) showed a statistically significant positive correlation between nusinersen cerebrospinal fluid (CSF) exposure and motor function (e.g., CHOP INTEND scores). Additional analyses in the same patient population from Studies CS3A and CS3B (n = 80, age 30 days to 8 months) showed that the near-steady-state CSF exposure (approximately 10 ng/mL) closely approximated the model-predicted concentration at 50% of the maximum observed biological effect (EC_{50}) using CHOP INTEND (change from baseline) as the primary efficacy endpoint. These results suggest that additional clinical efficacy may be possible with increased nusinersen central nervous system (CNS) exposure. Under the assumption of PK linearity, increasing the nusinersen dose to 24 mg, with a dosing frequency of 4 loading doses followed by maintenance doses administered every 4 months, should effectively increase the CSF trough concentration (C_{trough}) at steady state to approximately 20 ng/mL. This concentration is comparable to the predicted concentration at 90% of the maximum observed biological effect (EC_{90}) from the infantile-onset SMA population. This assumption is supported by nusinersen toxicokinetic results in nonhuman primates, which showed nearly dose-proportional PK in the plasma and CNS tissues (target site of action) up to 15 mg (human equivalent dose of 150 mg). It is important to highlight that the maximum response from the existing clinical data is limited because 12 mg was the highest dose administered in humans, and the majority of the dataset are within the CSF C_{trough} range of 5 to 15 ng/mL; therefore, extrapolation of the efficacy response above 20 ng/mL is not recommended. The PK/PD relationship has thus far been demonstrated primarily in the infantile-onset SMA population. However, the same positive PK/PD relationship is expected across SMA types and patient age groups because they share the same disease mechanism. This is supported by the preliminary correlation analysis from Study 232SM202, which showed a positive relationship between CSF C_{trough} and total motor milestones scores in participants with infantile- and later-onset SMA who received 12 mg of nusinersen as 4 loading doses followed by maintenance doses every 4 months.

Using 20 ng/mL as the clinical CSF C_{trough} target concentration and the predicted CSF PK profiles from 24 mg of nusinersen (4 loading doses followed by maintenance doses every 4 months) as the reference dosing regimen, simulations were performed to evaluate additional dosing scenarios with higher doses and reduced loading-dose frequency. Additional evaluation of the maintenance dosing frequency was not performed because previous modeling showed that a dosing frequency of every 4 months best maintained the CSF concentration achieved at steady state. Assuming PK linearity, PK simulations were performed in both infantile- and later-onset SMA populations after 2 years of treatment using a population PK model developed from patients across the age range of ≤ 6 months to 18 years old. Relative to the reference dosing regimen, both 28 mg administered as 3 loading doses (biweekly) and 50 mg administered as 2 loading doses (biweekly), each followed by maintenance doses of 28 mg every 4 months, were identified to achieve the desired CSF C_{trough} (approximately 20 ng/mL) more rapidly. Nusinersen

28 mg administered as 3 loading doses (biweekly) had a comparable predicted CSF maximum concentration (C_{max}) to the reference dosing regimen, whereas the 50-mg dosing regimen surpassed the predicted C_{max} from the reference dosing regimen. Toxicology studies in nonhuman primates evaluating the nonhuman primate equivalent of the 28- and 50-mg doses have been conducted and support the safety of these doses in a clinical study. Therefore, the 28-mg dose (administered as 3 loading doses at biweekly intervals), 50-mg dose (administered as 2 loading doses at biweekly intervals), and 28-mg maintenance dose were recommended for additional clinical evaluation.

The single bolus in Part C is supported by PK simulations showing that a titration dosing regimen of a single loading dose (50 mg) followed by maintenance doses of 28 mg every 4 months thereafter achieved and maintained the higher CSF C_{trough} target concentration (approximately 20 ng/mL) in the representative populations for later-onset and infantile-onset SMA, respectively. The predicted exposures of the proposed titration dosing regimens are covered by the levels demonstrated to be safe in nonhuman primates.

3.2. Background

3.2.1. Overview of SMA

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 8.5 to 10.3 per 100,000 live births, it is the most common monogenetic cause of infant mortality and a major cause of childhood morbidity due to weakness in the US [Arkblad 2009; Jedrzejowska 2010]. Historically, the natural history of SMA includes 4 major recognized phenotypes that are dependent on age of onset and achieved motor abilities. 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 2 years of age. Patients with Type II SMA are able to sit but never walk unaided, with symptoms 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 SMA typically have disease onset after the age of 18 years and have normal life expectancies.

Humans have a variable copy number of the survival motor neuron-2 (*SMN2*) gene (0 to 8 copies) [Wirth 2006]. The number of *SMN2* copies and the resulting amount of full-length SMN 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].

3.2.2. Current Therapies for SMA

In countries where nusinersen (Spinraza) is not approved, current medical care is limited to supportive care, focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and progressive kyphoscoliosis through bracing, physical therapy, and surgery, with specific guidelines according to age of SMA onset [Finkel 2017; Mercuri 2018].

A gene transfer agent, Zolgensma® (AveXis Inc.), an adeno-associated virus vector expressing a survival motor neuron-1 (*SMN1*) gene delivered intravenously, was approved in the US in 2019 and Japan in 2020 for the treatment of pediatric patients younger than 2 years of age with SMA with biallelic mutations in the *SMN1* gene. Investigational therapies include oral SMN-upregulating therapies such as RG7916 (Clinical Trials.gov identifier NCT02633709).

3.2.3. Profile of Previous Experience With Nusinersen

Nusinersen is an antisense oligonucleotide administered intrathecally via LP and increases SMN protein expression and significantly improves motor function in patients with SMA.

The primary support for the efficacy of nusinersen in the treatment of SMA derives from sham-controlled studies in participants with infantile-onset SMA (primarily Type I SMA) and later-onset SMA (may include Type II and Type III SMA). Results from uncontrolled studies in genetically diagnosed, presymptomatic infants, participants with infantile-onset SMA, and participants with later-onset SMA are highly supportive of the results of the pivotal sham-controlled efficacy studies and provide evidence of long-term benefit. Nusinersen has been administered to 352 unique participants with SMA in 10 clinical studies to date, with safety data available for 346 participants during 665 person-years of exposure. Treatment with nusinersen has been well tolerated, and the serious adverse event (SAE) profile is consistent with the events seen in infants and children with SMA.

Nusinersen was approved for the treatment of SMA under the tradename Spinraza™ in the US on 23 December 2016 (New Drug Application 209531). Spinraza is also approved for the treatment of SMA in the European Union (for 5q SMA [30 May 2017]), Canada (for 5q SMA [29 June 2017]), Brazil (for 5q SMA [28 August 2017]), Switzerland (for 5q-associated SMA [20 September 2017]), Japan (for infantile-onset SMA [03 July 2017] and for all other types of SMA [22 September 2017]), Australia (for 5q SMA [02 November 2017]), South Korea (for 5q SMA [29 December 2017]), Chile (for 5q SMA [25 January 2018]), Uruguay (for 5q SMA [31 July 2018]), New Zealand (for 5q SMA [23 August 2018]), Qatar (for 5q SMA [11 September 2018]), , United Arab Emirates (10 October 2018), Mexico (29 November 2018), China (for 5q SMA [22 February 2019]; Hong Kong [20 September 2018], Argentina (01 March 2019), Colombia (for 5q SMA with Hammersmith Functional Motor Scale ≥ 10 and ≤ 54 in children under 6 years with confirmed genetic diagnosis [11 April 2019]), Russia (SMA [16 August 2019]), Israel (5q SMA except type 0 and type IV [19 August 2019]), and Ukraine (5q SMA [11 January 2020]). Marketing applications are under review in other geographic locations.

As of 31 December 2019, more than 10,000 patients with SMA are being treated with nusinersen worldwide, based on the postmarketing setting, expanded access programs, and clinical trials.

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

3.3. Benefit-Risk Assessment

Nusinersen (Spinraza) has a positive benefit-risk profile, with more than 3 years of postmarketing experience and more than 10,000 patients treated. The safety profile to date does not preclude study of higher doses in any population.

Anticipating a potential enhancement of benefit with the dosing regimens proposed for Study 232SM203, substantiated by PK/PD modeling described in Section 3.1.2, the safety of the loading period for Study 232SM203 is supported by a nonclinical study conducted in monkeys (Study P058-17-05), with the dosing regimen matching with the most rigorous loading in Study 232SM203 (3 loading doses administered at 2-week intervals). The no-observed-adverse-effect level (NOAEL) for Study P058-17-05 was determined to be 15 mg (human equivalent dose of 150 mg), the high dose of the study, supported by the observation of non-adverse findings limited to dose-dependent/transient neurological clinical signs and histopathological findings in the brain and lymph nodes. This NOAEL provides a safety margin of at least 4.5-fold for the loading doses (based on cumulative doses during the loading period).

The safety of long-term exposure during the Study 232SM203 maintenance period is supported by a 53-week monkey study (Study 396443-AS06). This study implemented a more frequent dosing regimen than what is planned for Study 232SM203, 13 total doses during the 53-week duration, with the first 5 doses given once every week during the first 29 days, followed by an additional 8 doses given once every 6 weeks. Based on the 3 dose levels (0.3, 1, and 4 mg per dose) used in the study, for a duration of 53 weeks, the monkeys received a cumulative nusinersen dose of 3.9, 13, and 52 mg, respectively, at each dose level. Factoring in a CSF volume scale of 10 between humans and monkeys, the annual cumulative doses in monkeys from this study ranged from 3.0- to 7.2-fold (loading doses) and 6.2- to 14.4-fold (maintenance doses) higher than those planned for Study 232SM203. The major findings in monkeys were the histopathological changes in the hippocampus, which consisted of neuronal vacuolation and rare necrotic cells and cell debris at the 2 highest doses (1 and 4 mg). The overall no-observed-effect level (NOEL) for the study was 0.3 mg, driven by findings limited to the hippocampus, while no effects in any other tissues were observed up to the high dose (4 mg) on a comprehensive histopathology evaluation. PK scaling was used to estimate the nusinersen tissue concentration in patients with SMA during maintenance treatment at 28 mg from tissue concentrations measured in patients with SMA treated with 12 mg of nusinersen (scaled from the tissue concentrations measured during autopsy of participants from Study CS3A). Tissue concentrations measured in monkeys from the 53-week toxicology study at the NOEL (0.3 mg for the hippocampus and 4 mg for all other tissues evaluated) were compared to the estimated tissue concentrations in patients with SMA. Based on these data, the exposure-based safety margin is at least 1.1-fold.

The potential risks related to participation in this study are justified by the anticipated benefit to participants.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of nusinersen is provided in the Investigator's Brochure and informed consent form (ICF). A high-level summary of the benefits and risks known during study design is provided here.

4. STUDY OBJECTIVES AND ENDPOINTS

Part B Primary Objective	**Primary Endpoint**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA, as measured by change in CHOP INTEND total score	Infantile-Onset SMA • Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the joint-rank test
Part B Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	Infantile-Onset SMA • Proportion of HINE Section 2 Motor Milestone responders at Day 302 • Change from baseline to Day 302 in HINE Section 2 motor milestones total score accounting for mortality/dropout using the joint-rank test • Time to death or permanent ventilation (tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in the absence of an acute reversible event [Appendix A]) • Time to death (overall survival) Later-Onset SMA • Change from baseline in HFMSE score • Change from baseline in RULM score • Total number of new WHO Motor Milestones

	• Change from baseline in ACEND • Change from baseline in PedsQL
To examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA	• Incidence of AEs, including SAEs • Shifts from baseline in clinical laboratory parameters, ECGs, and vital signs • Change in growth parameters • Shifts from baseline in coagulation parameters (aPTT, PT, and INR) • Change in urine total protein • Change from baseline in neurological examination outcomes • The proportion of participants with a postbaseline platelet count below the lower limit of normal on at least 2 consecutive measurements • The proportion of participants with a postbaseline QTcF of > 500 msec and an increase from baseline to any postbaseline timepoint in QTcF of > 60 msec
To examine the effect of nusinersen administered intrathecally at higher doses compared to the currently approved dose in participants with SMA	• Number and duration of hospitalizations • CGIC (physician, caregiver) at Day 302 • Number of serious respiratory events • Proportion of time on ventilation (infantile-onset SMA population) • Ventilator use

	• Change in the PASA scale
Part B Exploratory Objectives	**Exploratory Endpoints**
To examine the effect of nusinersen treatment on biomarkers including but not limited to pNF-H levels (CSF and plasma) after intrathecal administration of nusinersen given at higher doses to participants with SMA	• CSF levels of pNF-H • Plasma levels of pNF-H • Association of levels of pNF-H at earlier timepoints after the first dose with change from baseline in motor function assessment at later timepoints
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	• Change from baseline in 10MWR (ambulatory participants) • Change from baseline in 6MWT (ambulatory participants)
To examine the PK of nusinersen (CSF and plasma) after intrathecal administration of nusinersen given at higher doses to participants with SMA	• CSF levels of nusinersen • Plasma levels of nusinersen

6MWT = 6-Minute Walk Test; 10MWR = 10-Meter Walk/Run Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; aPTT = activated partial thromboplastin time; CGIC = Clinical Global Impression of Change; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF = cerebrospinal fluid; ECG = electrocardiogram; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; INR = international normalized ratio; PASA = Parent Assessment of Swallowing Ability; PedsQL = Pediatric Quality of Life Inventory™; PK = pharmacokinetics; pNF-H = phosphorylated neurofilament heavy chain; PT = prothrombin time; QTcF = corrected QT interval using Fridericia's formula; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; WHO = World Health Organization

Parts A and C Primary Objective	**Primary Endpoints**
To examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA	• Incidence of AEs, including SAEs • Shifts from baseline in clinical laboratory parameters, ECGs, and vital signs • Change in growth parameters • Shifts from baseline in coagulation

	parameters (aPTT, PT, and INR) • Change in urine total protein • Change from baseline in neurological examination outcomes • The proportion of participants with a postbaseline platelet count below the lower limit of normal on at least 2 consecutive measurements • The proportion of participants with a postbaseline QTcF of > 500 msec and an increase from baseline to any postbaseline timepoint in QTcF of > 60 msec
Parts A and C Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	Parts A and C: • Change from baseline in HFMSE score • Change from baseline in RULM score • Total number of new WHO motor milestones • Change from baseline in ACEND • Change from baseline in PedsQL Part C only: • Change from baseline in CHOP INTEND • Change from baseline in HINE Section 2 motor milestones
To examine the effect of nusinersen administered intrathecally at higher doses to participants with SMA	Parts A and C: • Number and duration of hospitalizations

	• CGIC (physician, caregiver) at Day 302 • Number of serious respiratory events • Ventilator use • Change in the PASA scale (Part A only)
Parts A and C Exploratory Objectives	**Exploratory Endpoints**
To examine the effect of nusinersen treatment on biomarkers including but not limited to pNF-H levels (CSF and plasma) after intrathecal administration of nusinersen given at higher doses to participants with SMA	• CSF levels of pNF-H • Plasma levels of pNF-H • Association of levels of pNF-H at earlier timepoints after the first dose with change from baseline in motor function assessment at later timepoints
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA	• Change from baseline in 6MWT distance and 10MWR (ambulatory participants)
To examine the PK of nusinersen (CSF and plasma) after intrathecal administration of nusinersen given at higher doses to participants with SMA	• CSF levels of nusinersen • Plasma levels of nusinersen

6MWT = 6-Minute Walk Test; 10MWR = 10-Meter Walk/Run Test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; AE = adverse event; aPTT = activated partial thromboplastin time; CGIC = Clinical Global Impression of Change; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF = cerebrospinal fluid; ECG = electrocardiogram; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; INR = international normalized ratio; PASA = Parent Assessment of Swallowing Ability; PedsQL = Pediatric Quality of Life Inventory™; PK = pharmacokinetics; pNF-H = phosphorylated neurofilament heavy chain; PT = prothrombin time; QTcF = corrected QT interval using Fridericia's formula; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; WHO = World Health Organization

Residual samples collected in this clinical study may be used for future scientific and genetic research if participants provide separate optional consent or as allowed by local regulations. Objectives related to this future research have not been determined.

Statistical Hypotheses for Part B Infantile-Onset SMA Population

Primary hypothesis: The population mean change from baseline in CHOP INTEND in the 50/28-mg Group is different from that in the Study CS3B Sham Control Group at Day 183.

Secondary hypotheses:

1. The true population proportion of participants defined as a Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone responder in the 50/28-mg Group is different from that in the Study CS3B Sham Control Group at Day 302.

2. The hazard ratio (50/28-mg Group over CS3B Sham Control Group) for time to death or permanent ventilation is different from 1.

3. The hazard ratio (50/28-mg Group over Study CS3B Sham Control Group) for time to death is different from 1.

Exploratory hypotheses:

1. The population mean change from baseline in CHOP INTEND in the 50/28-mg Group is different from that in the 12-mg Group (Control Group + Study CS3B borrowed 12 mg participants) at Day 183.

2. The population mean change from baseline in population HINE Section 2 motor milestone total score in the 50/28-mg Group is different from that in the 12-mg Group (Control Group + Study CS3B borrowed 12 mg participants) at Day 302.

3. The true population proportion of participants defined as a HINE Section 2 motor milestone responder in the 50/28-mg Group is different from that in the 12-mg Group (Control Group + Study CS3B borrowed 12 mg participants) at Day 302.

4. The hazard ratio (50/28-mg Group over 12 mg Group) for time to death or permanent ventilation is different from 1.

5. The hazard ratio (50/28-mg Group over 12 mg Group) for time to death is different from 1.

5. STUDY DESIGN

5.1. Study Overview

This 3-part study will evaluate the efficacy and safety of a high dosing regimen of nusinersen in approximately 152 participants. The study will be conducted at approximately 65 sites globally. Following the completion of this study, all eligible participants may elect to enroll in a separate long-term extension study, pending study approval by ethics committees and the appropriate regulatory authorities. In regards to participants rolling over from Part B, this will be done without unblinding the participant's treatment group.

Participants will be followed for approximately 323 to 420 days in Parts A, B, and C.

The study consists of an open-label safety evaluation of a regimen consisting of nusinersen administered intrathecally at loading doses of 28 mg followed by maintenance dosing at 28 mg (Part A); a pivotal, double-blind, active-controlled portion (Part B) in which participants will be randomized to 1 of 2 regimens (loading doses of nusinersen at 50 mg followed by maintenance dosing at 28 mg [50/28-mg regimen] or loading and maintenance dosing at 12 mg [control dosing regimen]); and a third open-label portion (Part C) in which participants who have already been treated with nusinersen for at least 1 year prior to entry in this study will receive a single 50-mg bolus of nusinersen followed by maintenance dosing at 28 mg.

Part A will enroll a minimum of 6 participants with later-onset SMA, from 2 to ≤ 15 years of age, inclusive, at the signing of informed consent. Participants will receive 3 loading doses of 28 mg (Days 1, 15, and 29) followed by 2 maintenance doses of 28 mg (Days 149 and 269). Participants will remain at the clinic for at least 24 hours after each dose. A sentinel dosing approach will be used, in which the first participant will be enrolled and dosed with 28 mg of nusinersen. Following the availability of 72 hours of safety data after the first loading dose in the first participant, data for this participant will be reviewed by the Investigator and the Sponsor before the next 5 participants are enrolled. Only 1 participant can receive their first dose of study treatment on a given day.

After 6 participants have completed the loading period (i.e., when the last participant has available safety data through the Day 64 visit), an IDMC will review the available safety data to recommend whether Part B can be initiated. If deemed necessary by the Sponsor, additional participants may be enrolled in Part A to ensure sufficient data are available for the IDMC review prior to enrollment of participants in Part B. Details regarding the IDMC review of data may be found in the IDMC charter. Meanwhile, participants in Part A will proceed to maintenance dosing without interruption. Note that the IDMC can recommend to stop the study based on the safety findings.

Part B will consist of a pivotal, double-blind, active-controlled treatment period with either 2 or 4 loading doses of nusinersen (for the 50/28-mg Group and Control Group, respectively) administered intrathecally followed by maintenance doses approximately every 4 months

thereafter. Up to 126 participants with infantile- or later-onset SMA will be randomized in a 1:2 ratio to receive either the currently approved dosing regimen of 4 loading doses of 12 mg of nusinersen administered intrathecally (Days 1, 15, 29, and 64) followed by 2 maintenance doses of 12 mg on Days 183 and 279 (Control Group) or 2 loading doses of 50 mg of nusinersen administered intrathecally (Days 1 and 15) followed by 2 maintenance doses of 28 mg on Days 135 and 279 (50/28-mg Group). In order to maintain blinding, 1 sham procedure will be administered in the Control Group on Day 135 and 3 sham procedures will be administered in the 50/28-mg Group on Days 29, 64, and 183 to ensure the same dosing visit schedule as the Control Group. Participants will remain at the clinic for at least 24 hours after each study treatment administration or sham procedure.

Randomization in Part B will be performed using interactive response technology (IRT). For Part B, the randomization will be stratified as follows:

- For participants with infantile-onset SMA by disease duration: ≤ 12 weeks and > 12 weeks (time from age at symptom onset to age at informed consent)

- For participants with later-onset SMA by age at informed consent: < 6 years and ≥ 6 years

Once the fifteenth participant in Part B has been enrolled and administered the first dose of study treatment, no new participants will be dosed in Part B until after an IDMC review. The IDMC will review unblinded data from the first 15 participants in Part B who have completed the Day 29 visit (in order to achieve 6 or more participants who have received 50 mg in the 50/28-mg Group while maintaining the blind for the rest of the study team). This review will include safety data through the Day 29 visit at a minimum and all available individual CSF and plasma nusinersen concentration data for these participants, including the Day 15 samples at a minimum. Dosing of the remaining participants in Part B and dosing in Part C will occur only after this review has completed, provided that no safety concerns are identified. Note that the IDMC can recommend to stop the study based on the safety findings.

In Part C, approximately 20 participants will be enrolled and will consist of patients of any age or SMA status who have already initiated treatment with nusinersen and have been receiving the approved dose of 12 mg for at least 1 year prior to entry in this study. An attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants ≥ 18 years of age must be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in Part C after consultation with the Medical Monitor. Participants will receive a single bolus dose of 50 mg (which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241. Participants in Part C will remain at the clinic for at least 24 hours after the first (bolus) dose for the purpose of completing study assessments.

See Figure 1 for a schematic of the study design.

5.2. Study Duration for Participants

The total study duration for each participant will be approximately up to 420 days, divided as follows:

- Part A: approximately 323 to 410 days
  - Screening: 21 days
  - Loading period: 64 days
  - Maintenance period: 205 days
  - Follow-up: 33 to 120 days
- Part B: approximately 323 to 420 days
  - Screening: 21 days
  - Loading period: 64 days
  - Maintenance period: 215 days
  - Follow-up: 23 to 120 days
- Part C: approximately 323 to 382 days
  - Screening: 21 days
  - Loading period: 1 day
  - Maintenance period: 240 days
  - Follow-up: 61 to 120 days

Participants will have the following numbers of visits during the study:

- Part A: 8 to 9 visits
- Part B: 9 to 10 visits
- Part C: 5 to 6 visits

Visits during Days 1, 15, and 29 of the loading period of Parts A and B and Day 1 of the loading period of Part C should be performed ±1 day from the nominal visit day. Visits during Day 64 of the loading period of Parts A and B and the maintenance period of Parts A, B, and C should be performed ±7 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the date of first dose).

The end-of-study date for a participant may be the last study visit, last follow-up telephone conversation, last protocol-specified assessment, or, if the participant has ongoing SAEs that are being followed, the date of SAE resolution.

5.3. Study Stopping Rules

Dosing of all participants in Parts A and B will be suspended until safety information can be fully evaluated by the IDMC in the event of the following occurring in Parts A and/or B:

- Two or more participants experience the same SAE that is considered related to the study treatment by the Investigator or Sponsor.
- Two or more participants develop a similar AE that is considered related to the study treatment and is rated as severe by the Investigator or Sponsor.
- Any treatment-related AE is intolerable or poses a medically unacceptable safety risk as determined by the IDMC.

Dosing may resume only if, after review of safety information, the IDMC recommends that it is safe to proceed. The study may be stopped at the discretion of the Sponsor.

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

5.4. Unscheduled Visits

Data collected during unscheduled visits should be recorded on case report forms (CRFs) only if the data support protocol objectives and/or are required for safety monitoring. This includes laboratory assessments collected locally for the purposes of safety monitoring.

5.5. End of Study

The end of study is last participant, last visit (either in-person visit or telephone contact) for final collection of data.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

Inclusion criteria are presented separately for each study part.

Part A

1. Signed informed consent of parent or guardian and signed informed assent of the participant, if indicated per participant's age and institutional guidelines

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 (> 180 days) of age (i.e., later-onset SMA)

4. Age 2 to ≤ 15 years, inclusive, at the time of informed consent

5. Able to complete all study procedures, measurements, and visits and parent(s) or legal guardian(s)/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator

6. Must be compliant with the study travel policy (see Section 15.4)

7. Estimated life expectancy > 2 years from Screening, in the opinion of the Investigator

8. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either anesthesiologist or pulmonologist)

9. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations

10. All female participants of childbearing potential (defined as any female physiologically capable of becoming pregnant) and all male participants of reproductive age must practice contraception as described in Section 11.5

Part B

All participants

1. Signed informed consent of parent or guardian and signed informed assent of the participant, if indicated per participant's age and institutional guidelines

2. Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote)

3. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations

4. Able to complete all study procedures, measurements, and visits and parent(s) or legal guardian(s)/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator

5. Must be compliant with the study travel policy (see Section 15.4)

6. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either anesthesiologist or pulmonologist)

7. All female participants of childbearing potential (defined as any female physiologically capable of becoming pregnant) and all male participants of reproductive age must practice contraception as described in Section 11.5

Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile onset)

8. Age > 1 week to ≤ 7 months (≤ 210 days) at the time of informed consent

9. *SMN2* copy number = 2

10. Onset of clinical signs and symptoms consistent with SMA at ≤ 6 months (≤180 days) of age

11. At Screening, receiving adequate nutrition and hydration, in the opinion of the Investigator

12. Body weight in at least the third percentile for age using appropriate country-specific guidelines

13. Gestational age of 37 to 42 weeks for singleton births and 34 to 42 weeks for twins

Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset)

14. Onset of clinical signs and symptoms consistent with SMA at > 6 months (> 180 days) of age

15. Age 2 to < 10 years at the time of informed consent

16. Can sit independently but has never had the ability to walk independently

17. Hammersmith Functional Motor Scale – Expanded (HFMSE) score ≥ 10 and ≤ 54 at Screening

18. Estimated life expectancy > 2 years from Screening, in the opinion of the Investigator

Part C

1. Signed informed consent of parent or guardian and signed informed assent of the participant, if indicated per participant's age and institutional guidelines

2. Males and females of any age (individuals ≥ 18 years of age at Screening must be ambulatory)

3. Currently on nusinersen treatment at the time of Screening, with the first dose being at least 1 year prior to Screening

4. Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote)

5. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations

6. Able to complete all study procedures, measurements, and visits and parent(s) or legal guardian(s)/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator

7. Must be compliant with the study travel policy (see Section 15.4)

8. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either anesthesiologist or pulmonologist)

9. All female participants of childbearing potential (defined as any female physiologically capable of becoming pregnant) and all male participants of reproductive age must practice contraception as described in Section 11.5

10. Postmenopausal female participants must be amenorrheic without an alternative medical cause and have a serum follicle-stimulating hormone level > 40 mIU/mL for ≥ 12 months prior to Screening or ≥ 6 weeks postsurgical bilateral oophorectomy (with or without hysterectomy) prior to Screening

6.2. Exclusion Criteria

Exclusion criteria are presented separately for each study part.

Part A

1. Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening

2. Medical necessity for a gastric feeding tube, where the majority of feeds are given by this route, as assessed by the Investigator

3. Severe scoliosis evident on X-ray examination at Screening (with the participant supine, not in a supported sitting position). For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.

    - Cobb's angle > 40.0°: exclusionary for severe scoliosis

    - Cobb's angle < 33.0°: not exclusionary for severe scoliosis

    - For participants with a Cobb's angle between 33.0° and 40.0°, inclusive, discussion with the Medical Monitor must occur before determining eligibility.

4. Severe contractures evident at Screening, as determined by clinical judgment of the Investigator (with the participant supine, not in a supported sitting position)

5. Hospitalization for surgery (i.e., scoliosis surgery or other surgery), pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose

6. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period

7. History of brain or spinal cord disease that would interfere with the LP procedures, CSF circulation, or safety assessments

8. Presence of an implanted shunt for the drainage of CSF or of an implanted CNS catheter

9. History of bacterial meningitis, viral encephalitis, or hydrocephalus

10. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion

11. Prior scoliosis surgery that would interfere with the LP injection procedure

12. Participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study

13. Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, and hydroxyurea), biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any SMN2-splicing modifier or gene therapy; or prior antisense oligonucleotide treatment or cell transplantation

14. The participant's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study or does not agree to comply with the protocol-defined Schedule of Activities.

15. The participant's parent(s) or legal guardian(s) is not willing or able to meet guidelines in the consensus statement for standard of care in SMA [Finkel 2018; Mercuri 2018] (see Study Reference Guide) or provide nutritional and respiratory support throughout the study, per the Investigator's judgment. Note: Routine vaccinations and respiratory syncytial virus (RSV) prophylaxis are recommended per consensus guidelines on standard of care [Finkel 2018; Mercuri 2018] but are not required for study enrollment. Participants who are not currently on vaccinations or who are not receiving RSV prophylaxis but otherwise meet study inclusion criteria will be considered eligible for study enrollment.

16. Ongoing medical condition that, according to the Investigator, would interfere with the study conduct and assessments. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.

17. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrollment.

Part B

<u>All participants</u>

1. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period

2. History of brain or spinal cord disease that would interfere with the LP procedures, CSF circulation, or safety assessments

3. History of bacterial meningitis, viral encephalitis, or hydrocephalus

4. Presence of an implanted shunt for the drainage of CSF or of an implanted CNS catheter

5. Permanent tracheostomy or on permanent ventilation at Screening

6. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion

7. Prior scoliosis surgery that would interfere with the LP injection procedure

8. Prior injury (e.g., upper or lower limb fracture) or surgical procedure that affects the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline

9. Hospitalization for surgery (i.e., scoliosis surgery or other surgery), pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose

10. Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, and hydroxyurea), biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any SMN2-splicing modifier or gene therapy; or prior antisense oligonucleotide treatment or cell transplantation

11. The participant's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study or does not agree to comply with the protocol-defined Schedule of Activities.

12. The participant's parent(s) or legal guardian(s) is not willing or able to meet guidelines in the consensus statement for standard of care in SMA [Finkel 2018; Mercuri 2018] (see Study Reference Guide) or provide nutritional and respiratory support throughout the study, per the Investigator's judgment. Note: Routine vaccinations and RSV prophylaxis are recommended per consensus guidelines on standard of care [Finkel 2018; Mercuri 2018] but are not required for study enrollment. Participants who are not currently on vaccinations or who are not receiving RSV prophylaxis but otherwise meet study inclusion criteria will be considered eligible for study enrollment.

13. Ongoing medical condition that, according to the Investigator, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.

14. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrollment.

Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile onset)

15. Hypoxemia (O_2 saturation [awake or asleep] <96%, without ventilation support) at Screening

16. Signs or symptoms of SMA present at birth or within the first week after birth

Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset)

17. Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening

18. Medical necessity for a gastric feeding tube, where the majority of feeds are given by this route, as assessed by the Investigator

19. Severe scoliosis evident on X-ray examination at Screening (with the participant in a sitting or supported sitting position). For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.

    - Cobb's angle > 40.0°: exclusionary for severe scoliosis
    - Cobb's angle < 33.0°: not exclusionary for severe scoliosis
    - For participants with a Cobb's angle between 33.0° and 40.0°, inclusive, discussion with the Medical Monitor must occur before determining eligibility.

20. Severe contractures evident at Screening, as determined by clinical judgment of the Investigator (with the participant supine, not in a supported sitting position)

21. Participants who are pregnant or currently breastfeeding, and those intending to become pregnant during the study

Part C

1. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period

2. History of brain or spinal cord disease that would interfere with the LP procedures, CSF circulation, or safety assessments

3. History of bacterial meningitis, viral encephalitis, or hydrocephalus

4. Presence of an implanted shunt for the drainage of CSF or of an implanted CNS catheter

5. Permanent tracheostomy or on permanent ventilation at Screening

6. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion

7. Prior scoliosis surgery that would interfere with the LP injection procedure

8. Prior injury (e.g., upper or lower limb fracture) or surgical procedure that affects the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline

9. Hospitalization for surgery (i.e., scoliosis surgery or other surgery), pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose

10. Participants who are pregnant or currently breastfeeding, and those intending to become pregnant during the study

11. Concurrent or previous participation and/or administration of nusinersen in another clinical study.

12. Concomitant or previous administration of any SMN2-splicing modifier (excluding nusinersen) or gene therapy, either in a clinical study or as part of medical care.

13. Concurrent or previous participation in any interventional investigational study for any other drug or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening.

14. Ongoing medical condition that, according to the Investigator, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.

15. The participant or the participant's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study or does not agree to comply with the protocol-defined Schedule of Activities.

16. The participant or the participant's parent(s) or legal guardian(s) is not willing or able to meet guidelines in the consensus statement for standard of care in SMA [Finkel 2018; Mercuri 2018] (see Study Reference Guide) or provide nutritional and respiratory support throughout the study, per the Investigator's judgment. Note: Routine vaccinations and RSV prophylaxis are recommended per consensus guidelines on standard of care [Finkel 2018; Mercuri 2018] but are not required for study enrollment. Participants who are not currently on vaccinations or who are not receiving RSV prophylaxis but otherwise meet study inclusion criteria will be considered eligible for study enrollment.

17. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused even if the participant does not receive treatment. Study sites are required to document all screened participants initially considered for inclusion in the study.

6.3.2. Retesting

During the Screening period, participants who have an out-of-range result that is not clinically significant can be retested 1 time only at the discretion of the Investigator. The Screening period may be extended for up to 10 days for individuals who cannot complete the Day 1 Visit within 21 days of signing the ICF, as long as they continue to meet other eligibility criteria.

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently dosed or randomized. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

7. STUDY TREATMENT

7.1. Regimen

Participants will receive treatment as follows:

- Part A: Six participants with later-onset SMA will receive 3 loading doses of 28 mg of nusinersen administered intrathecally on Days 1, 15, and 29. A sentinel dosing approach will be used, in which the first participant will be enrolled and dosed with 28 mg of nusinersen. Following the availability of 72 hours of safety data after the first loading dose in the first participant, data for this participant will be reviewed by the Investigator and the Sponsor before the next 5 participants are enrolled. Only 1 participant can receive their first dose of study treatment on a given day. Maintenance doses of 28 mg of nusinersen will be administered on Days 149 and 269.

- Part B:

  – Control Group: A total of 42 participants (34 with infantile-onset SMA and 8 with later-onset SMA) will receive 4 loading doses of 12 mg of nusinersen administered intrathecally (Days 1, 15, 29, and 64), followed by maintenance doses of 12 mg on Days 183 and 279 (and a sham procedure on Day 135). See Table 4 for the blinded dosing schedule.

  – 50/28-mg Group: A total of 84 participants (68 with infantile-onset SMA and 16 with later-onset SMA) will receive 2 loading doses of 50 mg of nusinersen administered intrathecally (Days 1 and 15) and 2 sham procedures on Days 29 and 64, followed by maintenance doses of 28 mg on Days 135 and 279 (and a sham procedure on Day 183). See Table 4 for the blinded dosing schedule.

Table 4: Part B Blinded Dosing Schedule

Arm	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
50/28-mg Group	D1 (50 mg)	D15 (50 mg)	D29 (sham)	D64 (sham)	D135 (28 mg)	D183 (sham)	D279 (28 mg)[1]
Control Group (12/12 mg)	D1 (12 mg)	D15 (12 mg)	D29 (12 mg)	D64 (12 mg)	D135 (sham)	D183 (12 mg)	D279 (12 mg)[2]

D = day
[1] Delayed by 24 days from targeted dosing day of D255
[2] Moved up 24 days from the targeted dosing day of D303

- Part C: Approximately 20 participants who have already been receiving treatment with nusinersen for at least 1 year prior to entry in this study will receive a single bolus dose of 50 mg of nusinersen administered intrathecally on Day 1 of this study

(which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg), followed by 2 maintenance doses of 28 mg of nusinersen on Days 121 and 241.

If a loading dose is delayed or missed, nusinersen should be administered as soon as possible, with at least 14 days between doses, and dosing should be continued at the prescribed dosing frequency. In the maintenance phase, if a planned dose is delayed or missed, nusinersen should be administered as soon as possible and dosing should be continued at the prescribed dosing frequency.

7.2. Modification of Dose

The dosage cannot be modified.

7.3. Study Treatment Management

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Site staff should follow the Directions for Handling and Administration (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 appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment is for 1-time use only; do not use any study treatment remaining in the vial for another participant.

7.3.1. Nusinersen

The proposed new formulation contains 12 mg/mL nusinersen, 0.034 mg/mL sodium dihydrogen phosphate dihydrate, 0.111 mg/mL sodium phosphate dibasic anhydrous, 7.96 mg/mL sodium chloride, 0.224 mg/mL potassium chloride, 0.206 mg/mL calcium chloride dihydrate, and 0.163 mg/mL magnesium chloride hexahydrate in water for injection, adjusted, if necessary, to a target pH of 7.2 with hydrochloric acid or sodium hydroxide during compounding. The drug product will be diluted at the clinical site with supplied artificial CSF diluent to enable ascending doses in the proposed clinical study, as described in the DHA.

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

7.3.1.1. Preparation

The individual preparing nusinersen 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 vial(s) or study treatment, do not use the study treatment. The vial(s) in question should be saved at the study site and the problem immediately reported to the Sponsor (or designee).

Contact information for reporting a problem is provided in the Study Reference Guide.

7.3.1.2. Storage

Study treatment must be stored in a secure location.

Nusinersen is to be protected from light and is to be stored at 2°C to 8°C, in a locked refrigerator with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.1.3. Handling and Disposal

The Investigator must return all used and unused vials of nusinersen as instructed by the Sponsor (or designee) unless approved for onsite destruction.

If any used nusinersen supplies are to be destroyed at the study site, the institution or appropriate site staff 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.

7.3.1.4. 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 (participant-by-participant accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

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

Please refer to the DHA for additional details and instructions.

7.4. Blinding Procedures

Part B is the only study part that will be blinded; Parts A and C will be open-label.

To maintain the study blind in Part B, the procedure will be performed in a dedicated room by dedicated study personnel who are unblinded to the treatment group; this will not include any of the key study site personnel (i.e., the Investigator, Study Coordinator, or Outcomes Assessors). The key study site personnel and the parent/guardians (if applicable) will not be present during the procedure to ensure blinding.

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 site of the needle prick will be covered in the same manner as that of the LP injection, thus simulating the appearance of an LP injection. If anesthesia and/or sedation is used for the LP procedure for an individual participant, in order to maintain the blind, that participant will receive equivalent anesthesia and/or sedation (according to institutional procedures) for all of the sham procedures and LP injections. Participants who receive the sham procedure will be kept in the procedure room for the same amount of time as that for participants who were administered study treatment, thus simulating the time period of a study treatment administration procedure.

Study treatment and sham kits will be packaged in a blinded fashion. Blinded kits for sham procedures will contain artificial CSF that will not be injected but will be used to simulate CSF samples for a participant who has undergone sham procedure at a specific visit, as described in the DHA.

At the end of the study, if unblinding of Part B will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to Section 11.4.3.

7.5. Compliance

Study treatment will be administered by the site staff.

7.6. Concomitant Therapy and Procedures

7.6.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between screening and the final study visit/telephone call.

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

7.6.1.1. Allowed Concomitant Therapy

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

7.6.1.2. Disallowed Concomitant Therapy

Participants are prohibited from receiving other experimental or approved agents for the treatment of SMA, including gene therapy, biological agent, or device, during the study. This includes marketed agents at experimental doses that are being tested for the treatment of SMA (oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.).

7.6.2. 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 Screening and the final study visit/telephone call.

7.7. Continuation of Treatment

Following completion of this study, all eligible participants may elect to enroll in a separate long-term extension study, pending study approval by ethics committees and the appropriate regulatory authorities. In regards to participants rolling over from Part B, this will be done without unblinding the participant's treatment group.

8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

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

- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 11.4.1.
- The participant or the participant's parent(s)/legal guardian(s) withdraws consent to continue study treatment.
- The participant experiences an AE that necessitates permanent discontinuation of study treatment.
- The participant is not tolerating a given dose.
- The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment (or unblinding of the participant's treatment assignment in Part B).
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The primary reason for discontinuation of study treatment must be recorded in the participant's CRF.

Participants who discontinue treatment may remain in the study and continue protocol-required tests and assessments.

8.2. Lost to Follow-Up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site staff must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with the primary reason of "lost to follow-up."

8.3. Withdrawal of Participants From the Study

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

- The participant or the participant's parent(s)/legal guardian(s) withdraws consent for participation in the study.

- The participant enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

- The participant is unwilling or unable to comply with the protocol.

The primary reason for the participant's withdrawal from the study must be recorded in the participant's CRF.

Participants should undergo an early termination visit unless withdrawal is due to death or withdrawal of consent.

Participants who withdraw from the study may not be replaced.

9. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

9.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of nusinersen in all study participants.

All Participants

- Number of serious respiratory events
- Number and duration of hospitalizations
- Clinical Global Impression of Change (CGIC; physician and caregiver assessment)
- Ventilator use

The following clinical assessments will be performed to evaluate the efficacy of nusinersen in participants enrolled in specific parts of the study.

Part A

Participants with Later-Onset SMA:

- HFMSE
- RULM
- World Health Organization (WHO) Motor Milestones
- 6-Minute Walk Test (6MWT; ambulatory participants ≥ 3.5 years of age at the time of visit, at the discretion of the Investigator)
- 10-Meter Walk/Run Test (10MWR; ambulatory participants only)
- QoL questionnaires
- Dysphagia assessments (Parent Assessment of Swallowing Ability [PASA])

Part B

Participants with Infantile-Onset SMA:

- CHOP INTEND
- HINE Section 2 Motor Milestones
- Daily ventilator use (number of hours/day), using a daily ventilator use diary
- Dysphagia assessments (PASA)

Participants with Later-Onset SMA:

- HFMSE
- RULM
- WHO Motor Milestones
- 6MWT (ambulatory participants ≥ 3.5 years of age at the time of visit, at the discretion of the Investigator)
- 10MWR (ambulatory participants only)
- QoL questionnaires
- Dysphagia assessment (PASA)

Part C

The Investigator will select efficacy assessments based on criteria described below. The assessments selected at screening will be used to evaluate the participant throughout the entire duration of the trial, from screening to follow-up.

- CHOP-INTEND and HINE Section 2 should be performed by the following participants:
  - 1 to < 2 years of age at the time of informed consent
  - 2 to ≤ 5 years of age at the time of informed consent if they did not achieve independent sitting prior to screening
- HFMSE and RULM should be performed by the following participants:
  - ≥ 2 years of age at the time of informed consent (If unable to sit independently, CHOP-INTEND and HINE Section 2 will also be performed.)

  - ≥ 2 years of age after informed consent obtained while in the study. HFMSE and RULM should start to be collected for participants ≥ 2 years of age while continuing to collect CHOP-INTEND and HINE Section 2 until the end of study.

- WHO motor milestones should be collected for all participants.
- 10MWR should be performed by all ambulatory participants.
- 6MWT should be performed by ambulatory adult participants. 6MWT should be performed by ambulatory children ≥ 3.5 years of age at the time of visit at the discretion of the Investigator.
- QoL questionnaires should be assessed for participants ≥2 years of age at the time of informed consent.

Sitting independently will be defined as able to sit without support per WHO motor milestone (Test Item No. 1 – sitting without support), ambulatory will be defined as any participant who has achieved independent walking as defined by the WHO motor milestone criteria (Test Item No. 6 – Walking Alone).

Videotaping of all motor milestone and motor function assessments will be optional.

9.1.1. Motor Milestones

The assessments to be performed will depend on the participant's age at enrollment and current motor abilities. Videotaping of the WHO and/or HINE motor milestone assessments will be optional.

Motor milestones will be assessed using the WHO motor milestone criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004] and/or Section 2 of the HINE, as per the Schedule of Activities (Table 1, Table 2, and Table 3). Section 2 of the HINE is composed of the following 8 motor milestone categories: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each motor milestone category, 3 to 5 levels can be achieved. All 8 motor milestones will be tested during each assessment. A participant whose results after testing all appear in the first column (no grasp, no kicking, unable to maintain head upright, and so on) has not achieved any motor milestone. Motor milestone achievement is depicted by movement from the left side of Table 5 to the right side of the table, as denoted by the Milestone Level Progression arrow in the table [Haataja 1999].

WHO motor milestones will be assessed by the Investigator and caregiver. Adult participants who do not require a caregiver during the study visit will only have WHO motor milestones assessed by the Investigator.

Table 5: Hammersmith Infant Neurological Examination Section 2 - Motor Milestones

Motor Milestone Category	Milestone Level Progression Score (Age Expected in Heathy Infants[1]) → Improvement				
	0	**1**	**2**	**3**	**4**
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb/ immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) [3 months]	Touches leg (4 to 5 months)	Touches toes (5 to 6 months)
Head control	Unable to maintain upright (< 3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolls to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sits with support at the hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) [10 months]
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4 to 5 months)	Crawls flat on the abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4 to 5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) [11 months]	Walks independently (15 months)	

[1] Values for healthy infants in [De Sanctis 2016; Haataja 1999]

The definition of a motor milestone responder is based on the motor milestones categories in Section 2 of the HINE, with the exclusion of voluntary grasp, as follows:

- Participant demonstrates at least a 2-point increase in the category of ability to kick or increase to the maximal score on that category (touching toes) or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking AND

- Among the 7 motor milestone categories (with the exclusion of voluntary grasp), the participant demonstrates improvement in more categories than worsening.

Note: For the category of ability to kick, similar to the definition of improvement in (1), worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease.

Participants who die or withdraw from the study will be counted as nonresponders and will be included in the denominator for the calculation of the proportion.

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

CHOP INTEND will be assessed in participants in Part B with infantile-onset SMA. Participants in Part C will have CHOP INTEND assessed as described in Section 9.1.

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

9.1.3. Hammersmith Functional Motor Scale – Expanded

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

9.1.4. Revised Upper Limb Module

Participants with later-onset SMA will be evaluated using the Revised Upper Limb Module (RULM) [Mazzone 2016]. The RULM will continue to be performed should participants subsequently become ambulatory.

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

The purpose of an upper limb scale for use in SMA is to assess the change that occurs in the motor performance of the upper limb over time. Motor performance in SMA is defined as a

demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be impacted by muscle strength, contractures, and maturational development (puberty), and the RULM aims to incorporate the performance of the shoulder, elbow, wrist, and hand.

9.1.5. 10-Meter Walk/Run Test

The 10MWR is a measure of the time required to walk/run 10 meters and will be performed in participants who are ambulatory or become ambulatory. For the purposes of this protocol, "ambulatory" will be defined as any participant who has achieved independent walking as defined by the WHO motor milestone criteria (Test Item No. 6 – Walking Alone). For participants who are ambulatory at any point during the study per the WHO criteria, the 10MWR will continue to be performed through the end of the study, regardless of subsequent changes in ambulatory status. If an assistive device is used for the 10MWR test, it should be documented and used consistently at each visit.

9.1.6. 6-Minute Walk Test

The 6MWT is an objective evaluation of functional exercise capability that measures the distance a person can walk quickly in 6 minutes. At the discretion of the Investigator, the 6MWT will be performed by participants with SMA who are ≥ 3.5 years of age and ambulatory at the time of visit. Ambulatory will be defined as any participant who has achieved independent walking by WHO motor milestone (Test Item No. 6 – Walking Alone).

The 6MWT can be performed safely in ambulatory patients with SMA and correlates with standard SMA outcome measures, including timed walking tests [Montes 2010]. The 6MWT has also been used as a primary outcome measure in several clinical studies in neuromuscular disease, including Duchenne muscular dystrophy [McDonald 2010] and late-onset Pompe disease [van der Ploeg 2010].

9.1.7. Clinical Global Impression of Change

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

The CGIC is a 7-point scale that requires the clinician to assess how much the patient's illness has changed relative to a baseline state at the beginning of the intervention and is rated as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

CGIC should be assessed consistently by the same rater for each study participant. A separate CGIC assessment will be performed by the Investigator (Principal Investigator or Subinvestigator) and caregiver. Adult participants who do not require a caregiver during the study visits will only have the CGIC assessment assessed by the Investigator.

9.1.8. Quality-of-Life Questionnaires

QoL questionnaires include the Pediatric Quality of Life Inventory™ (PedsQL) and Assessment of Caregiver Experience with Neuromuscular Disease (ACEND). QoL questionnaires will be collected on the days specified in Table 1, Table 2, and Table 3.

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

Participants with later-onset SMA will be evaluated using the PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module [Varni 1999]. This assessment has been validated by the American Spinal Muscular Atrophy Randomized Trials Group [Iannaccone 2009].

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. The PedsQL consists of brief, practical, generic core scales, as well as condition-specific modules for use in designated clinical populations. Pediatric self-report is measured in children and adolescents 5 to 18 years of age, and parent proxy-report of child HRQOL is measured for children and adolescents 2 to 18 years of age. The PedsQL 4.0 Generic Core Scales include an assessment of physical functioning, emotional functioning, social functioning, and school functioning. The PedsQL 3.0 Neuromuscular Module was designed to measure HRQOL dimensions specific to children 2 to 18 years of age with neuromuscular disorders, including SMA.

In Parts A and B, all participants with later-onset SMA will be evaluated using the PedsQL. In Part C, the PedsQL (in addition to ACEND) will be evaluated in participants who are ≥2 years of age at Screening.

If a participant is assessed on PedsQL at baseline, then the age range of the scale used at Screening for that participant will continue to be used up to Day 302, regardless of changes in the participant's age.

9.1.8.2. Assessment of Caregiver Experience With Neuromuscular Disease

Parents/caregivers of participants will complete the ACEND questionnaire. The ACEND questionnaire will not be collected for adult participants who do not require a caregiver during the study visits. This assessment instrument has been designed to quantify the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases,

including children with SMA [Matsumoto 2011]. ACEND includes domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance).

9.1.9. Parent Assessment of Swallowing Ability

Dysphagia will be assessed in Parts A and B at the timepoints specified in the Schedule of Activities (Table 1 and Table 2) using the PASA questionnaire. Caregivers will be asked a series of questions regarding the mealtime behavior of the participant.

The PASA questionnaire was developed by a Biogen team in order to assess the signs and symptoms of dysphagia. This questionnaire consists of 33 items across 4 domains that cover general feeding, drinking liquids, eating solid foods, and assessment of swallowing concerns. The first 3 of these domains are generally assessed with 5 levels of response (Never, Rarely, Sometimes, Often, and Always), although 2 items are assessed with a simple "Yes"/"No" answer. In the final domain, the assessment of swallowing concerns has 4 levels of response: Strongly Agree, Agree, Disagree, and Strongly Disagree. In answering each item, the caregiver is directed to consider the previous 7 days.

9.1.10. Ventilator Use

9.1.10.1. All Participants

The participant's ventilator use will be collected at every study visit. If ventilation is used daily, the average number of hours per day for the past 7 days will be recorded (except for participants with infantile-onset SMA enrolled in Part B; see Section 9.1.10.2).

9.1.10.2. Participants With Infantile-Onset SMA in Part B

The participant's ventilator use (number of hours/day) will be recorded daily by the caregiver using a daily ventilator use diary for the duration of the study. This information will be obtained by the site during study visits and telephone contacts and entered into the CRF.

9.2. Pharmacokinetic Assessments

Plasma and CSF concentrations of nusinersen will be measured using validated assays.

9.3. Pharmacodynamic Assessments

The PD properties of nusinersen will be assessed using the following:

- Plasma concentration of biomarkers related to SMA (including but not limited to phosphorylated neurofilament heavy chain [pNF-H])
- CSF concentration of biomarkers related to SMA (including but not limited to pNF-H)

pNF-H will be analyzed in plasma and CSF to explore its role as a potential predictive and treatment-sensitive PD biomarker in SMA.

9.4. Immunogenicity Assessments

Incidence and titer of antibodies to nusinersen in plasma will be assessed.

9.5. Pharmacogenetic and Genetic Assessments

All participants will undergo genetic testing through a central laboratory to confirm *SMN1* gene mutation and *SMN2* gene count. For the purpose of determining study eligibility, historical genetic testing results may be acceptable with appropriate documentation, but confirmatory testing through a central laboratory will also be performed. Deoxyribonucleic acid (DNA) is to be collected from all participants to assess sequence variations at the *SMN1* and *SMN2* loci that might affect *SMN1* and *SMN2* gene activity or the binding of nusinersen.

9.6. Future Scientific Research Assessments

In participants who provide additional optional consent, residual blood and CSF samples may be stored for future, unspecified exploratory biomarker analysis. Participants will sign a separate written ICF if they agree to their samples being used in this way.

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

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

10.1. Clinical Safety Assessments

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

- AE and SAE recording
- Medical (including SMA) history. This will include assessment of contractures.
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry
- Growth parameters: body length/height (for all participants), head, chest, and arm circumference (for participants with infantile-onset SMA), and ulnar length (for participants with later-onset SMA) will be measured. Additional parameters of weight-for-age, weight-for-length, and head-to-chest circumference ratio will be calculated.
- Neurological examinations: HINE Sections 1 and 3 will be administered to participants in Part B with infantile-onset SMA, and participants in Part C < 2 years of age at the time of informed consent. A neurological examination will be performed in participants in Parts A and B with later-onset SMA and participants in Part C ≥ 2 years of age at the time of informed consent.
- Physical examinations (videotaping of physical examinations is optional)
- Electrocardiograms (ECGs)
- LP opening pressure: details available in the DHA
- Concomitant therapy and procedure recording

10.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of nusinersen:

- Hematology: complete blood cell count, with differential and platelet count, and absolute neutrophil count
- Coagulation parameters (by local laboratory): activated partial thromboplastin time, prothrombin time, and international normalized ratio
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, creatine phosphokinase, and creatine kinase
- Urinalysis: urine total protein (by local laboratory); specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, and crystals
- CSF local lab sample: cell count, protein, and glucose

The laboratory analytes to be measured are shown in Appendix B.

10.3. Telephone Assessments

For all study parts, from 2 to 14 days after each maintenance dose, participants will be contacted via a telephone call to capture any clinical changes, such as new AEs, ventilator use/status updates, and changes in concomitant therapies. Telephone calls will also be made in Part A 2 weeks (±3 days) after the Day 29 dose, in Part B 2 weeks (±3 days) after the Day 29 dose for the first 20 participants, and in Part C 2 weeks (±3 days) after the Day 1 bolus dose.

11. 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 participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant and/or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of site staff for reporting SAEs, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a contract research organization (CRO).

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject (participant) 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 an abnormal assessment such as an abnormal laboratory value), 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 assessment (e.g., laboratory value, vital sign, and ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the participant to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

11.1.2. 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 participant 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.

- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant 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.)

11.1.3. 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 participant 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 the participant's consent to be 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 participant's consent to be 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 participant 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 11.1.2 is met.

11.2. Safety Classifications

11.2.1. 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 11.1.2
- The relationship of the event to study treatment as defined in Section 11.2.2
- The severity of the event as defined in Section 11.2.3

11.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment or the LP/sham procedure. Relationship of events to study treatment and relationship of events to LP/sham procedure will be documented separately.

Relationship of Event to Study Treatment or LP/Sham Procedure	
Not related	An AE will be considered "not related" to the use of the investigational product or the LP/sham procedure if there is not a reasonable possibility that the event has been caused by the product under investigation or the LP/sham procedure. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product or the LP/sham procedure and the AE, the presence of a biologically implausible relationship between the product or the LP/sham procedure and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product or the LP/sham procedure if there is a reasonable possibility that the event may have been caused by the product under investigation or the LP/sham procedure (e.g., bleeding from the puncture site). Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product or the LP/sham procedure and the AE, a known response pattern of the suspected product or the LP/sham procedure, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product or the LP/sham procedure and the AE, or a lack of an alternative explanation for the AE.

11.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of participant.
Moderate	Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.

11.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor according to the current Investigator's Brochure for nusinersen.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Any AE experienced by the participant between the time of signing of the ICF and the last study visit/telephone contact is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved or become stable. AE outcome will be recorded on the CRF, as applicable.

11.3.2. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the last study visit/telephone contact is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor within 24 hours, as described in Section 11.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Participants will be followed for all SAEs until the last study visit/telephone contact. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

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

11.3.3. 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 Sponsor within 24 hours of the 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

A report ***must be submitted*** to the Sponsor regardless of the following:

- Whether or not the participant has undergone study-related procedures
- Whether or not the participant 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; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.3.3.1. 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 the Sponsor. The term "death" should be reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.4. Suspected Unexpected Serious Adverse Reactions

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

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

For Part B, which is blinded, appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. For Part B, the Sponsor will submit SUSARs to Investigators in a blinded fashion.

11.4. Procedures for Handling Special Situations

11.4.1. Pregnancy

Participants should not become pregnant or impregnate their partners for the duration of the study. If a female participant becomes pregnant, study treatment must be discontinued **immediately**.

The Investigator must report a pregnancy occurring in a female participant or in the partner of a male participant from the first dose of study treatment by faxing or emailing the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The

Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period or 120 days from their last dose of study treatment.

11.4.2. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

11.4.3. Medical Emergency

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

11.4.3.1. Unblinding for Medical Emergency

Part B is the only part of the study that is blinded. In a medical emergency when knowledge of the participant's treatment assignment may influence the participant's clinical care, the Investigator may access the participant's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual who is not directly involved in managing the medical emergency or to personnel involved with the analysis and conduct of the study. The Investigator can contact the Sponsor to discuss such situations.

11.5. Contraception Requirements

All female participants of childbearing potential and all male participants of reproductive age must ensure that effective contraception is used for the duration of the study. In addition, participants should not donate sperm or eggs for the duration of the study.

For the purposes of this study, females of childbearing potential are defined as all females physiologically capable of becoming pregnant, **unless** they meet one of the following conditions:

- Postmenopausal
  - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level > 40 mIU/mL
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as the use of one of the following:

For females:

- Female surgical sterilization (e.g., bilateral tubal ligation), where applicable, according to local guidelines.
- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation
- Established use of oral, injected, or implanted hormonal methods of contraception
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Barrier methods of contraception, where applicable according to local guidelines
- Bilateral tubal occlusion
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate)

For males:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception.
- Condoms with spermicide, where applicable according to local guidelines
- Sex with a woman who uses the methods described for females if she is of childbearing potential

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 11.4.1.

11.6. Safety Responsibilities

11.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF 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.
- Monitor and record all pregnancies in female participants and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

11.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Medical Monitor is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study, the endpoints to be analyzed, and the statistical hypotheses are listed in Section 4. In Part B, the primary and secondary hypotheses are that there will be a difference in the 50/28-mg Group compared to participants who received sham control in Study CS3B; these analyses will be performed using the 50/28-mg Group within this study and the data from the Study CS3B Sham Control Group. The exploratory hypotheses compare the 50/28-mg Group to participants who received 12 mg. This 12-mg group comprises participants within this study who are dosed with 12 mg (i.e., the Control Group), with the possibility of including participants from Study CS3B who received 12 mg via borrowing, which is detailed further in the following sections.

12.1. General Considerations

12.2. Analysis Sets

The Intent-to-Treat (ITT) Set is defined as all participants who are randomized (or enrolled, as in Parts A and C) and receive nusinersen; participants will be analyzed in the treatment group to which they are randomized.

The Safety Set is defined as all participants who receive nusinersen; participants will be analyzed in the treatment group based on what they actually received. The PK Set is defined as all participants who were dosed for which there is at least 1 evaluable postdose PK sample.

The ITT, Safety, and PK Sets will be defined separately for each of the following populations: Part A, Part B infantile-onset, Part B later-onset, and Part C.

A Per-Protocol Set will be defined for the Part B infantile-onset SMA population and will include the subset of the ITT Set who complete at least the initial 4 doses of drug/sham procedure, have a baseline assessment and at least a Day 183 efficacy assessment, and have no significant protocol deviations that would be expected to affect efficacy assessments.

12.3. Definition of Baseline

The baseline for all assessments except CHOP INTEND is defined as the last nonmissing assessment prior to the first dose of study treatment. The baseline for CHOP INTEND is defined as the average of the 2 assessments taken during the Screening/Baseline period.

12.4. Methods of Analysis for Efficacy Endpoints

Within Part B to control the overall Type 1 error at a 2-sided alpha level of 0.05, a sequential testing procedure ranked in the order of the primary, secondary, and then exploratory hypotheses will be utilized. In this procedure, the primary hypothesis of mean change in CHOP INTEND

total score from baseline to Day 183 for the Study CS3B Sham Control Group compared to the 50/28-mg Group will be tested once, when all of the infantile-onset participants have reached Day 183. If this is statistically significant, no further statistical testing will be performed until all infantile-onset participants have reached Day 302. Then the first secondary endpoint of the proportion of motor milestone responders at Day 302 for the Study CS3B Sham Control Group compared to the 50/28-mg Group will be tested and so forth in the order of the remaining endpoints as detailed in Table 6. Inferential conclusions about each successive analysis require statistical significance of the prior one.

Use of Historical Data

The statistical testing of the primary and secondary hypotheses will use the Sham Control Group from Study CS3B. Within Study CS3B, there are 41 participants in the ITT set, 37 participants with an opportunity to attend the Day 183 visit, and 28 participants with an opportunity to attend the Day 302 visit. No prospective formal assessment of the similarity in baseline characteristics is planned for these analyses between Study CS3B and the present study, since the natural history of infantile-onset SMA is well established, the 12-mg dose has been demonstrated to be highly efficacious versus sham, and it is reasonable to expect a similar or better result for a 50-mg dose.

The statistical testing of exploratory hypotheses in the infantile-onset analysis population in Part B will comprise this study's ITT Set as defined in Section 12.2. In the event that borrowing is utilized, then the analysis population will comprise the ITT Set with at least 25 additional matched participants selected from the 73 participants in the Day 183 evaluable set in Study CS3B.

The approach to matching will utilize propensity scores calculated using sex, disease duration, age at onset of symptoms, and baseline CHOP INTEND score. Other covariates may be included for the propensity score calculation.

The feasibility of being able to "borrow" from Study CS3B will be assessed at an interim analysis by the similarity of the following: 1) baseline characteristics and 2) comparability in efficacy.

Further details of the methodology will be described in the Statistical Analysis Plan.

For the CHOP INTEND endpoint and the time to event endpoints, all matched participants will be used.

In the event that participants from Study CS3B are borrowed, then at the end of the study, the main analysis for the exploratory hypotheses will be performed using the combined population of this study and matched participants from Study CS3B. It is possible that some of the matched Study CS3B participants did not have the opportunity to attend the Day 302 visit in Study CS3B. Therefore, for the second exploratory hypothesis, which is evaluated on Day 302, the subset of matched Study CS3B participants with the opportunity for a Day 302 assessment will be used for the main analysis.

As a sensitivity analysis of the exploratory hypotheses, this analysis will be repeated using the ITT Set from this study (i.e., no data from Study CS3B).

12.4.1. Analysis of the Primary Endpoint in Part B

The primary analysis will be performed when all participants with infantile-onset SMA in Part B have had the opportunity to reach the Day 183 visit.

CHOP INTEND

The primary efficacy endpoint of change from baseline to Day 183 in CHOP INTEND total score will be analyzed using the joint-rank methodology to account for mortality [Berry 2013]. This joint-ranking procedure allows for a statistical test of the treatment effect on the CHOP INTEND total score while accounting for loss of data due to deaths. In this analysis, a participant's Combined Assessment of Function and Survival score will be calculated by comparing each participant to every other participant in the study, resulting in a score of +1 if the outcome was better than the participant being compared, -1 if worse, and 0 if the same. The participant's score will then be calculated by summing up their comparison to all the other participants in the study. For example, if 2 participants complete the study up to Day 183, their comparison score will be based on the change from baseline in CHOP INTEND total score at Day 183. A participant who dies prior to the Day 183 visit will rank lower than any participant who completes the study up to Day 183. Two participants who both die prior to the Day 183 visit will be ranked based on the time of death with longer time to death corresponding to the higher rank. Hence, in general, these comparisons will result in participants who die being assigned the worst scores and ranked according to the time of death. Participants who survive and complete the study will be ranked more favorably than participants who die. The ranked scores will be analyzed using an analysis of covariance model with treatment included as a fixed effect and adjusted for baseline CHOP INTEND total score and disease duration.

The trimmed-means method [Permutt and Li 2017] will be performed as a sensitivity analysis to assess the robustness of the primary conclusion. The analysis will be performed treating all dropouts and deaths as bad outcomes and trimming them out with other observed bad outcomes to form balanced comparison groups. In the trimmed-mean approach, response scores are ranked from best to worst, and participants who died are considered as having worse outcomes than those who survived and completed the study. All response scores in the treatment group with high mortality/dropout rate will be retained. In the treatment group with the higher survival/completion rate, only the same proportion (as the survival rate in the high-mortality group) of the top response scores will be retained. The trimmed-mean difference can be interpreted as the difference between the top fraction of responses between the 2 groups. An analysis of covariance model will be fitted to the trimmed sample, with treatment as a factor and adjusting for covariates of baseline score and disease duration to obtain the adjusted mean difference. The p-value associated with the adjusted-difference test statistic will be calculated using a reference distribution generated by a re-randomization procedure.

12.4.2. Analysis of the Secondary and Exploratory Endpoints in Part B

When all participants with infantile-onset SMA in Part B have completed Day 302, the secondary and exploratory hypotheses will be tested.

HINE Motor Milestone Responders

The difference in the proportion of responders between treatment groups will be compared using logistic regression with the number of motor milestones at Baseline, age at symptom onset, and disease duration at Screening as covariates. Should the number of responders be less than 5 in either group, Fisher's exact test will be used instead. If Fisher's exact test is used, the unconditional confidence interval for the difference in response rates will be provided [Santner and Snell 1980].

Time to Death or Permanent Ventilation

Permanent ventilation is defined as tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in the absence of an acute reversible event (Appendix A).

An independent endpoint adjudication committee (EAC) will determine, in a blinded fashion, the date at which a participant is considered to have met the definition of an event. The procedures for reviewing and adjudicating events will be described in a charter.

The time to death or permanent ventilation (tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days in the absence of an acute reversible event) and time to death (overall survival) will be analyzed using the log-rank test stratified by disease duration at Screening. The null hypothesis is that the control and 50-mg doses have the same "survival" function. Participants who do not meet the endpoint definition will be censored at the last occasion the participant was seen (either in-person visit or by telephone contact), irrespective of whether the participant has completed the full course of treatment and whether the participant has completed the study or permanently withdrawn. The exception is time to death or permanent ventilation in cases in which a participant has begun a ventilator diary, in which case the latest entry in the diary will be used as the date of censoring. The proportion of participants meeting an event at timepoints of interest will be estimated using the Kaplan-Meier method.

For participants in this study, available study data from the separate long-term extension study will be utilized to give a more comparable follow-up to what was included in Study CS3B.

Time to Death

Overall survival will be analyzed in the same way as time to death or permanent ventilation.

Total HINE Section 2 – Motor Milestones

Change from baseline to Day 302 will be analyzed using the same methodology as described for CHOP INTEND.

Table 6 and Table 7 summarize the planned statistical testing.

Table 6: Primary and Secondary Hypotheses - Comparing the 50/28-mg Group to Study CS3B Sham Control

Rank	Endpoint and Comparison	Analysis Method	Population
1	Change in CHOP INTEND from baseline to Day 183	Joint rank	50/28 mg ITT population versus Study CS3B Sham Control Day 183 efficacy set
2	Proportion of HINE Section 2 motor milestone responders at Day 302	Fisher's Exact Test	50/28 mg ITT population versus Study CS3B Sham Control Day 302 efficacy set
3	Time to death or permanent ventilation	Log rank test	50/28 mg ITT population (additional follow-up from extension study) versus Study CS3B Sham Control ITT Set
4	Time to death	Log rank test	50/28 mg ITT population (additional follow-up from extension study) versus Study CS3B Sham Control ITT Set

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; ITT = Intent-to-Treat

Table 7: Exploratory Hypotheses - Comparing the 50/28-mg Group to the 12-mg Group

Rank	Endpoint and Comparison	Main Analysis Method	Population
1	Change in CHOP INTEND from baseline to Day 183	Joint rank	50/28 mg ITT population versus Control Group ITT + (Study CS3B borrowed 12 mg)
2	Change from baseline in HINE Section 2 motor milestones total score at Day 302	Joint rank	50/28 mg ITT population versus Control Group ITT + (Study CS3B borrowed 12 mg)
3	Proportion of motor milestone responders at Day 302	Logistic regression or Fisher's Exact Test	50/28 mg ITT population versus Control Group ITT + (Study CS3B borrowed 12 mg)
4	Time to death or permanent ventilation	Log rank test	50/28 mg ITT population (additional follow-up from extension study) versus Control Group ITT + (Study CS3B borrowed 12 mg)

Rank	Endpoint and Comparison	Main Analysis Method	Population
5	Time to death	Log rank test	50/28 mg ITT population (additional follow-up from extension study) versus Control Group ITT + (Study CS3B borrowed 12 mg)

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; ITT = Intent-to-Treat

12.4.3. Analysis of the Remaining Endpoints

For Parts A, B, and C, summary statistics will be presented to characterize the efficacy data over time. For continuous endpoints, the summary statistics will generally include the number of participants with data, mean, standard deviation, median, minimum, and maximum. For categorical endpoints, the summary statistics will generally include the number of participants with data and the percentage of those with data in each category. Frequency distributions will be presented as appropriate. The change from baseline to each visit will be summarized. The number of hospitalizations will be analyzed using the rate at which they occur, and the time on a ventilator will be prorated based on the time on study. Further details will be provided in the Statistical Analysis Plan.

Fatigue will be summarized for participants using the 6MWT (for ambulatory participants). The "percentage fatigue" will be calculated using the distance walked in the first and sixth minutes.

12.5. Methods of Analysis for Pharmacokinetic Endpoints

The PK analysis will be performed on all participants for whom there is at least 1 evaluable PK sample after the first intrathecal injection.

Results of CSF and plasma nusinersen concentrations will be summarized by sampling time. A noncompartmental analysis will be conducted to estimate the plasma PK parameters of nusinersen, if applicable, and summary statistics will be performed.

12.6. Methods of Analysis for Pharmacodynamic Endpoints

The analysis population for PD will include all participants with available PD data.

Plasma and CSF biomarker levels related to SMA (including but not limited to pNF-H) will be summarized. The baseline concentrations and the actual score and change (including absolute and percentage) will be presented by visit. In addition, the correlation between the baseline level and measurements, including weight, disease duration, and age at the first dose, will be presented. In addition, plasma and CSF PK concentrations will be analyzed with plasma and CSF biomarkers to establish PK/PD correlation. PK/PD and exposure-response may also be conducted on efficacy. The results of this study may be combined with other nusinersen studies to perform population PK/PD analyses, including exposure-response analysis.

12.7. Methods of Analysis for Biomarkers/Pharmacogenetics

Results from any unspecified exploratory pharmacogenetic or biomarker research, if performed, will be documented separately, and details related to the analyses will not be described in the protocol.

Plasma and CSF samples (collected as specified in Section 1.3) may be assayed for biomarkers including but not limited to pNF-H.

Exploratory potential biomarker candidates related to nusinersen biological activity will be summarized using descriptive statistics and will be presented by dose group.

Sampling for this analysis will be approved at the discretion of each site's ethics committee. If a site's ethics committee does not approve the sampling for the analysis, this section will not be applicable to that site.

12.8. Methods of Analysis for Safety Endpoints

The analysis of safety will be performed separately for the Safety Set for Part A, Part B infantile-onset, Part B later-onset, and Part C. In addition, the Part B participants will be presented by treatment group. The duration of treatment and the amount of study treatment will be summarized.

12.8.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities.

The incidence of treatment-emergent AEs and SAEs will be presented for Parts A, B, and C. 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 receiving the first dose of nusinersen and subsequently worsened in severity or was not present prior to receiving the first dose of nusinersen but subsequently appeared.

The number and percentage of participants who experienced SAEs, AEs, and discontinuation from nusinersen due to an AE will be summarized. Additionally, AEs will be summarized by severity and relationship to nusinersen.

A participant 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 nusinersen will be used in the calculation of incidence by relationship to nusinersen.

AEs will be further tabulated by subgroup (e.g., age, race, sex, administration status of nusinersen [90-day intervals], and SMA history).

12.8.2. Clinical Laboratory Results

Clinical laboratory evaluations, including coagulation, hematology, blood chemistry, and urinalysis parameters, will be summarized using shift tables, presenting changes relative to each parameter's normal range. Summary statistics for actual values and changes from baseline will also be presented.

12.8.3. Vital Signs

The analysis of vital signs will focus on clinically significant abnormalities. Changes from baseline in vital signs and ECGs will be summarized.

12.8.4. Neurological Examinations

Changes from baseline in neurological examinations will be summarized.

12.9. Methods of Analysis for Immunogenicity Data

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

Results from the immunogenicity analysis for anti-nusinersen plasma antibody concentrations will be summarized.

12.10. Interim Analyses

Interim and final analyses for Parts A and C may occur prior to completion of Part B of the study.

An interim analysis may occur in Part B after 75 or more participants with infantile-onset SMA have completed baseline assessments and received their first dose and after 36 or more participants have had the opportunity to attend the Day 183 visit. At the interim, the feasibility of using participants from the 12-mg arm in Study CS3B to augment the Control Group in this study will be assessed. In a scenario in which it is considered likely that 25 participants could be borrowed, then the recruitment of participants with infantile-onset SMA may be stopped. There will be no multiplicity adjustment for the interim analysis, as it is designed to assess the feasibility of borrowing historical data from Study CS3B. The analysis of the primary endpoint in Part B will be performed when all participants with infantile-onset SMA have had the opportunity to reach the Day 183 visit.

Full details of the analyses and controlled access to the unblinded data will be documented in the Statistical Analysis Plan, the unblinding plan, and the IDMC charter.

12.11. Sample Size Considerations

A total sample size of approximately 152 participants is planned for this study, with a possibility of stopping recruitment in the infantile-onset SMA population in Part B based on the interim

analysis (Table 8). The justification for the sample size for the infantile-onset SMA population in Part B is detailed as follows. The sample sizes for the remaining groups are not based on statistical considerations.

A minimum of 6 participants with later-onset SMA will be enrolled in Part A to characterize the safety, tolerability, and PK profile of a 28/28-mg dose of nusinersen (28-mg loading dose; 28-mg maintenance dose). A total of 24 participants with later-onset SMA will be randomized to the Control Group and 50/28-mg Group in Part B in a ratio of 1:2; this will allow the exploration of the safety, tolerability, PK profile, and efficacy of the 50/28-mg dose of nusinersen in this population. A total of approximately 20 participants will be enrolled in Part C to characterize the safety, tolerability, and PK profile of a 50/28-mg dose of nusinersen in participants transitioning from maintenance dosing at the currently approved dose of 12 mg of nusinersen.

Table 8: Number of Participants in Each Study Part, by Symptom Onset

Part/Dose	**Number of Participants**		
	Later Onset	**Infantile Onset**	**Total**
Part A (28-mg loading dose; 28-mg maintenance dose)	6		6
Part B			
Control Group (12-mg loading dose; 12-mg maintenance dose)	8	34	42
50/28-mg Group (50-mg loading dose; 28-mg maintenance dose)	16	68	84
Part C (50-mg loading dose; 28-mg maintenance dose)			20
Total			152

For the infantile-onset SMA population in Part B, a sample size of up to 68 participants in the 50/28-mg Group will provide at least approximately 99% power to detect an improvement of 24 points on CHOP INTEND and 23% survival rate benefit (compared to that observed in Study CS3B participants receiving sham control) at Day 183 based on the joint-rank test at a 2-sided significance level of 0.05. This power calculation is based on simulations using data generated from a joint model of survival and functional change. The model used a difference of 24 points for the Day 183 change from baseline in CHOP INTEND total score (50/28-mg Group – Study CS3B Sham Control Group) and a population standard deviation of 8.8 for change from baseline.

An exploratory hypothesis for this study is that the efficacy in the 50/28-mg Group compared to the Control Group will be different. If an interim analysis is performed that deems it feasible to borrow participants from Study CS3B, then recruitment in the Part B infantile-onset SMA population may be stopped and the final analysis of the exploratory hypotheses will be conducted borrowing 25 or more participants from Study CS3B to augment the 25 participants randomized to the Control Group in this study to yield a total number of 50 participants in each arm.

For Part B, the randomization will be stratified as follows:

- For participants with infantile-onset SMA by disease duration: ≤ 12 weeks and > 12 weeks (time from age at symptom onset to age at informed consent)

- For participants with later-onset SMA by age at informed consent: < 6 years and ≥ 6 years

For Part C, an attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants ≥ 18 years of age must be ambulatory).

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, 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 Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the electronic data capture system, such as laboratory, imaging, and electronic clinical outcomes assessment data. Investigators must approve all their data on completed CRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent relock. The electronic data capture system does not prohibit Investigator approval or signing in any way.

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. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

13.1. Declaration of Helsinki

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

13.2. 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 study sites in countries other than the US.

If the Investigator makes any changes to the ICF, the Sponsor 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. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

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 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, where required, the study site must submit a close-out letter to the ethics committee and the Sponsor.

13.3. Changes to the Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant 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 may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. 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 13.4).

13.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, informed consent with the approved ICF must be obtained.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the participant must be explained to the participant and/or the participant's legally authorized representative. The participant and/or the participant's legally authorized representative must be given sufficient time to consider whether to participate in the study.

In addition, participants who have the capacity should provide their assent to participate in the study. The level of information provided to participants 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 must be given to the participant and/or the participant's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with regarding the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent and assent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

13.5. Participant Data Protection

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

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

Study reports will be used for research purposes only. The participant will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The 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 participant's personal medical data confidential.

13.6. Compensation for Injury

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

13.7. Conflict of Interest

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

13.8. Study Report Signatory

The Sponsor will designate one or more of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution

to the study in terms of design, management, and/or participant enrollment; or other factors determined to be relevant by the Sponsor.

13.9. Registration of Study and Disclosure of Study Results

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

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

13.10. 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, national, or regional 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.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Vendors

Biogen will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.1.1. Contract Research Organization

A CRO will be responsible for the administrative aspects of the study, including but not limited to study initiation, management of SAE reports, monitoring, and data management.

14.1.2. Interactive Response Technology

IRT will be used in this study. Before participants 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.

14.1.3. Electronic Data Capture

Participant information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture tool configured by the CRO and hosted by Medidata.

14.1.4. Central Laboratories for Laboratory Assessments

A central laboratory will be selected by the Sponsor to analyze all hematology, blood chemistry, urinalysis, and CSF samples (except for local analysis of CSF protein, cell count, and glucose) collected for this study. PK samples will be analyzed at a laboratory selected by the Sponsor.

A blood sample will be collected at Screening for *SMN2* copy number for those participants without acceptable historical genetic documentation of *SMN2* copy number. For all other participants, a blood sample will be collected during the study (preferably before or on the first maintenance dosing visit) for the analysis of both *SMN1* copy number and deletion/mutation and *SMN2* copy number by the central laboratory.

14.2. Study Committees

14.2.1. Endpoint Adjudication Committee

Time to death or permanent ventilation will be determined in a blinded fashion by a central, independent EAC. Procedures for reviewing and adjudicating events are described in the charter that governs the operation of the EAC.

14.2.2. Independent Data Monitoring Committee

An IDMC will be formed to review ongoing safety and tolerability data. An IDMC review of participant data through Day 64 of Part A will occur prior to enrollment of participants into Part B. An IDMC review of unblinded data from the first 15 participants in Part B (Section 5.1) will occur prior to dosing of the remaining participants in Part B and dosing in Part C of the study. Note that the IDMC can recommend to stop the study based on the safety findings.

The IDMC will also have a role in the interim analysis, where the intention is to assess whether it will be feasible to use participants from the 12-mg arm in Study CS3B to augment the Control Group in this study or whether recruitment will continue as originally planned. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

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.

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Site Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate, or may perform monitoring activities remotely (where permitted by local regulations) only during the COVID-19 pandemic where on-site monitoring is not allowed per local/regional restrictions. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of the review. It also will provide the monitoring strategy, with emphasis on participant safety, data integrity, and critical data and processes.

CRFs, supporting documentation, and essential documentation related to the study will be reviewed, and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data may also be conducted and reported as defined in the monitoring plan.

Monitoring must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participants' rights and well-being, protocol adherence, quality of data (accurate,

complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

15.4. Travel Policy

Sites must review the study travel policy prior to screening any study participants. Consultation and/or approval may be required from the Medical Monitor depending on the study participant's place of residence and travel distance to the site. Please refer to the Study Travel Policy for specific details and guidelines.

15.5. 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, the Investigator, and Biogen.

15.6. Publications

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

16. REFERENCES

Arkblad E, Tulinius M, Kroksmark AK, et al. A population-based study of genotypic and phenotypic variability in children with spinal muscular atrophy. Acta Paediatr. 2009;98(5):865-72.

Berry JD, Miller R, Moore DH, et al. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(3):162-8. Epub 2013/01/17.

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.

De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. Neuromuscul Disord. 2016;26(11):754-759. Epub 2016/10/05.

Feldkötter M, Schwarzer V, Wirth R, et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002;70(2):358-68.

Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2017 Epub 2017/11/23.

Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197-207. Epub 2017/11/23.

Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010;20(3):155-61.

Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011;23(4):322-6.

Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976.

Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr. 1999;135(2 Pt 1):153-61.

Iannaccone ST, Hynan LS, Morton A, et al. The PedsQL in pediatric patients with Spinal Muscular Atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Neuromuscular Module. Neuromuscul Disord. 2009;19(12):805-12.

Jedrzejowska M, Milewski M, Zimowski J, et al. Incidence of spinal muscular atrophy in Poland--more frequent than predicted? Neuroepidemiology. 2010;34(3):152-7.

Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. Nat Genet. 1997;16(3):265-9.

Main M, Kairon H, Mercuri E, et al. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. Eur J Paediatr Neurol. 2003;7(4):155-9.

Matsumoto H, Clayton-Krasinski DA, Klinge SA, et al. Development and initial validation of the assessment of caregiver experience with neuromuscular disease. J Pediatr Orthop. 2011;31(3):284-92.

Mazzone ES, Mayhew A, Montes J, et al. Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve. 2016 Epub 2016/10/04.

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve. 2010;41(4):500-10.

Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(2):103-115. Epub 2017/11/23.

Montes J, McDermott MP, Martens WB, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology. 2010;74(10):833-8.

O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 2007;17(9-10):693-7.

Permutt T, Li F. Trimmed means for symptom trials with dropouts. Pharm Stat. 2017;16(1):20-28. Epub 2016/08/15.

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.

Santner TJ, Snell MK. Small-Sample Confidence Intervals for p 1 - p 2 and p 1 /p 2 in 2 × 2 Contingency Tables. J Am Statist Assoc. 1980;75:386-94.

van der Ploeg AT, Clemens PR, Corzo D, et al. A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease. New England Journal of Medicine. 2010;362(15):1396-1406.

Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37(2):126-39.

WHO Multicentre Growth Reference Study Group. Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study. Acta Paediatr Suppl. 2006;450:56-65.

Wijnhoven TM, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull. 2004;25(1 Suppl):S37-45.

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.

17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy," 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)

18. APPENDICES

APPENDIX A. PERMANENT VENTILATION DEFINITION CRITERIA: ACUTE REVERSIBLE EVENT

Purpose: Acute, intercurrent events may result in transient utilization of increased respiratory support for participants with spinal muscular atrophy (SMA) in this study. Such events may not reflect irreversible SMA disease progression and may complicate the ability to detect the effects of nusinersen on SMA disease progression.

A secondary endpoint is defined as the time to death or permanent ventilation (tracheostomy or ≥ 16 hours of ventilation/day continuously for > 21 days **in the absence of an acute reversible event**).

The purpose of this appendix is to define an acute reversible event and to indicate how this prespecified definition will be used in this study.

Any one of the following that occur between **7 days before and 7 days after** the onset of threshold-level respiratory support (≥ 16 hours/day) meet the definition of an acute reversible event:

1. Fever ≥ 102°F/38.9°C (tympanic, rectal, axillary, skin, sublingual)
2. Infection
    - Blood, sputum, throat, or cerebrospinal fluid (CSF) culture positive × 2 for virus, bacteria, or fungus
    - Blood, throat, sputum, or CSF viral polymerase chain reaction positive
    - Blood, throat, sputum, or CSF for infectious antigen diagnostic (e.g., streptococcus+ or hepatitis B surface antigen positive)
    - Blood, throat, sputum, or CSF positive for direct microscopic visualization (e.g., bronchoalveolar lavage or Gram stain revealing the presence of bacteria by tissue biopsy)
3. Surgical procedure
    - Operation (i.e., gastrostomy/jejunostomy tube or an orthopedic procedure)
    - Any procedure in which regional or general anesthesia is administered

If any of the above is verified by appropriate source documents (e.g., emergency room visit summary, outpatient clinic note, inpatient hospital summary, operative report, etc.), the endpoint is **NOT** met until the participant requires threshold-level ventilation (≥ 16 hours/day) continuously for > 21 days beginning 14 days after the acute reversible event. The rationale is

that, in the context of an acute reversible event, the SMA participant is given a “grace period” of 14 days to clear the event or recover from surgery/anesthesia. Once the grace period has expired, if the participant requires threshold-level ventilation for > 21 consecutive days, this respiratory dependence is likely to be due to SMA disease progression, and the endpoint is met.

APPENDIX B. LABORATORY ANALYTES

Clinical Safety Assessments (Minimum Requirements)		Other Assessments
Blood Chemistry Sodium Potassium Chloride Total protein Albumin Calcium Phosphorus Bicarbonate Glucose BUN Creatinine Cystatin C Total serum bilirubin (direct and indirect) Alkaline phosphatase AST (SGOT) ALT (SGPT) CPK CK GGT	Urinalysis Specific gravity pH Protein Glucose Ketones Bilirubin Blood Red blood cells White blood cells Epithelial cells Bacteria Casts Crystals Hematology Red blood cells Hemoglobin Hematocrit Platelets WBCs WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	PK CSF and plasma nusinersen levels Pharmacodynamics pNF-H Immunogenicity Evaluation Plasma anti-nusinersen Abs **The following are to be assessed by local laboratory only:** Urine total protein Coagulation (aPTT, PT, and INR) CSF Local Lab Sample Cell count Protein Glucose Pregnancy Urine hCG Serum pregnancy test

Ab = antibody; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CPK = creatine phosphokinase; CSF = cerebrospinal fluid; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; PK = pharmacokinetic(s); pNF-H = phosphorylated neurofilament heavy chain; PT = prothrombin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell