COVER PAGE

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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:	7	
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, [redacted] 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).

Previous PK modeling predicted that the median concentration of nusinersen within the CSF immediately prior to the administration of the subsequent maintenance dose (i.e., trough concentration [C_{trough}]) would be approximately 10 ng/mL at steady state with the label-approved maintenance dosing regimen (i.e., 12 mg administered every 4 months) and approximately 20 ng/mL at steady state with the proposed maintenance dosing regimen for Study 232SM203 (i.e., 28 mg administered every 4 months). This model was subsequently updated to include additional data from Studies 232SM201 and CS11 not previously modeled, resulting in an adjustment of CSF C_{trough} predictions in all patient populations, which are still consistent with the prior predictions. As a consequence, population PK modeling now predicts that with increasing the maintenance dose from 12 to 28 mg administered every 4 months, CSF C_{trough} should increase from 5 to 12 ng/mL at steady state. The exposure-response (PK/PD) relationship between steady-state CSF C_{trough} and CHOP-INTEND response continuously increases as a function of PK and is on an upward trajectory at concentrations consistent with the 12 mg maintenance dose (i.e., 5 ng/mL). It is predicted that additional clinical benefit (i.e., a 5-point increase in CHOP-INTEND score) could be achieved by increasing CSF exposures to 12 ng/mL. Therefore, administration of this higher dose of nusinersen may lead to meaningful clinical benefit to patients. At this time, no dose-limiting toxicity has been identified with nusinersen. The PK modeling therefore suggests that it is unlikely that the higher doses of nusinersen would have a less favorable risk-benefit profile compared with standard dose nusinersen.

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 12 ng/mL as the clinical CSF C_{trough} target concentration and the predicted CSF PK profiles from 28 mg of nusinersen (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.

The assumption of PK linearity is supported by nusinersen toxicokinetic results in nonhuman primates, which showed nearly dose-proportional PK in the plasma and central nervous system tissues (target site of action) up to 15 mg (human equivalent dose of 150 mg). 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. Based on the most recent PK modeling performed, relative to the approved 12-mg label regimen (CSF C_{trough} of approximately 5 ng/mL), 28 mg administered as 3 loading doses (biweekly) or 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 12 ng/mL) more rapidly at the end of the loading dose period. 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. Moreover, the 28-mg maintenance dosing regimen adequately maintained the higher CSF C_{trough} target (approximately 12 ng/mL) during the maintenance dose period. 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 (see Section 3.3). 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 dose 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 12 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 in the 232SM203 50/28 mg Group compared to the CS3B Matched Sham Control Group, 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 (comparison of higher dose to matched sham control)
Part B Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA in the 232SM203 50/28 mg Group compared to: • CS3B Matched Sham Control Group AND • 232SM203 nusinersen 12 mg Group	Infantile-Onset SMA • Proportion of Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone responders at Day 183 (comparison of higher dose to matched sham control) • Change from baseline to Day 183 in HINE Section 2 motor milestones total score (comparison of higher dose to matched sham control) • Change from baseline to Day 183 in plasma concentration of NF-L (comparison of higher dose to matched sham control) • Change from baseline to Day 302 in CHOP-INTEND total score

	(comparison of higher dose to 12 mg dose) • Change from baseline to Day 302 in HINE Section 2 motor milestones total score (comparison of higher dose to 12 mg dose) • Change from baseline to Day 29 in plasma concentration of NF-L (comparison of higher dose to 12 mg dose) • 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]) (comparison of higher dose to matched sham control) • Time to death (overall survival) (comparison of higher dose to matched sham control) • 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]) (comparison of higher dose to 12 mg dose) • Time to death (overall survival) (comparison of higher dose to 12 mg dose)
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses compared to the currently approved 12 mg dose in participants with SMA	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) • Change from baseline in CSF concentration of NF-L • Change from baseline in plasma concentration of NF-L
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 12 mg dose in participants with SMA	Infantile-Onset and Later-Onset 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 Infantile-Onset SMA only • Change from baseline in CSF concentration of NF-L
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	**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 A and Part C Cohort 1 only) Part C (Cohort 1 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)

[redacted]

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 (232SM302), pending study approval by ethics committees and the appropriate regulatory authorities. In regard 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. Approximately 99 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 study treatment administration on Days 1 and 15; inpatient stays at other visits may occur based on the Investigator's discretion. If the primary reason for the inpatient stay is due to an AE or SAE, reporting requirements per Section 11.3 must be followed.

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. By the time of implementation of Protocol Version 6, the IDMC reviewed these data and recommended that the study may continue with dosing of the remaining participants in Part B and initiating dosing in Part C without any modifications to the study.

In Part C, up to approximately 40 participants 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 will be enrolled. The initial cohort in Part C (i.e., Cohort 1) consists of up to approximately 20 participants of any age or SMA status. For Cohort 1, an attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants in Cohort 1 ≥ 18 years of age must be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in Cohort 1 of Part C after consultation with the Medical Monitor. An additional cohort (i.e., Cohort 2) consisting of up to approximately 20 adult participants (≥ 18 years of age) was subsequently added to Part C in Protocol Version 5 in order to enable collection of data in adults transitioning from the currently approved nusinersen dosing regimen to higher

dose. Participants in Cohort 2 can be either ambulatory on nonambulatory.

All participants in Part C 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:

  Cohort 1:
  - 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

  Cohort 2:

- Males and females ≥ 18 years of age (can be ambulatory or nonambulatory)
- 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 145 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 33 participants (25 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 66 participants (50 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: Up to approximately 40 participants (i.e., up to approximately 20 participants each in Cohorts 1 and 2) 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 145 participants is planned for this study (Table 9). 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, [redacted] 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, [redacted], and efficacy of a 50/28 mg dose of nusinersen in this population. A total of up to approximately 40 participants will be enrolled in Part C (i.e., up to approximately 20 participants each in Cohorts 1 and 2) to characterize the safety, tolerability, [redacted] 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 approximately 50 participants in the 50/28-mg Group and a minimum of N=20 sham participants will provide at least approximately 99% power for the primary endpoint 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 periods 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, Table 3, and Table 4).
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) 12 mg has a positive benefit-risk profile, with more than 4 years of postmarketing experience and more than 11,000 patients treated. The safety profile to date does not preclude study of higher doses in any population.

Detailed information about the known and expected benefits and risks, reasonably expected AEs, and nonclinical toxicology studies supporting investigation of higher doses of nusinersen in the clinic are 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.

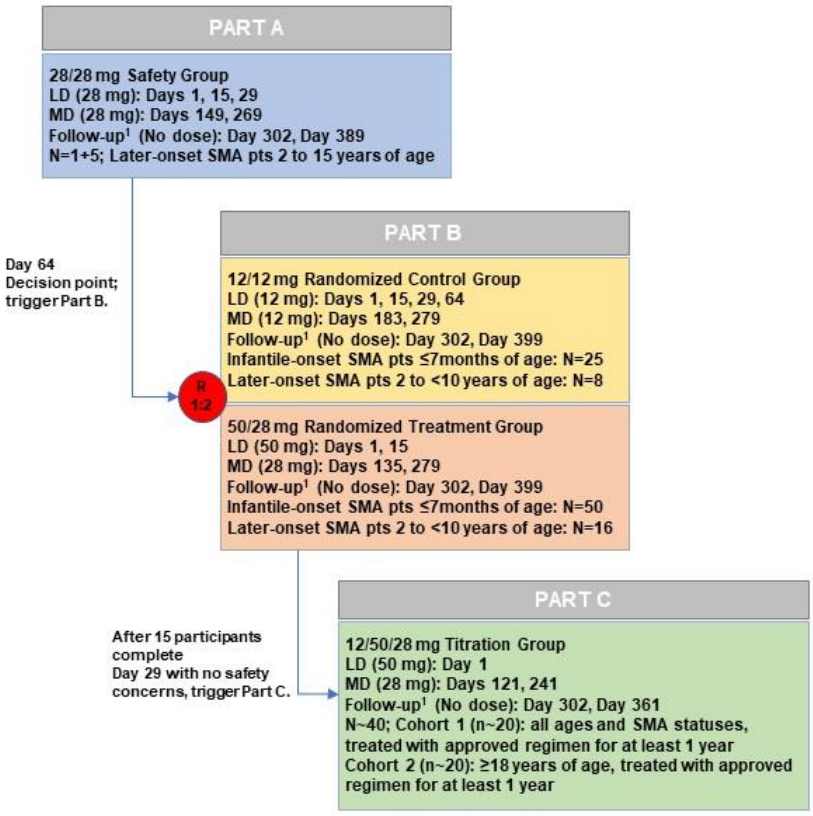
Anticipating a potential enhancement of benefit with the dosing regimens proposed for Study 232SM203, substantiated by PK/PD modeling described in Section 3.1.2, the safety of the loading period for Study 232SM203 is supported by a nonclinical study conducted in monkeys (Study P058-17-03). In this study, the no-observed-adverse-effect level (NOAEL) was 15 mg (human equivalent dose of 150 mg). As such, dosing for Study 232SM203 has a safety margin of at least 4.5-fold for cumulative doses during the loading period and a 3-fold margin for a single loading dose of 50 mg.

The safety of long-term exposure during the Study 232SM203 maintenance period is supported by a 53-week monkey study (Study 396443-AS06). Monkeys received a cumulative dose of 3.9, 13, and 52 mg at each dose level (0.3, 1, and 4 mg per dose, respectively) during the 52-week treatment duration. The overall NOAEL was determined to be 4 mg. Tissue concentrations measured in monkeys from the 53-week toxicology study at the NOAEL (4 mg) were compared to the estimated tissue concentrations in patients with SMA. The exposure-based safety margin is at least 1.4-fold based on exposure in the spinal cord (safety margins are higher for other tissues).

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 do not meet the criteria for contraception use will have their last visit on Day 302. Participants who meet the criteria for contraception use (see Section 11.5) will have a Day 302 visit and a Day 389, Day 399, or Day 361 visit for Part A, Part B, or Part C, respectively. Male participants who meet the criteria may complete the Day 389 (Part A), Day 399 (Part B), or Day 361 (Part C) visit via a telephone interview; female participants who meet the criteria will return to the site for these visits. For participants in Parts B and C who meet the criteria for contraception use and enroll into the long-term extension study (232SM302) at the Day 302 visit, that will be their final visit in Study 232SM203.

1.3. Schedule of Activities

Study assessments conducted at each visit are listed in Table 1, Table 2, Table 3, and Table 4.

Participants in Part B who discontinue treatment may remain in the study to continue the protocol-required tests and assessments described in Table 5 (unless the reason for discontinuation is to initiate treatment with a disallowed concomitant therapy per Section 7.6.1.2).

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		
[redacted]											
CSF Local Laboratory Sample (cell count, total protein, and glucose)		X				X					
[redacted]											

	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, [redacted][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										

[redacted]; 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™; [redacted]; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN1* = survival motor neuron-1 gene; *SMN2* = survival motor neuron-2 gene; 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 the criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 389 visit. Male participants who meet the criteria may complete the Day 389 visit via a telephone interview. Female participants who meet the criteria will return to the site to complete this assessment. Participants who do not meet the 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; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by central laboratory (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.

[redacted]

[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. [redacted]

[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 9.1.14).

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									
Standard of Care	X								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[6]			X[6]				
Study Treatment Injection/Sham Procedure[7]			X			X				
Inpatient Stay				X[8]						
Vital Signs and Pulse Oximetry[9]	X	X		X[10]	X		X[10]		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)**			**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**			
Growth Parameters (including height/body length/ulnar length, and head/chest/arm circumference)[11]	X	X			X[12]				X	
Physical Examination[13]	X	X			X				X	
Neurological Examination[14]	X	X		X	X		X		X	
ECG[15]		X		X			X		X	
Safety Laboratory Tests[16]	X	X			X				X	
Local Coagulation Laboratory Tests[17]	X	X			X					
Safety Follow-Up Telephone Contact				X[18]				X		
[redacted]										
CSF Local Laboratory Sample (cell count, total protein, and glucose)[6]		X			X					
CSF Biomarker		X			X					
Plasma Biomarker		X			X[12]				X	
Efficacy Assessments[21] for Participants With Infantile-Onset SMA (CHOP-INTEND and HINE Section 2 Motor Milestones)	X[22]	X[23]			X[12]				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**			
Efficacy Assessments[21] for Participants With Later-Onset SMA (HFMSE, RULM, WHO Motor Milestones, [redacted])	X[22]	X[23]			X[12]				X	
CGIC[25]		X			X				X	
PedsQL and ACEND[26]		X			X[12]				X	
Dysphagia Assessment (PASA)	X	X[27]			X[12, 27]				X	
[redacted]										
Ventilator Use[28]	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

[redacted] 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; COVID-19 = coronavirus disease 2019; 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™; [redacted]; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN1* = survival motor neuron-1 gene; *SMN2* = survival motor neuron-2 gene; 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. 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 do not meet the criteria for contraception use will have their last visit on Day 302. Participants who meet the criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 399 visit. Male participants who meet the criteria may complete the Day 399 visit via a telephone interview. Female participants who meet the criteria will return to the site for the Day 399 visit. Day 399 will take place at least 120 days after the final dose. For participants who meet the criteria for contraception use and enroll into the long-term extension study (232SM302) at the Day 302 visit, that will be their final visit in Study 232SM203.

[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] For all participants, a blood sample will be collected during the study to evaluate *SMN1* status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number by the central laboratory. For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory but may be determined by local laboratory genetic testing, if needed). For participants with documentation of these genetic testing results before Screening or whose sample was analyzed locally during the Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening or by Day 29 but must be collected by the Day 135 visit) for confirmatory testing through 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] LP opening pressure will only be evaluated for participants with later-onset SMA. Only measure LP opening pressure and assess CSF local laboratory 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] Participants will remain at the clinic for at least 24 hours after study treatment administration on Days 1 and 15; inpatient stays at other visits may occur based on the Investigator's discretion. If the primary reason for the inpatient stay is due to an AE or SAE, reporting requirements per Section 11.3 must be followed.

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

[10] On Days 1 and 15, postdose vital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. On Days 29, 64, 135, 183, and 279, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.

[11] Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height or body length (for participants who are not able to stand independently) and ulnar length will be measured in participations with later-onset SMA. The same measurement (height or body length) should be evaluated at all study visits wherever possible.

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

[13] Videotaping of physical examinations is optional.

[14] 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. A neurological examination will be performed at Screening; 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 on Days 1 and 15; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 29, 64, 135, 183, and 279; and at Day 302/ET. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[15]ECGs will be performed predose, at 5 hours (± 1 hour) postdose, and at 24 hours (± 2 hours) postdose on Days 1 and 15; predose and at 5 hours (± 1 hour) postdose on Days 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.

[16]Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. For the Screening visit only, a local laboratory may be used instead for analysis, if needed, for the timely treatment of the participant at the discretion of the Investigator. If a local laboratory is used for the Screening visit, the samples should be collected on Day 1 for central laboratory evaluation (even if within 7 days of Screening). 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; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by central laboratory. (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. When the safety laboratory sample analysis is at risk due to logistical difficulties or issues with access to the central laboratory (e.g., due to COVID-19–related disruptions or humanitarian emergencies), these samples may be analyzed by the local laboratory. Any use of a local laboratory under these circumstances must be approved by the Sponsor prior to being implemented.

[17]Coagulation testing will be conducted locally at Screening and predose (within 7 days prior to dosing) at each dosing visit; results should 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.

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

[redacted]

[21]Videotaping of all motor milestone and motor function assessments is optional; however, if the participant/caregiver consents to video recording, all assessments should be recorded.

[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, they should be completed on different days and the assessments do not need to be repeated on Day 1.

[23]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.

[redacted]

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

[26]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.

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

[28]Ventilator use will be collected at every study visit (see Section 9.1.14).

Table 3: Schedule of Activities for Part C Cohort 1

	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				X						
Vital Signs and Pulse Oximetry[8]	X	X		X[9]	X		X[9]		X	
Weight	X	X			X				X	
Growth Parameters (including height/body length/ulnar length, and head/chest/arm circumference)[10]	X	X			X[11]				X	
Physical Examination[12]	X	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		
[redacted]										
CSF Local Laboratory Sample (cell count, total protein, and glucose)		X			X					
[redacted]										
CGIC[20]					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**			
Efficacy Assessments Based on Clinical Status[21] (CHOP-INTEND, HINE Section 2 Motor Milestones, HFMSE, RULM, WHO Motor Milestones, [redacted])	X[23]	X[23]			X[11]				X	
PedsQL and ACEND[24]		X			X[11]				X	
Ventilator Use[25]	X	X			X			X	X	
AE Recording	X----------X									
SAE Recording	X----------X									
Concomitant Therapy and Procedures Recording	X----------X									

[redacted]; 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™; [redacted]; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN1* = survival motor neuron-1 gene; *SMN2* = survival motor neuron-2 gene; 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. 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 do not meet the criteria for contraception use will have their last visit on Day 302. Participants who meet the criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 361 visit. Male participants who meet the criteria may complete the Day 361 visit via a telephone interview. Female participants who meet the criteria will return to the site for the Day 361 visit. Day 361 will take place at least 120 days after the final dose. For participants who meet the criteria for contraception use and enroll into the long-term extension study (232SM302) at the Day 302 visit, that will be their final visit in Study 232SM203.

[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] For all participants, a blood sample will be collected to evaluate *SMN1* status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number by the central laboratory. For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory but may be determined by local laboratory genetic testing, if needed). For participants with documentation of genetic testing results before Screening or whose sample was analyzed locally during the Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening but must be collected by the Day 121 visit) for confirmatory testing through the central laboratory.

[6] Up to 5 participants with severe scoliosis and/or severe contractures will be enrolled in Cohort 1. 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] On Day 1, postdose vital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. On Days 121 and 241, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.

[10] Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height or body length (for participants who are not able to stand independently) and ulnar length will be measured in participants with later-onset SMA. The same measurement (height or body length) should be evaluated at all study visits whenever possible.

[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. A neurological examination will be performed at Screening; 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 on Day 1; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 121 and 241; and at Day 302/ET. 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. For the Screening visit only, a local laboratory may be used instead for analysis if needed for the timely treatment of the participant at the discretion of the Investigator. If a local laboratory is used for the Screening visit, the samples should be collected on Day 1 for central laboratory evaluation (even if within 7 days of Screening). 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; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by central laboratory. (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 should 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.

[redacted]

[20]Adult participants who do not require a caregiver during the study visits will only have the CGIC assessed by the Investigator.

[21]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; however, if the participant/caregiver consents to video recording, all assessments should be recorded.

[redacted]

[23]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, they should be completed on different days and the assessments do not need to be repeated on Day 1.

[24]PedsQL and ACEND will be assessed only in participants ≥ 2 years of age at Screening. The ACEND questionnaire will not be collected for adult participants who do not require a caregiver during the study visits. Assessments will be performed on Day 1, Day 241, and at Day 302/ET.

[25]Ventilator use will be collected at every study visit (see Section 9.1.14).

Table 4: Schedule of Activities for Part C Cohort 2

	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 (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				X						
Vital Signs and Pulse Oximetry[8]	X	X		X[9]	X		X[9]		X	
Weight	X	X			X				X	
Growth Parameters (including height/body length/ulnar length, and head/chest/arm circumference)[10]	X	X			X[11]				X	
Physical Examination[12]	X	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		
[redacted]										
CSF Local Laboratory Sample (cell count, total protein, and glucose)		X			X					
[redacted]										
CGIC[20]					X				X	
HFMSE[21]	X[22]	X[22]			X[11]				X	
RULM[21]	X[22]	X[22]			X[11]				X	
WHO Motor Milestones[21]	X				X[11]				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**			
ACEND[23]		X							X	
[redacted]										
Ventilator Use[26]	X	X			X			X	X	
AE Recording	X----------									----X
SAE Recording	X----------									----X
Concomitant Therapy and Procedures Recording	X----------									----X

[redacted] 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; [redacted]; ET = early termination; [redacted] HFMSE = Hammersmith Functional Motor Scale Expanded; ICF = informed consent form; LP = lumbar puncture; [redacted]; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; [redacted]; *SMN1* = survival motor neuron-1 gene; *SMN2* = survival motor neuron-2 gene; [redacted] 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. 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 do not meet the criteria for contraception use will have their last visit on Day 302. Participants who meet the criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 361 visit. Male participants who meet the criteria may complete the Day 361 visit via a telephone interview. Female participants who meet the criteria will return to the site for the Day 361 visit. Day 361 will take place at least 120 days after the final dose. For

participants who meet the criteria for contraception use and enroll into the long-term extension study (232SM302) at the Day 302 visit, that will be their final visit in Study 232SM203.

[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] For all participants, a blood sample will be collected to evaluate *SMN1* status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number by the central laboratory. For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory but may be determined by local laboratory genetic testing, if needed). For participants with documentation of genetic testing results before Screening or whose sample was analyzed locally during the Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening but must be collected by the Day 121 visit) for confirmatory testing through the central laboratory.

[6] 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.

[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] On Day 1, postdose vital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. On Days 121 and 241, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.

[10] Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height or body length (for participants who are not able to stand independently) and ulnar length will be measured in participants with later-onset SMA. The same measurement (height or body length) should be evaluated at all study visits whenever possible.

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

[12] Videotaping of physical examinations is optional.

[13] A neurological examination will be performed at Screening; 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 on Day 1; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 121 and 241; and at Day 302/ET. 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. For the Screening visit only, a local laboratory may be used instead for analysis if needed for the timely treatment of the participant at the discretion of the Investigator. If a local laboratory is used for the Screening visit, the samples should be collected on Day 1 for central laboratory evaluation (even if within 7 days of Screening). 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; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by central laboratory (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 should 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.

[redacted]

[20]Adult participants who do not require a caregiver during the study visits will only have the CGIC assessed by the Investigator.

[redacted]

[22]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, they should be completed on different days and the assessments do not need to be repeated on Day 1.

[23]The ACEND questionnaire will not be collected for adult participants who do not require a caregiver during the study visits.

[24]Assessment will be performed on Day 121 only.

[redacted]

[26]Ventilator use will be collected at every study visit (see Section 9.1.14).

Table 5: Schedule of Activities for Participants in Part B Who Discontinue Study Treatment but Agree to Remain in the Study

Assessment[1]	**Follow-Up Visits**[2]
Weight	X
Growth Parameters	X
Physical Examination	X
Vital Signs (temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry)	X
Neurological Examination[3]	X
Urine/Serum Pregnancy Test for Females of Childbearing Potential[4]	X
Safety Laboratory Tests	X
WHO Motor Milestones	X
HINE Section 2 Motor Milestones (as appropriate)	X
Motor Function Assessments (as appropriate, including CHOP-INTEND, HFMSE, RULM, [redacted])	X
Plasma Biomarker Assessment (optional)	X
Ventilator Use	X
Ventilator Use Diary (participants with infantile-onset SMA)	X
Concomitant Therapy and Procedure Recording	X
AE and SAE Recording	X

[redacted]; AE = adverse event; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale Expanded; HINE = Hammersmith Infant Neurological Examination; PD = pharmacodynamic(s); [redacted] RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; WHO = World Health Organization

Note: See Section 9 for additional details regarding efficacy, [redacted], and PD assessments.

[1] Participants who initiate treatment with a disallowed concomitant therapy (see Section 7.6.1.2) must be withdrawn from Study 232SM203; they are not eligible to remain in the study for follow-up visits per Table 5.

[2] Participants should return to the clinic according to the original visit schedule per Table 2 (i.e., Days 1, 15, 29, 64, 135, 183, 279, and 302) for follow-up visits after discontinuing treatment but will follow a reduced Schedule of Activities at these visits.

[3] 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.

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

2. LIST OF ABBREVIATIONS

[redacted]	[redacted]
[redacted]	[redacted]
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
aPTT	activated partial thromboplastin time
[redacted]	[redacted]
ASO	antisense oligonucleotide
BLQ	below limit of quantification
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
ECG	electrocardiogram
EOS	end of study
[redacted]	[redacted]
ET	early termination
EU	European Union
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
[redacted]	[redacted]
INR	international normalized ratio
IRT	interactive response technology
ITT	Intent-to-Treat
LLOQ	lower limit of quantification
LP	lumbar puncture
MI	multiple imputation
NF-L	neurofilament light chain
NOAEL	no-observed-adverse-effect level

PASA	Parent Assessment of Swallowing Ability
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory™
PK	pharmacokinetic(s)
PT	prothrombin time
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
[redacted]	[redacted]
SMN	survival motor neuron protein
SMN1	survival motor neuron-1 gene
SMN2	survival motor neuron-2 gene
SUSAR	suspected unexpected serious adverse reaction
US	United States
[redacted]	[redacted]
WHO	World Health Organization

3. INTRODUCTION

Nusinersen is an ASO administered intrathecally via LP; it increases SMN expression and significantly improves motor function in patients with SMA. Nusinersen was approved for the treatment of SMA under the tradename Spinraza™ in the US, EU, 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. PK and 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 [redacted] 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 higher dosing regimen (50-mg loading/28-mg maintenance) in the pivotal portion of the study.

In Part B, in order to evaluate the proposed higher 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 supplement the number of participants available for the analysis 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, may 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 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 higher dosing regimen via the administration of a single bolus dose

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 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 [redacted] modeling and simulations showed that an improvement in 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 with SMA who have been receiving nusinersen treatment for at least 1 year prior to entry in this study across participants of all ages (Cohort 1) and participants ≥ 18 years of age (Cohort 2). Participants should be receiving nusinersen as per local label and have no missed doses in the last year prior to Screening. This part is designed to evaluate the safety of transitioning participants from the currently approved dosing regimen to the higher 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 CSF exposure and motor function (e.g., CHOP-INTEND scores).

Previous PK modeling predicted that the median concentration of nusinersen within the CSF immediately prior to the administration of the subsequent maintenance dose (i.e., C_{trough}) would be approximately 10 ng/mL at steady state with the label-approved maintenance dosing regimen (i.e., 12 mg administered every 4 months) and approximately 20 ng/mL at steady state with the proposed maintenance dosing regimen for Study 232SM203 (i.e., 28 mg administered every 4 months). This model was subsequently updated to include additional data from Studies 232SM201 and CS11 not previously modeled, resulting in an adjustment of CSF C_{trough} predictions in all patient populations, which are still consistent with the prior predictions. As a consequence, population PK modeling now predicts that with increasing the maintenance dose from 12 to 28 mg administered every 4 months, CSF C_{trough} should increase from 5 to 12 ng/mL at steady state. The exposure-response (PK/PD) relationship between steady-state CSF C_{trough} and CHOP-INTEND response continuously increases as a function of PK and is on an upward trajectory at concentrations consistent with the 12 mg maintenance dose (i.e., 5 ng/mL). It is predicted that additional clinical benefit (i.e., a 5-point increase in CHOP-INTEND score) could be achieved by increasing CSF exposures to 12 ng/mL. Therefore, administration of this higher dose of nusinersen may lead to meaningful clinical benefit to patients. At this time, no dose-limiting toxicity has been identified with nusinersen. The PK modeling therefore suggests that it is unlikely that the higher doses of nusinersen would have a less favorable risk-benefit profile compared with standard dose nusinersen.

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 12 ng/mL as the clinical CSF C_{trough} target concentration and the predicted CSF PK profiles from 28 mg of nusinersen (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.

The assumption of PK linearity 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). 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. Based on the most recent PK modeling performed, relative to the approved 12-mg label regimen (CSF C_{trough} of approximately 5 ng/mL), 28 mg administered as 3 loading doses (biweekly) or 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 12 ng/mL) more rapidly at the end of the loading dose period. Nusinersen 28 mg administered as 3 loading doses (biweekly) had a comparable predicted CSF C_{max} to the reference dosing regimen, whereas the 50-mg dosing regimen surpassed the predicted C_{max} from the reference dosing regimen. Moreover, the 28-mg maintenance dosing regimen adequately maintained the higher CSF C_{trough} target (approximately 12 ng/mL) during the maintenance dose period. 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 (see Section 3.3). 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 dose 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 12 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 *SMN2* (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 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 and/or other SMA therapies are not approved, current medical care is limited to supportive care, focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery, with specific guidelines according to age of SMA onset [Finkel 2017; Mercuri 2018].

A gene transfer agent, Zolgensma®, an adeno-associated virus vector expressing a *SMN1* delivered intravenously, was approved in the US in 2019 and Japan in 2020 for the treatment of SMA Type 1 in patients younger than 2 years of age, and in the EU in May 2020 for the treatment of patients with 5q SMA with dosing guidance for body weight up to 21 kg. Risdiplam (Evrysdi™, formerly RG7916) is an oral *SMN2*-directed splicing modifier indicated for the treatment of SMA in patients ≥ 2 months of age. It was first approved in the US in 2020 and has since received approval in at least 5 other markets.

3.2.3. Profile of Previous Experience With Nusinersen

Nusinersen is an ASO administered intrathecally via LP and increases SMN 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 SAE profile is consistent with the events seen in infants and children with SMA.

Nusinersen was first approved for the treatment of SMA under the tradename Spinraza™ in the US on 23 December 2016 (New Drug Application 209531). Subsequently, it was approved in the EU (5q SMA) [May 2017] and other major markets (5q SMA, infantile SMA, and all other SMAs).

As of December 2020, more than 11,000 patients with SMA have been treated with nusinersen worldwide, in 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) 12 mg has a positive benefit-risk profile, with more than 4 years of postmarketing experience and more than 11,000 patients treated. The safety profile to date does not preclude study of higher doses in any population.

Detailed information about the known and expected benefits and risks, reasonably expected AEs, and nonclinical toxicology studies supporting investigation of higher doses of nusinersen in the clinic are provided in the Investigator's Brochure and ICF. A high-level summary of the benefits and risks known during study design is provided here.

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 P058-17-03). In this study, the NOAEL was 15 mg (human equivalent dose of 150 mg). As such, dosing for Study 232SM203 has a safety margin of at least 4.5-fold for cumulative doses during the loading period and a 3-fold margin for a single loading dose of 50 mg.

The safety of long-term exposure during the Study 232SM203 maintenance period is supported by a 53-week monkey study (Study 396443-AS06). Monkeys received a cumulative dose of 3.9, 13, and 52 mg at each dose level (0.3, 1, and 4 mg per dose, respectively) during the 52-week treatment duration. The overall NOAEL was determined to be 4 mg. Tissue concentrations measured in monkeys from the 53-week toxicology study at the NOAEL (4 mg) were compared to the estimated tissue concentrations in patients with SMA. The exposure-based safety margin is at least 1.4-fold based on exposure in the spinal cord (safety margins are higher for other tissues).

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 in the 232SM203 50/28 mg Group compared to the CS3B Matched Sham Control Group, 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 (comparison of higher dose to matched sham control)
Part B Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA in the 232SM203 50/28 mg Group compared to: • CS3B Matched Sham Control Group AND/OR • 232SM203 nusinersen 12 mg Group	Infantile-Onset SMA • Proportion of HINE Section 2 motor milestone responders at Day 183 (comparison of higher dose to matched sham control) • Change from baseline to Day 183 in HINE Section 2 motor milestones total score (comparison of higher dose to matched sham control) • Change from baseline to Day 183 in plasma concentration of NF-L (comparison of higher dose to matched sham control) • Change from baseline to Day 302 in CHOP-INTEND total score, accounting for mortality/dropout using the joint rank test (comparison of higher dose to matched 12 mg dose) • Change from baseline to Day 302 in HINE Section 2 motor milestones total score (comparison of higher dose to 12 mg dose)

	• Change from baseline to Day 29 in plasma concentration of NF-L (comparison of higher dose to 12 mg dose) • 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]) (comparison of higher dose to matched sham control) • Time to death (overall survival) (comparison of higher dose to matched sham control) • 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]) (comparison of higher dose to 12 mg dose) • Time to death (overall survival) (comparison of higher dose to 12 mg dose)
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses compared to the currently approved 12 mg dose in participants with SMA	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

	• Change from baseline in CSF concentration of NF-L • Change from baseline in plasma concentration of NF-L
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 12 mg dose in participants with SMA	Infantile-Onset and Later-Onset 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 Infantile-Onset SMA only • Change from baseline in CSF concentration of NF-L
[redacted]	

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 A and Part C Cohort 1 only) Part C (Cohort 1 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)
[redacted]	

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.

5. STUDY DESIGN

5.1. Study Overview

This 3-part study will evaluate the efficacy and safety of a higher dosing regimen of nusinersen in approximately 145 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 (232SM302), pending study approval by ethics committees and the appropriate regulatory authorities. In regard 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. Approximately 99 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 study treatment administration on Days 1 and 15; inpatient stays at other visits may occur based on the Investigator's discretion. If the primary reason for the inpatient stay is due to an AE or SAE, reporting requirements per Section 11.3 must be followed.

Randomization in Part B will be performed using 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. By the time of implementation of Protocol Version 6, the IDMC reviewed these data and recommended that the study may continue with dosing of the remaining participants in Part B and initiating dosing in Part C without any modifications to the study.

In Part C, up to approximately 40 participants 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 will be enrolled in Part C. The initial cohort in Part C (i.e., Cohort 1) consists of up to approximately 20 participants of any age and of any SMA status. For Cohort 1, an attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants in Cohort 1 ≥ 18 years of age must be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in Cohort 1 of Part C after consultation with the Medical Monitor. An additional cohort (i.e., Cohort 2) consisting of up to approximately 20 adult participants (≥ 18 years of age) was subsequently added to Part C in Protocol Version 5 in order

to enable collection of data in adults transitioning from the currently approved nusinersen dosing regimen to a higher dose. Participants in Cohort 2 can be either ambulatory or nonambulatory.

All participants in Part C 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 periods 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.

[redacted]

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 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 EOS 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. Infants with a lower gestational age may be considered for enrollment if there are no complications due to prematurity and approval by the Medical Monitor has been granted.

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. HFMSE score ≥ 10 and ≤ 54 at Screening

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

Part C

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

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

4. 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

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. 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)

8. 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

9. 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

Participants in Cohort 1

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

Participants in Cohort 2

11. Males and females ≥ 18 years of age at Screening (can be ambulatory or nonambulatory)

12. HFMSE total score ≥ 4 points at Screening

13. RULM entry item A score ≥ 3 points at 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 blood 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 *SMN*2-splicing modifier or gene therapy; or prior ASO 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 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

All Participants

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 blood chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion

7. History of systemic hypersensitivity reaction to the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study

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

9. 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

10. Treatment with an investigational drug including but not limited to 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 ASO treatment (e.g., nusinersen) 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, without ventilation support] < 96% at an altitude of < 1500 meters, < 92% at an altitude of 1500 to 2000 meters, or < 90% at an altitude > 2000 meters) 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. 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

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

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

20. 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.

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

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

Part C

All Participants

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 blood chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion

7. History of systemic hypersensitivity reaction to nusinersen, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study

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

9. 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

10. 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

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

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

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

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

Participants in Cohort 2

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.

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 and Rescreening

During the Screening period, participants who have an out-of-range result may be retested 1 time only at the discretion of the Investigator within the Screening process, without the need for a repeat full Screening. 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.

Participants who fail Screening (see Section 6.3.3) may be rescreened once at the discretion of the Investigator. Participants who are rescreened will be assigned a new identification number.

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 33 participants (25 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 6 for the blinded dosing schedule.

  – 50/28-mg Group: A total of 66 participants (50 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 6 for the blinded dosing schedule.

Table 6: 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: Up to approximately 40 participants (i.e., up to approximately 20 participants each in Cohorts 1 and 2) 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 (as per the Schedule of Activities), a protocol deviation should be recorded and nusinersen should be administered as soon as possible, with at least 14 days between doses, and dosing should be continued according to the Schedule of Activities. 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 according to the Schedule of Activities.

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 DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the 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

Nusinersen will be supplied as specified in the DHA. The study treatment is supplied as a formulation that contains nusinersen, sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, potassium chloride, calcium chloride dihydrate, and 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. Further details on drug preparation and administration may be found 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, *SMN2*-splicing modifier, 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.). In addition, participants will not be allowed to enroll in other interventional studies during Study 232SM203.

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 (232SM302), pending study approval by ethics committees and the appropriate regulatory authorities. In regard 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 in Part B who discontinue treatment may remain in the study to continue the protocol-required tests and assessments described in Table 5 (unless the reason for discontinuation is to initiate treatment with a disallowed concomitant therapy per Section 7.6.1.2). Participants should return to the clinic according to the original visit schedule per Table 2 until the Day 302 study visit but will follow a reduced Schedule of Activities at these visits.

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 or initiates treatment with a disallowed concomitant therapy as described in Section 7.6.1.2.

- 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 ET visit unless withdrawal is due to death or withdrawal of consent.

Participants who withdraw from the study may not be replaced.

9. EFFICACY, [redacted], 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
- 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.

Sitting independently will be defined as able to sit without support per WHO motor milestone (Test Item No. 1 – sitting without support), and 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; however, if the participant/caregiver consents to video recording, all assessments should be recorded.

Part A

<u>Participants with Later-Onset SMA:</u>

- HFMSE
- RULM
- WHO motor milestones
- [redacted]

- [redacted]
- QoL questionnaires (PedsQL and ACEND)
- Dysphagia assessments (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)
- [redacted]

Participants with Later-Onset SMA:

- HFMSE
- RULM
- WHO motor milestones
- [redacted]
- [redacted]
- QoL questionnaires (PedsQL and ACEND)
- Dysphagia assessment (PASA)
- [redacted]

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.

Cohort 1:

- CHOP-INTEND and HINE Section 2 motor milestones should be performed by the following participants:
  - Participants 1 to < 2 years of age at the time of informed consent.
  - Participants 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:
  - Participants ≥ 2 years of age at the time of informed consent. If unable to sit independently, CHOP-INTEND and HINE Section 2 motor milestones will also be performed.
  - Participants ≥ 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 motor milestones until the end of study.
- WHO motor milestones [redacted] should be collected for all participants.
- [redacted]
- [redacted]
- QoL questionnaires (PedsQL and ACEND) should be assessed for participants ≥ 2 years of age at the time of informed consent.

Cohort 2:

- HFMSE, RULM, WHO motor milestones, QoL questionnaires (ACEND and [redacted]), [redacted], [redacted] should be evaluated for all participants.

[redacted]

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, Table 3, and Table 4). 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 7 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 site clinical evaluator and caregiver. Adult participants who do not require a caregiver during the study visit may self-report WHO motor milestone achievement.

Whenever possible, for each participant, motor milestone assessments across all study visits should be conducted consistently by the same clinical evaluator.

Table 7: 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].

Whenever possible, for each participant, CHOP-INTEND assessments across all study visits should be conducted consistently by the same clinical evaluator.

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.

Whenever possible, for each participant, HFSME assessments across all study visits should be conducted consistently by the same clinical evaluator.

9.1.4. Revised Upper Limb Module

Participants with later-onset SMA will be evaluated using the 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 (e.g., puberty), and the RULM aims to incorporate the performance of the shoulder, elbow, wrist, and hand.

Whenever possible, for each participant, RULM assessments across all study visits should be conducted consistently by the same clinical evaluator.

[redacted]

9.1.8. 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.

9.1.9. 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. Quality-of-Life Questionnaires

QoL questionnaires include the PedsQL, ACEND, [redacted]. QoL questionnaires will be collected on the days specified in Table 1, Table 2, Table 3, and Table 4.

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

Participants with later-onset SMA will be evaluated using the age-appropriate modules of the PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module [Varni 1999], which include age 2 to 4 years, 5 to 7 years, 8 to 12 years, 13 to 18 years, 18 to 25 years, and ≥ 26 years. 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 HRQOL in children, adolescents, and adults. The PedsQL consists of brief, practical, generic core scales, as well as condition-specific modules for use in designated clinical populations. The PedsQL 4.0 Generic Core Scales include an assessment of physical functioning, emotional functioning, social functioning, and school functioning and will be assessed for participants 2 to ≥ 26 years of age. The PedsQL 3.0 Neuromuscular Module was designed to measure HRQOL dimensions specific to patients with neuromuscular disorders, including SMA, and will be assessed in participants 2 to 25 years of age. Patient self-report will be measured in participants starting at 5 years of age, while parent proxy-report of HRQOL will be measured for participants starting at 2 years of age.

In Parts A and B, all participants with later-onset SMA will be evaluated using the PedsQL. In Part C Cohort 1, the PedsQL (in addition to ACEND) will be evaluated in participants who are ≥ 2 years of age at Screening. The PedsQL will not be evaluated for participants in Part C Cohort 2.

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.

9.1.10.2. 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. 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).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.14. Ventilator Use

9.1.14.1. 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 9.1.14.2).

9.1.14.2. 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, regardless of whether or not a ventilator is being utilized. This information will be obtained by the site during study visits and telephone contacts and entered into the CRF.

9.1.15. Standard of Care

All participants are expected to follow standard of care as referenced in Section 6.2 throughout the entire duration of the study. Investigators will document standard of care information for Part B participants at Screening and Day 302.

[redacted]

9.3. Pharmacodynamic Assessments

The PD properties of nusinersen will be assessed (where data are available) by evaluating the plasma and CSF levels of NF-L to explore its role as a potential biomarker of treatment response in SMA.

[redacted]

9.5. Pharmacogenetic and Genetic Assessments

All participants will undergo genetic testing through a central laboratory to confirm *SMN1* status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number. For the purpose of determining study eligibility, historical genetic testing results may be acceptable with appropriate documentation or analysis may be performed at a local laboratory if needed, but confirmatory testing through a central laboratory will also be performed. Deoxyribonucleic acid is to be collected from all participants to assess sequence variations at the *SMN1* and *SMN2* loci that might affect *SMN1* and *SMN2* activity or the binding of nusinersen.

9.6. Future Scientific Research Assessments

[redacted]

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. [redacted]
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry
- Growth parameters: body length/height (for all participants; body length will be measured for participants who are not able to stand independently), 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)
- ECGs
- LP opening pressure: Details available in the DHA. LP opening pressure will be evaluated for all participants in Parts A and C, but only for participants with later-onset SMA in Part B.
- 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): aPTT, PT, and INR
- 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 except if local analysis is not possible without a 24-hour urine collection, in which case samples will be analyzed by a central laboratory); specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, and crystals
- CSF local laboratory sample: cell count, total protein, and glucose

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

When the safety laboratory sample analysis is at risk due to logistical difficulties or issues with access to the central laboratory (e.g., due to COVID-19–related disruptions or humanitarian emergencies), these samples may be analyzed by the local laboratory. Any use of a local laboratory under these circumstances must be approved by the Sponsor prior to being implemented.

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 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 or LP/Sham Procedure

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 or according to national law, as described in Section 11.3.3. Follow-up information regarding an SAE also must be reported within 24 hours or according to national law.

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 or according to national law. 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 or according to national law. 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

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 or according to national law.
- 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 or according to national law.
- 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

12.1. General Considerations

The objectives of the study, the endpoints to be analyzed, and the statistical hypotheses are listed in Section 4.

In Part B, the primary endpoint and a subset of the secondary endpoints will compare the 50/28-mg Group 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. A matching algorithm will be used to select a group of participants who are similar to the 232SM203 higher dose group. The remaining secondary endpoints will compare the arms within Study 232SM203 Part B (50/28 mg Group versus 12 mg Group). This is detailed further in the following sections.

12.2. Analysis Sets

The 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. [redacted]

The ITT, Safety, [redacted] 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.

The Matched Sham Set will be defined for the analysis of the primary and secondary endpoints comparing to sham. This will comprise of sham participants identified by the matching algorithm and all 50/28 mg participants in the ITT Set.

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 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 and secondary endpoints will be utilized. In this procedure, the primary endpoint of 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. If this is statistically significant, then the first secondary endpoint of the proportion of motor milestone responders at Day 183 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 8. Inferential conclusions about each successive analysis require statistical significance of the prior one.

The statistical testing of the primary endpoint and a subset of secondary endpoints will use the Sham Control Group from Study CS3B. Within Study CS3B, there are 37 participants with an opportunity to attend the Day 183 visit.

An algorithm will be used to select a group of sham participants from the pool of 37. The algorithm will attempt to match the largest number of participants and if unsuccessful, smaller pools will be selected and the minimum matched will be 20 participants. [redacted]

The main analysis for the primary endpoint and secondary endpoints comparing nusinersen 50/28 mg to sham will be performed using the 50/28 mg participants in the ITT Set and the set of at least 20 sham participants selected via the matching algorithm.

The main analyses for secondary endpoints comparing 50/28 mg to 12 mg will be performed using the ITT Set. [redacted]

12.4.1. Analysis of the Primary Endpoint in Part B

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. Multiple imputation will be utilized to impute a missing Day 183 value of CHOP-INTEND for participants who discontinued for a reason other than death or where it was not assessed. Participants who have an imputed or available Day 183 score 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 supplementary analysis. 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 pvalue associated with the adjusted-difference test statistic will be calculated using a reference distribution generated by a rerandomization procedure.

12.4.2. Analysis of the Secondary Endpoints in Part B

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].

The proportion of HINE Section 2 motor milestone responders will be assessed at Day 183 for 50/28 mg versus sham.

Total HINE Section 2 – Motor Milestones

Change from baseline to Day 183 for 50/28 mg versus sham and change from baseline to Day 302 for 50/28 mg versus 12 mg will be analyzed using the same methodology as described for the primary endpoint.

Plasma Neurofilament

For plasma NF-L, if the baseline assessment is missing, then the first available assessment post dose within Day 2 will be used instead as baseline.

Values that are BLQ will be set to half of the diluted LLOQ.

Change in plasma NF-L from (ratio to) baseline to Day 183 will be analyzed for 50/28 mg versus sham, and change in plasma NF-L from baseline to Day 29 will be analyzed for 50/28 mg versus 12 mg using the same method as for the primary endpoint.

CHOP-INTEND

Change in CHOP-INTEND from baseline to Day 302 will be analyzed for 50/28 mg versus 12 mg using the same methodology as described for the primary endpoint.

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 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 comparison groups (ie., sham and 50/28 mg dose) 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.

The analysis will also be perfomed for the comparison of sham versus 50/28 mg doses and the comparison of 12 mg versus 50/28 mg doses.

Time to Death

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

Table 8 summarizes the planned statistical testing.

Table 8: Primary and Secondary Endpoints

Rank	Endpoint and Comparison	Analysis Method	Comparison of higher dose (50/28 mg) to
1	Change in CHOP-INTEND from baseline to Day 183 total score	Joint rank using MI	CS3B Matched Sham Control
2	Proportion of HINE Section 2 motor milestone responders at Day 183	Logistic regression or Fisher's Exact Test	CS3B Matched Sham Control
3	Change from baseline to Day 183 in HINE Section 2 total score	Joint rank using MI	CS3B Matched Sham Control
4	Change from baseline to Day 183 in plasma NF-L from baseline to Day 183	Joint rank using MI	CS3B Matched Sham Control
5	Change from baseline to Day 302 in CHOP-INTEND total score	Joint rank using MI	232SM203 12 mg Control
6	Change from baseline to Day 302 in HINE Section 2 Motor Milestones total score	Joint rank using MI	232SM203 12 mg Control
7	Change from baseline to Day 29 in plasma NF-L	Joint rank using MI	232SM203 12 mg Control
8	Time to death or permanent ventilation	Log-rank test stratified by disease duration at Screening	CS3B Matched Sham Control
9	Time to death	Log-rank test stratified by disease duration at Screening	CS3B Matched Sham Control
10	Time to death or permanent ventilation	Log-rank test stratified by disease duration at Screening	232SM203 12 mg Control
11	Time to death	Log-rank test stratified by disease duration at Screening	232SM203 12 mg Control

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.

[redacted]

12.6. Methods of Analysis for Pharmacodynamic Endpoints

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

Plasma and CSF NF-L levels will be summarized using available results. 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. [redacted]

For Part B, plasma NF-L and CSF NF-L levels will be analyzed as secondary endpoints (Section 12.4.2).

12.7. Methods of Analysis for Biomarkers/Pharmacogenetics

Plasma and CSF samples (collected as specified in Section 1.3) may be assayed for NF-L and data will be summarized using descriptive statistics and will be presented by dose group.

[redacted]

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.

[redacted]

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 of the primary endpoint in Part B may 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 145 participants is planned for this study (Table 9). 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 [redacted] of a 28/28-mg dose of nusinersen (28-mg loading dose; 28mg 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, [redacted], and efficacy of the 50/28 mg dose of nusinersen in this population. A total of up to approximately 40 participants will be enrolled in Part C (i.e., up to approximately 20 participants each in Cohorts 1 and 2) to characterize the safety, tolerability, and [redacted] 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 9: 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	25	33
50/28-mg Group (50-mg loading dose; 28-mg maintenance dose)	16	50	66
Part C (50-mg loading dose; 28-mg maintenance dose)			40[1]
Total			145[1]

[1] The sample size is an estimate that may be up to approximately the stated number.

For the infantile-onset SMA population in Part B, a sample size of approximately 50 participants in the 50/28-mg Group and at least N= 20 sham participants from CS3B will provide at least approximately 99% power for the primary endpoint 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.

A secondary endpoint for this study is that the efficacy in the 50/28 mg Group compared to the 12 mg Control Group will be different based on the change from baseline to Day 302 in CHOP-INTEND.

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 Cohort 1 of 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). For Cohort 2 of Part C, all participants must be ≥ 18 years of age and can be either ambulatory or nonambulatory.

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 ICH and 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 [redacted] of the study treatment. SMA is caused by the loss of SMN due to a homozygous deletion or mutation or a compound heterozygous mutation in the *SMN1* on chromosome 5q11-q13. Thus, patients with SMA are completely dependent on the amount of SMN produced by the *SMN2*. Genetic modifiers, such as the number of copies of the *SMN2*, 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 hematology, blood chemistry, urinalysis, and CSF samples (except for local analysis of CSF total protein, cell count, and glucose) collected for this study. Analysis of urine total protein will be conducted by local laboratories; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by a central laboratory. Analysis of coagulation, pregnancy tests, and CSF total protein/cell count/glucose will be conducted by local laboratories. [redacted], [redacted], and NF-L samples will be analyzed at a laboratory selected by the Sponsor (Appendix B).

When the safety laboratory sample analysis is at risk due to logistical difficulties or issues with access to the central laboratory (e.g., due to COVID-19–related disruptions or humanitarian emergencies), these samples may be analyzed by the local laboratory. Any use of a local laboratory under these circumstances must be approved by the Sponsor prior to being implemented.

For all participants, a blood sample will be collected during the study to evaluate *SMN1* status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number by the central laboratory. For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory but may be determined by local laboratory genetic testing, if needed). For participants with documentation of these genetic testing results before Screening or whose sample was analyzed locally during the

Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening but must be collected by the first maintenance dosing visit) for confirmatory testing through the central laboratory.

Sample analysis for participants from China will be performed within China.

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.

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.

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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[1] 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[1] Specific gravity pH Protein Glucose Ketones Bilirubin Blood Red blood cells White blood cells Epithelial cells Bacteria Casts Crystals Hematology[1] Red blood cells Hemoglobin Hematocrit Platelets WBCs WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	[redacted] Pharmacodynamics NF-L [redacted] **The following are to be assessed by local laboratory only:** Urine total protein (quantitative)[2] Coagulation (aPTT, PT, and INR) CSF Local Laboratory Sample Cell count Total protein Glucose Pregnancy Urine hCG Serum pregnancy test

[redacted]; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; COVID-19 = coronavirus disease 2019; CPK = creatine phosphokinase; CSF = cerebrospinal fluid; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; [redacted] NF-L = neurofilament light chain; PT = prothrombin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

[1] Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. For the Screening visit only, a local laboratory may be used instead for analysis if needed for the timely treatment of the participant at the discretion of the Investigator. When the safety laboratory sample analysis is at risk due to logistical difficulties or issues with access to the central laboratory (e.g., due to COVID-19–related disruptions or humanitarian emergencies), these samples may be analyzed by the local laboratory. Any use of a local laboratory under these circumstances must be approved by the Sponsor prior to being implemented.

[2] Quantitative urine total protein should be prioritized if there is not enough urine sample for all tests. For urinary protein concentration > 0.2 g/L, repeat testing and further evaluation should be considered. Urine total protein will be analyzed by local laboratory; however, if local analysis is not possible without a 24-hour urine collection, then samples will be analyzed by a central laboratory.

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 7

Date: 11 June 2024

EUDRA CT Number: 2019-002663-10

Version 7 of the protocol has been prepared for this amendment, which supersedes Version 6.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 is to implement the following changes to the endpoints of Part B of the study:

- The comparisons of nusinersen higher dose (50/28 mg) versus sham in participants with infantile-onset SMA were updated to utilize a matched sham control group consisting of participants from the Study CS3B sham arm selected through a matching algorithm.
- The previous hypothesis testing framework was updated to clearly indicate the primary and secondary comparisons as nusinersen 50/28 mg versus sham or nusinersen 50/28 mg vs. 12mg.
- Change from baseline in CSF NF concentration and change from baseline in plasma NF concentration [redacted] to secondary endpoints, and the neurofilament biomarker was changed from [redacted] to NF-L.
- Proportion of HINE Section 2 responders (higher dose vs. sham) was changed from evaluation at Day 302 to evaluation at Day 183.
- Change from baseline in CHOP-INTEND (higher dose v.s 12 mg) was changed from evaluation at Day 183 to evaluation at Day 302.

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

Section 4, Study Objectives and Endpoints

Now reads:

Part B Primary Objective	**Primary Endpoint**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA **in the 232SM203 50/28 mg Group compared to the CS3B Matched Sham Control Group,** 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 **(comparison of higher dose to matched sham control)**

Part B Secondary Objectives	**Secondary Endpoints**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA **in the 232SM203 50/28 mg Group compared to:** • **CS3B Matched Sham Control Group** **AND/OR** • **232SM203 nusinersen 12 mg Group**	Infantile-Onset SMA • Proportion of HINE Section 2 motor milestone responders at Day ~~302~~**183 (comparison of higher dose to matched sham control)** • **Change from baseline to Day 183 in HINE Section 2 motor milestones total score (comparison of higher dose to matched sham control)** • **Change from baseline to Day 183 in plasma concentration of NF-L (comparison of higher dose to matched sham control)** • **Change from baseline to Day 302 in CHOP-INTEND total score accounting for mortality/dropout using the joint rank test (comparison of higher dose to 12 mg dose)** • Change from baseline to Day 302 in HINE Section 2 motor milestones total score ~~accounting for mortality/dropout using the joint rank test~~ **(comparison of higher dose to 12 mg dose)** • **Change from baseline to Day 29 in plasma concentration of NF-L (comparison of higher dose to 12 mg dose)** • 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]) **(comparison of**

	higher dose to matched sham control) • Time to death (overall survival) **(comparison of higher dose to matched sham control)** • **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]) (comparison of higher dose to 12 mg dose)** • **Time to death (overall survival) (comparison of higher dose to 12 mg dose)**
To examine the clinical efficacy of nusinersen administered intrathecally at higher doses **compared** to **the currently approved 12 mg dose in** participants with SMA	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 • **Change from baseline in CSF concentration of NF-L** • **Change from baseline in plasma concentration of NF-L**

…

To examine the effect of nusinersen administered intrathecally at higher doses	**Infantile-Onset and Later-Onset SMA** • Number and duration of hospitalizations

compared to the currently approved **12 mg** dose in participants with SMA	• 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 **Infantile-Onset SMA only** • **Change from baseline in CSF concentration of NF-L**

…

[redacted]	[redacted]
[redacted]	[redacted]

…

~~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 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.~~

[redacted]

…

Section 12.4, Methods of Analysis for Efficacy Endpoints

Now reads:

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~~,~~ **and** secondary~~, and then exploratory hypotheses~~ **endpoints** will be utilized. In this procedure, the primary ~~hypothesis~~**endpoint** 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~~**then** the first secondary endpoint of the proportion of motor milestone responders at Day ~~302~~**183** 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 8. Inferential conclusions about each successive analysis require statistical significance of the prior one.

~~Use of Historical Data~~

The statistical testing of the primary **endpoint** and **a subset of** secondary ~~hypotheses~~ **endpoints** 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~~.

[redacted]

The main analysis for the primary endpoint and secondary endpoints comparing nusinersen 50/28 mg to sham will be performed using the 50/28 mg participants in the ITT Set and the set of at least 20 sham participants selected via the matching algorithm.

The main analyses for secondary endpoints comparing 50/28 mg to 12 mg will be performed using the ITT Set. [redacted]

…

Table 8: Primary and Secondary ~~Hypotheses – Comparing the 50/28 mg Group to Study CS3B Sham Control~~ **Endpoints**

Rank	**Endpoint and Comparison**	**Analysis Method**	~~Population~~ **Comparison of higher dose (50/28 mg) to**
1	Change in CHOP-INTEND from baseline to Day 183 **total score**	Joint rank **using MI**	~~50/28 mg ITT population versus~~ ~~Study~~ CS3B **Matched** Sham Control ~~Day 183 efficacy set~~
2	Proportion of HINE Section 2 motor milestone responders at Day ~~302~~**183**	**Logistic regression or** Fisher's Exact Test	~~50/28 mg ITT population versus~~ ~~Study~~ CS3B **Matched** Sham Control ~~Day 302 efficacy set~~
3	**Change from baseline to Day 183 in HINE Section 2 total score**	**Joint rank using MI**	**CS3B Matched Sham Control**
4	**Change from baseline to Day 183 in plasma NF-L from baseline to Day 183**	**Joint rank using MI**	**CS3B Matched Sham Control**
5	**Change from baseline to Day 302 in CHOP-INTEND total score**	**Joint rank using MI**	**232SM203 12 mg Control**
6	**Change from baseline to Day 302 in HINE Section 2 Motor Milestones total score**	**Joint rank using MI**	**232SM203 12 mg Control**
7	**Change from baseline to Day 29 in plasma NF-L**	**Joint rank using MI**	**232SM203 12 mg Control**
8~~3~~	Time to death or permanent ventilation	Log-rank test **stratified by disease duration at Screening**	~~50/28 mg ITT population (additional follow-up from extension study) versus~~ ~~Study~~ CS3B **Matched** Sham Control ~~ITT Set~~
9~~4~~	Time to death	Log-rank test **stratified by disease duration at Screening**	~~50/28 mg ITT population (additional follow-up from extension study) versus~~ ~~Study~~ CS3B **Matched** Sham Control ~~ITT Set~~

Rank	Endpoint and Comparison	Analysis Method	~~Population~~ Comparison of higher dose (50/28 mg) to
10	**Time to death or permanent ventilation**	**Log-rank test stratified by disease duration at Screening**	**232SM203 12 mg Control**
11	**Time to death**	**Log-rank test stratified by disease duration at Screening**	**232SM203 12 mg Control**

[redacted]

Rationale:

CS3B Matched Sham Control Group:

For analysis of the primary and secondary endpoints comparing nusinersen 50/28 mg versus sham in infantile-onset SMA, the control group was updated from all 37 sham participants that

completed a Day 183 visit in Study CS3B to a Matched Sham Group of 20 or more participants selected from the CS3B sham arm using a matching algorithm. Compared to using all CS3B sham participants, the matching algorithm will minimize the potential bias caused by the time gap of when Studies 232SM203 and CS3B were conducted and provide a robust analysis in the context of well-characterized natural history of untreated SMA. Analysis of the remaining secondary endpoints comparing nusinersen 50/28 mg versus 12 mg will utilize only the participants within 232SM203 Part B.

Comparisons of nusinersen 50/28 mg versus 12 mg:

Given the clinical importance of understanding the relative benefit of the higher dose (50/28 mg) versus standard dose (12 mg) nusinersen regimens, formal comparisons between these regimens [redacted] to secondary analyses. The methods of analysis in the protocol describe the updated sequential testing order and comparison populations of the efficacy endpoints for participants with infantile-onset SMA in Part B. The primary and secondary endpoints will be tested sequentially with a 2-sided alpha of 0.05. Statistical significance needs to be declared for an endpoint before testing the next endpoint in the sequence.

Neurofilament biomarker:

Neurofilaments are a nonspecific marker of axonal injury and neurodegeneration. Across neurodegenerative diseases, including SMA, higher levels of NF have been found to be prognostic for faster disease progression. As such, a treatment-driven reduction in NF levels provides objective evidence of a slowing of the neurodegenerative process that is central to the underlying pathophysiology of SMA. As such, NF levels will be measured as a secondary measure of treatment response in participants with infantile-onset SMA and later-onset SMA. The NF biomarker was changed from [redacted] to NF-L due to recent technical issues with the [redacted]. Internally, assays for [redacted] NF-L have been fully qualified for SMA research, and samples collected from other Biogen studies on nusinersen have been analyzed for both NF proteins.

Proportion of HINE Section 2 responders (higher dose vs. sham):

The secondary endpoint of proportion of HINE Section 2 responders (higher dose vs. sham) was changed to the same timepoint as the primary endpoint (Day 183) to allow use of the same set of matched sham participants/data for the primary endpoint and to increase the likelihood of closest match given the greater sample size of CS3B sham participants from which to match. Follow-up to Day 183 is considered sufficient to see a clear separation for higher dose versus sham control.

CHOP-INTEND (higher dose vs. 12 mg):

The endpoint of change from baseline in CHOP-INTEND (higher dose vs. 12 mg), [redacted] to a secondary endpoint, was changed to a timepoint of Day 302 to provide a greater opportunity to show a difference between the higher dose compared to the approved, highly efficacious 12 mg dose.

These changes also affect Section 1.1, Synopsis; Section 9.3, Pharmacodynamic Assessments; Section 12.1, General Considerations; Section 12.2, Analysis Sets; Section 12.4.2, Analysis of the Secondary Endpoints in Part B; Section 12.6, Methods of Analysis for Pharmacodynamic Endpoints; Section 12.7, Methods of Analysis for Biomarkers/Pharmacogenetics; Section 12.11, Sample Size Considerations; Section 14.1.4, Central Laboratories for Laboratory Assessments; and Appendix B, Laboratory Analytes.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 9.1.15, Standard of Care

Change: A standard of care assessment was added to the clinical efficacy assessments.

Now reads:

All participants are expected to follow standard of care as referenced in Section 6.2 throughout the entire duration of the study. Investigators will document standard of care information for Part B participants at Screening and Day 302.

Rationale: A new section was added for a standard of care assessment to reflect the implementation of a Standard of Care CRF. The CRF was added to further understand access to health care specialists in the many countries that enrolled.

This change also affects Section 1.3, Schedule of Activities.

Section 10.2, Laboratory Safety Assessments

Change: Text was added to clarify whether urine total protein analysis will be performed by the local or central laboratory.

Now reads:

…

- Urinalysis: urine total protein (by local laboratory **except if local analysis is not possible without a 24-hour urine collection, in which case samples will be analyzed by a central laboratory**); specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, and crystals

…

Rationale: As some sites (e.g., sites in China) are unable to perform local urine total protein analysis without collecting urine over a 24-hour period, accommodations have been set up for central laboratory analysis for these affected sites only.

This change also affects Section 1.3, Schedule of Activities; Section 14.1.4, Central Laboratories for Laboratory Assessments; and Appendix B, Laboratory Analytes.

Section 16, Public Health or Humanitarian Emergencies

Change: Section 16, Public Health or Humanitarian Emergencies was removed from the protocol.

Now reads:

~~In the event of public health or humanitarian emergencies that result in site closure, travel restrictions, and/or clinical research activities being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health or humanitarian emergency. If a protocol-specified clinical visit cannot occur due to a public health or humanitarian emergency, the following mitigating options should be pursued: 1) transfer to another active study site that is open and 2) local laboratory visit. These mitigating options only apply in the setting of a public health or humanitarian emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely due to the participant's preference. If the participant does not participate in one of these options, a safety telephone call must be conducted within 14 days of the last dosing visit.~~

~~If any participants with later onset SMA enrolled in Part B are unable to comply with study visits in areas affected by public health or humanitarian emergencies and are withdrawn early from the study (prior to the Day 183 dose and assessments), up to 4 additional participants may be enrolled at the Sponsor's discretion.~~

Rationale: Section 16 was previously removed as a country-specific protocol amendment for Germany (dated 07 November 2022) to comply with local regulations. After review, text elsewhere in the protocol sufficiently captures key mitigation activities related to COVID-19-related disruptions or humanitarian emergencies. Therefore, this section was removed from the global protocol.

This change also affects Section 1.1, Synopsis; and Section 12.11, Sample Size Considerations.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected throughout the protocol.
- Section numbers and table numbers were updated where applicable.
- Sponsor Information was updated.
- The Sponsor Signature Page was updated to change the signatory.
- Section 2, List of Abbreviations, was updated.
- In Section 4, Objectives and Endpoints, clarification was added that the Part B Primary Objective and Endpoint will compare the 232SM203 50/28 mg Group to the CS3B Matched Sham Control Group.
- In Section 12.4.1, Analysis of the Primary Endpoint in Part B, clarification was added that MI will be utilized to impute a missing Day 183 value of CHOP-INTEND for participants who discontinued for a reason other than death or where it was not assessed.
- In Section 12.4.2, Analysis of the Secondary Endpoints in Part B, clarification was added that for plasma NF-L, if the baseline assessment is missing, then the first available assessment postdose within Day 2 will be used instead as baseline, and that values that are BLQ will be set to half of the diluted LLOQ.

LIST OF ABBREVIATIONS

ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
[redacted]	[redacted]
BLQ	below limit of quantification
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CGIC	Clinical Global Impression of Change
COVID-19	coronavirus disease 2019
CRF	case report form
CSF	cerebrospinal fluid
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
ITT	Intent-to-Treat
LLOQ	lower limit of quantification
MI	multiple imputation
NF	neurofilament
NF-L	neurofilament light chain
PASA	Parent Assessment of Swallowing Ability
PedsQL	Pediatric Quality of Life Inventory™
[redacted]	[redacted]
RULM	Revised Upper Limb Module
SMA	spinal muscular atrophy
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 6

Date: 05 May 2022

EUDRA CT Number: 2019-002663-10

Version 6 of the protocol has been prepared for this amendment, which supersedes Version 5.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 is to reduce the sample size for Part B infantile onset participants to 75. As a result, the total sample size for the study was adjusted to 145 participants.

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

Section 12.11, Sample Size Considerations

Now reads:

A total sample size of ~~up to~~ approximately ~~172~~ **145** 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 10). 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.

…

Table 10: 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~~ **25**	~~42~~ **33**
50/28-mg Group (50-mg loading dose; 28-mg maintenance dose)	16	~~68~~ **50**	~~84~~ **66**
Part C (50-mg loading dose; 28-mg maintenance dose)			40[1]
Total			~~172~~ **145**[1]

[1] The sample size is an estimate that may be up to approximately the stated number.

For the infantile-onset SMA population in Part B, a sample size of ~~up to 68~~ **approximately 50** participants in the 50/28-mg Group will provide at least approximately 99% power **for the primary endpoint** 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.

[redacted]

…

Rationale: Part B of the DEVOTE study design includes primary and secondary hypotheses that compare the high-dose nusinersen arm from DEVOTE to the historical sham-control arm from Study CS3B (ENDEAR). [redacted]

With 75 participants, the primary and secondary hypotheses that compare the higher dose of nusinersen to sham from ENDEAR all have a power of ≥ 95%, as shown in the table below. Enrolling an additional 27 participants (as planned in the original design based on initial determination of borrowing) does not meaningfully increase the power for the primary and secondary hypothesis testing, since these are already high.

Summary of Power for Testing Statistical Hypotheses in Part B of DEVOTE With a Total of 75 or 102 Participants and Assuming No Borrowing

Order	Endpoint	Comparison	Assumptions for Higher-Dose Nusinersen	Power	
				DEVOTE Enrolled Sample Size	
				N = 75	N = 102
1P	Change from baseline to Day 183 in CHOP-INTEND total score, accounting for mortality/dropout using the joint-rank test	DEVOTE high dose (n = 50/68) versus ENDEAR sham (n = 37)	At Day 183, high dose 4.5 points better AND survival 3% better than 12 mg in ENDEAR	> 99%	> 99%
2S	Proportion of HINE Section 2 motor milestone responders at Day 302	DEVOTE high dose (n = 50/68) versus ENDEAR sham (n = 28)	At Day 302, high dose proportion of responders same as 12 mg from ENDEAR	> 99%	> 99%
3S	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)	DEVOTE high dose (n = 50/68) versus ENDEAR sham (n = 41)	At Day 302, 40% of participants reach death or permanent ventilation in high-dose arm	98%	>99%
4S	Time to death (overall survival)	DEVOTE high dose (n = 50/68) versus ENDEAR sham (n = 41)	At Day 302, 15% of subjects die	95%	>99%

Two-sided alpha = 0.05 used for all endpoints
Hypotheses to test: P = primary; S = secondary.
Power determined by simulations: for the primary and secondary hypotheses, data from simulated high-dose participants were compared to actual sham-control data from ENDEAR.

This change also affects Section 1.1, Synopsis; Section 1.2, Study Design Schematic; Section 5.1, Study Overview; Section 7.1, Regimen; and Section 12.10, Interim Analyses.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 3.1.2, Rationale for Dosing Regimen

Change: Additional details regarding the revision of the target CSF C_{trough} and the clinical relevance of this change were included.

Now reads:

Previous PK modeling predicted that the median concentration of nusinersen within the CSF immediately prior to the administration of the subsequent maintenance dose (i.e., C_{trough}) would be approximately 10 ng/mL at steady state with the label-approved maintenance dosing regimen (i.e., 12 mg administered every 4 months) and approximately 20 ng/mL at steady state with the proposed maintenance dosing regimen for Study 232SM203 (i.e., 28 mg administered every 4 months). This model was subsequently updated to include additional data from Studies 232SM201 and CS11 not previously modeled, resulting in an adjustment of CSF C_{trough} predictions in all patient populations, which are still consistent with the prior predictions. As a consequence, ~~P~~population PK modeling **now** predicts that with increasing the maintenance dose from 12 to 28 mg administered every 4 months, CSF C_{trough} should increase from 5 to 12 ng/mL at steady state. The exposure-response (PK/PD) relationship between steady-state CSF C_{trough} and CHOP-~~-~~INTEND response continuously increases as a function of PK~~,~~ and is on an upward trajectory at concentrations consistent with the 12 mg maintenance dose **(i.e., 5 ng/mL)**. It is ~~therefore~~ predicted that additional clinical benefit (i.e., a 5-point increase in CHOP-~~-~~INTEND score) could be achieved by increasing CSF exposures to 12 ng/mL. ~~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).~~ **Therefore, administration of this higher dose of nusinersen may lead to meaningful clinical benefit to patients. At this time, no dose-limiting toxicity has been identified with nusinersen. The PK modeling therefore suggests that it is unlikely that the higher doses of nusinersen would have a less favorable risk-benefit profile compared with standard dose nusinersen.**

…

The assumption of PK linearity 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). 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. Based on the most recent PK modeling performed, relative to the approved 12-mg label regimen (CSF C_{trough} of approximately 5 ng/mL), 28 mg administered as 3 loading doses (biweekly) or 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 12 ng/mL) more rapidly at the end of the loading dose period. Nusinersen 28 mg administered as 3 loading doses (biweekly) had a comparable predicted CSF C_{max} to the reference dosing regimen, whereas the 50-mg dosing regimen surpassed the predicted C_{max} from the reference dosing regimen. Moreover, the 28-mg maintenance dosing regimen adequately maintained the higher CSF C_{trough} target (approximately 12 ng/mL) during the maintenance dose period. 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 (see Section 3.3). 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.

Rationale: Since the development of the original protocol for Study 232SM203, more recent PK modeling data have become available. These data have impacted the predicted steady-state CSF C_{trough} values for the different nusinersen dosing regimens used in this study. Additional information describing the change in CSF C_{trough} predictions was added to this protocol amendment for clarity and to further explain why the target CSF C_{trough} has changed. In addition, text was added to show that the potential predicted clinical benefit (in the form of an increase in CHOP-INTEND score) is also greater now based on the new PK modeling data available.

This change also affects Section 1.1, Synopsis.

Section 5.1, Study Overview

Change: Details regarding the IDMC review of safety and PK data for the first 15 participants in Part B were added to the protocol.

Now reads:

…

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. **By the time of implementation of Protocol Version 6, the IDMC reviewed these data and recommended that the study may continue with dosing of the remaining participants in Part B and initiating dosing in Part C without any modifications to the study.**

Rationale: The prespecified IDMC review of the first 15 participants enrolled in Part B has now occurred. As such, a statement was added to the protocol to acknowledge that this review has been completed and that no study design changes were required as a result. This enabled dosing to continue in Part B and for participants to begin enrolling in Part C of the study.

This change also affects Section 1.1, Synopsis.

Section 6.2, Exclusion Criteria

Change: For Part B, exclusion criterion 10 was revised to apply only to participants with SMA symptom onset > 6 months (> 180 days) of age (later onset).

Now reads:

…

Part B

All Participants

…

9. 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

10. ~~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~~

11. Treatment with an investigational drug including but not limited to 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 ASO treatment (e.g., nusinersen) or cell transplantation

…

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

17. 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

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

Rationale: For the primary endpoint analysis, participants in this study will be compared to participants who received sham treatment in the ENDEAR study. As such, this change was implemented to ensure consistency with participant selection criteria in the ENDEAR study.

Section 9.1.10.1, Pediatric Quality of Life Inventory (Generic Core Scales and Neuromuscular Module)

Change: The PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module for participants ≥ 26 years of age were added.

Now reads:

Participants with later-onset SMA will be evaluated using the **age-appropriate modules of the** PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module [Varni 1999]**, which include age 2 to 4 years, 5 to 7 years, 8 to 12 years, 13 to 18 years, 18 to 25 years, and ≥ 26 years**. 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 HRQOL in children~~, and~~ adolescents**, and adults**. The PedsQL consists of brief, practical, generic core scales, as well as condition-specific modules for use in designated clinical populations. ~~Patient self-report is measured in children and adolescents 5 to 25 years of age, and parent proxy-report of child HRQOL is measured for children and adolescents 2 to 25 years of age. Patient self-report and parent proxy-report are available for participants who are ≥ 26 years of age for the Generic Core Scale.~~ The PedsQL 4.0 Generic Core Scales include an assessment of physical functioning, emotional functioning, social functioning, and school functioning **and will be assessed for participants 2 to ≥ 26 years of age**. The PedsQL 3.0 Neuromuscular Module was designed to measure HRQOL dimensions specific to ~~children 2 to 18 years of age~~ **patients** with neuromuscular disorders, including SMA**, and will be assessed in participants 2 to 25 years of age**. **Patient self-report will be measured in participants starting at 5 years of age, while parent proxy-report of HRQOL will be measured for participants starting at 2** years of age.

Rationale: Details regarding the available modules by age for the PedsQL Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module were included for completeness. In addition, assessment requirements by age were updated for the study in order to enable assessment for participants up to 25 and ≥ 26 years of age, which is applicable for participants in Cohort 1 of Part C.

Section 10.2, Laboratory Safety Assessments

Change: The CSF local laboratory sample protein was updated to "total protein."

Now reads:

…

- CSF local lab**oratory** sample: cell count, **total** protein, and glucose

Rationale: This change was implemented to further specify that total protein would be measured for the CSF local laboratory sample.

This change also affects Table 1, Schedule of Activities for Part A; Table 2, Schedule of Activities for Part B; Table 3, Schedule of Activities for Part C Cohort 1; Table 4, Schedule of Activities for Part C Cohort 2; Section 14.1.4, Central Laboratories for Laboratory Assessments; and Appendix B, Laboratory Analytes.

Section 10.2, Laboratory Safety Assessments

Change: Language was added to allow use of a local laboratory when necessary (e.g., difficult transportation of samples to the central laboratory).

Now reads:

…

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

When the safety laboratory sample analysis is at risk due to logistical difficulties or issues with access to the central laboratory (e.g., due to COVID-19–related disruptions or humanitarian emergencies), these samples may be analyzed by the local laboratory. Any use of a local laboratory under these circumstances must be approved by the Sponsor prior to being implemented.

Rationale: For various clinical sites globally (e.g., Saudi Arabia and Russia), transporting safety laboratory samples to the central laboratory could take longer than usual and result in the samples arriving outside the stability period. Allowing these samples to be sent to the local laboratory offers the flexibility to have the samples processed and evaluated in a timely manner, ensuring the safety of trial participants and analysis of these important study data.

This change also affects footnote 16 of Table 2, Schedule of Activities for Part B; Section 14.1.4, Central Laboratories for Laboratory Assessments; and footnote 1 of Appendix B, Laboratory Analytes.

Section 12.10, Interim Analyses

[redacted]

Now reads:

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

An interim analysis [redacted] -of the primary endpoint in Part B [redacted] **may** be performed when all participants with infantile-onset SMA have had the opportunity to reach the Day 183 visit.

[redacted]

This change also affects Section 12.4, Methods of Analysis for Efficacy Endpoints; Section 12.11, Sample Size Considerations; and Section 14.2.2, Independent Data Monitoring Committee.

Section 12.11, Sample Size Considerations

Change: [redacted]

Now reads:

…

[redacted]

Rationale: [redacted]

This change also affects Section 3.1, Study Rationale.

Section 16, Public Health or Humanitarian Emergencies

Change: This section was added to address contingencies in areas affected by public health or humanitarian emergencies.

Now reads:

In the event of public health or humanitarian emergencies that result in site closure, travel restrictions, and/or clinical research activities being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health or humanitarian emergency. If a protocol-specified clinical visit cannot occur due to a public health or humanitarian emergency, the following mitigating options should be pursued: 1) transfer to another active study site that is open and 2) local laboratory visit. These mitigating options only apply in the setting of a public health or humanitarian emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely due to the participant's preference. If the participant does not participate in one of these options, a safety telephone call must be conducted within 14 days of the last dosing visit.

If any participants with later-onset SMA enrolled in Part B are unable to comply with study visits in areas affected by public health or humanitarian emergencies and are withdrawn early from the study (prior to the Day 183 dose and assessments), up to 4 additional participants may be enrolled at the Sponsor's discretion.

Rationale: This section was added to provide guidance in the event of public health or humanitarian emergencies. In case any such emergency impacts the Sponsor's ability to collect data from a significant portion of the later-onset participants enrolled in Part B, conditional language has been added to allow enrollment of additional later-onset participants for effective data analyses.

This change also affects Section 1.1, Synopsis; footnote 16 of Table 2, Schedule of Activities for Part B; Section 10.2, Laboratory Safety Assessments; Section 12.11, Sample Size Considerations; Section 14.1.4, Central Laboratories for Laboratory Assessments; and footnote 1 of Appendix B, Laboratory Analytes.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected throughout the protocol.
- Some wording was revised throughout the protocol for clarity.
- Abbreviations and wording were modified to align with the program-specific style guide.
- Section numbers, eligibility criteria numbering, and footnote numbering were updated where applicable.
- The business address of Biogen Australia was updated.
- Details from Section 6.3.2 regarding the extension of the Screening period, which were inadvertently removed in version 5.0, were added back to footnote 1 of Tables 2 (Schedule of Activities for Part B), 3 (Schedule of Activities for Part C Cohort 1), and 4 (Schedule of Activities for Part C Cohort 2).
- Figure 1 footnote 1 was revised to clarify that the visits that male participants can complete via telephone interview and the visits that female participants need to return to the site for completion, if they meet the criteria for contraception use, are the Day 389, 399, or 361 visit for Part A, B, or C, respectively. A change related to this was also applied to footnote 2 of Table 1.
- Section 2, List of Abbreviations, was updated.
- References to Schedule of Assessments were revised to Schedule of Activities throughout to match Tables 1 to 5 captions.
- Section 11.2.2 header was updated to "Relationship of Events to Study Treatment **or LP/Sham Procedure**" to reflect the section contents more accurately.
- Numbering of sections adjusted to reflect insertion of new Section 16.
- Appendix B, Laboratory Analytes was updated as follows:
  - Urine total protein was specified as quantitative. A corresponding footnote was added to state that quantitative urine total protein should be prioritized if there is not enough urine sample for all tests and that repeat testing and further evaluation should be considered if urinary protein concentration is > 0.2 g/L.

- A footnote stating that for the Screening visit only, a local laboratory instead of the central laboratory may be used for the analysis of blood chemistry, hematology, and urinalysis samples, if needed, for the timely treatment of the participant at the discretion of the Investigator, for consistency with the footnotes in the Schedules of Activities.

LIST OF ABBREVIATIONS

[redacted]	[redacted]
ASO	antisense oligonucleotide
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
CSF	cerebrospinal fluid
C_{trough}	trough concentration
HINE	Hammersmith Infant Neurological Examination
HRQOL	health-related quality of life
IDMC	independent data monitoring committee
LP	lumbar puncture
PedsQL	Pediatric Quality of Life Inventory™
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SMA	spinal muscular atrophy
SMN2	survival motor neuron-2 gene
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 5

Date: 01 October 2021

EUDRA CT Number: 2019-002663-10

Version 5 of the protocol has been prepared for this amendment, which supersedes Version 4.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 is to increase the sample size for Part C by adding a second cohort consisting of up to approximately 20 adult participants.

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

Section 5.1, Study Overview

Now reads:

In Part C, **up to** approximately ~~20~~**40** 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~~ **will be enrolled in Part C. The initial cohort in Part C (i.e., Cohort 1) consists of approximately 20 participants of any age and of any SMA status. For Cohort 1, an**~~. An~~ attempt will be made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants **in Cohort 1** ≥ 18 years of age must be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in **Cohort 1 of** Part C after consultation with the Medical Monitor. **An additional cohort (i.e., Cohort 2) consisting of up to approximately 20 adult participants (≥ 18 years of age) was subsequently added to Part C in Protocol Version 5 in order to enable collection of data in adults transitioning from the currently approved nusinersen dosing regimen to a higher dose. Participants in Cohort 2 can be either ambulatory or nonambulatory.**

All ~~P~~**p**articipants **in Part C** 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.

Rationale: Increasing the sample size by including an additional cohort of up to approximately 20 adult participants in Part C will allow collection of clinical data in adults transitioning from the currently approved nusinersen dosing regimen to a higher dose. Since the previous design of Part C did not require enrollment of any adults, adding Cohort 2 will enable data collection in this SMA patient population. Results will be descriptive in nature, with no formal hypothesis testing performed.

Relevant inclusion and exclusion criteria have been modified or added as appropriate for this cohort. The assessment includes safety, tolerability, [redacted] and efficacy assessments, consistent with Part C objectives.

This change also affects Section 1.1, Synopsis; Section 1.2, Study Design Schematic; Section 1.3, Schedule of Activities (Tables 3 and 4); Section 3.1.1, Rationale for Study Population; Section 4, Study Objectives and Endpoints; Section 6.1, Inclusion Criteria; Section 6.2, Exclusion Criteria; Section 7.1, Regimen; Section 9.1, Clinical Efficacy Assessments; Section 12.11, Sample Size Considerations.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 1.3, Table 2: Schedule of Activities for Part B; Table 3: Schedule of Activities for Part C Cohort 1

Change: The timepoints for collection of vital signs, neurological examinations, and ECGs and the collection windows for [redacted] were updated for Parts B and C. The impacted footnotes for Tables 2 and 3 are presented below.

Now reads:

Table 2: Schedule of Activities for Part B[9][10] **On Days 1 and 15, postdose ~~V~~v**ital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. **On Days 29, 64, 135, 183, and 279, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.**

…

[13][14] 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~~**A** neurological examination will be performed **at Screening;** 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 **on Days 1 and 15; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 29, 64, 135, 183, and 279; and at Day 302/ET**. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

[14][15] ECGs will be performed predose, at 5 hours (± 1 hour) postdose, and at 24 hours (± 2 hours) postdose on Days 1~~,~~ **and** 15**; predose and at 5 hours (± 1 hour) postdose on Days**~~,~~ 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.

…

[redacted]

Table 3: Schedule of Activities for Part C Cohort 1

[9] **On Day 1, postdose ~~V~~v**ital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. **On Days 121 and 241, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.**

…

[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~~ **A** neurological examination will be performed **at Screening;** 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 **on Day 1; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 121 and 241; and at Day 302/ET**. Predose neurological examinations should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing.

…

[redacted]

Rationale: Postdose timepoints for vital signs, neurological examinations, and ECGs were revised to align with the change in the requirements for the 24-hour inpatient stay in Part B. Since participants are only required to remain in the clinic for the first 2 dosing visits (i.e., Days 1 and 15) with this protocol amendment, timepoints for these assessments at the subsequent study visits were reduced. Similarly, the footnotes in the Part C Schedule of Activities tables regarding timepoints for postdose vital signs and neurological examinations were corrected to align with the 24-hour inpatient stay occurring at the Day 1 study visit only. In addition, [redacted]

This change also affects Table 4, Schedule of Activities for Part C Cohort 2.

Section 1.3, Table 4: Schedule of Activities for Part C Cohort 2

Change: A schedule of activities table specifically for Part C Cohort 2 (Table 4) was added, given that this is exclusively focused on a different population and therefore some assessments are different. Consequently, Table 3 was revised to correspond specifically to Cohort 1 of Part C. Table 4 is presented below. Major relevant changes affecting Tables 2, 3, and/or 4 include the following:

- Assessments for vital signs, weight, growth parameters, and physical examination at Screening were added to Part C (Cohorts 1 and 2) to align with the baseline data collected for Parts A and B.

- [redacted]

- Flexibility to perform assessments up to 7 days prior to dosing at the maintenance dose visits was added for the following assessments: [redacted] PASA (Part B only); ACEND and PedsQL (Part B and Part C Cohort 1 only); [redacted]

Now reads:

Table 4: Schedule of Activities for Part C Cohort 2

	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 (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				X						
Vital Signs and Pulse Oximetry[8]	X	X		X[9]	X		X[9]		X	
Weight	X	X			X				X	
Growth Parameters (including height/body 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[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**			
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		
[redacted]										
[redacted]										
CSF Local Lab Sample (cell count, protein, and glucose)		X			X					
[redacted]										
CGIC[20]					X				X	
HFMSE[21]	X[22]	X[22]			X[11]				X	
RULM[21]	X[22]	X[22]			X[11]				X	
WHO Motor Milestones[21]	X				X[11]				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**			
ACEND[23]		**X**							**X**	
[redacted]										
Ventilator Use[26]	**X**	**X**			**X**			**X**	**X**	
AE Recording	**X----------X**									
SAE Recording	**X----------X**									
Concomitant Therapy and Procedures Recording	**X----------X**									

[redacted] 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; [redacted] ET = early termination; [redacted] HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; ICF = informed consent form; LP = lumbar puncture; [redacted]; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; [redacted] SMN = survival motor neuron; [redacted] 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.

[2] Participants who do not meet the criteria for contraception use will have their last visit on Day 302. Participants who meet the criteria for contraception use (see Section 11.5) will have a Day 302 and a Day 361 visit. Male participants who meet the criteria may complete the Day 361 visit

via a telephone interview. Female participants who meet the criteria will return to the site for the Day 361 visit. Day 361 will take place at least 120 days after the final dose. For participants who meet the criteria for contraception use and enroll into the long-term extension study (232SM302) at the Day 302 visit, that will be their final visit in Study 232SM203.

[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] **For all participants, a blood sample will be collected to evaluate *SMN1* gene status (copy number, deletion, and mutation where necessary to confirm 5q SMA) and *SMN2* copy number by the central laboratory. For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory, but may be determined by local lab genetic testing if needed). For participants with documentation of genetic testing results before Screening or whose sample was analyzed locally during the Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening, but must be collected by the Day 121 visit) for confirmatory testing through the central laboratory.**

[6] **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.**

[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] **On Day 1, postdose vital signs will be collected at 1, 2, 4, 6, and 8 hours (± 15 minutes) postdose and at 24 hours (± 2 hours) postdose. On Days 121 and 241, postdose vital signs will be collected at 1 hour (± 30 minutes) and 6 hours (± 1 hour) postdose.**

[10] **Length and head, chest, and arm circumference will be measured in participants with infantile-onset SMA, and height or body length (for participants who are not able to stand independently) and ulnar length will be measured in participants with later-onset SMA. The same measurement (height or body length) should be evaluated at all study visits whenever possible.**

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

[12] **Videotaping of physical examinations is optional.**

[13] **A neurological examination will be performed at Screening; 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 on Day 1; predose and at 1 and 3 hours (± 30 minutes) postdose on Days 121 and 241; and at Day 302/ET. 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. For the Screening visit only, a local laboratory may be used for analysis instead if needed for timely treatment of the participant at the discretion of the Investigator. If a local laboratory is used for the Screening visit, the samples should be collected on Day 1 for central laboratory evaluation (even if within 7 days of Screening). 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 should 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.

[redacted]

[20]Adult participants who do not require a caregiver during the study visits will only have the CGIC assessed by the Investigator.

[21]Videotaping of all motor milestone and motor function assessments is optional; however, if the participant/caregiver consents to video recording, all assessments should be recorded.

[22]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, they should be completed on different days and the assessments do not need to be repeated on Day 1.

[23]The ACEND questionnaire will not be collected for adult participants who do not require a caregiver during the study visits.

[24]Assessment will be performed on Day 121 only.

[redacted]

[26]Ventilator use will be collected at every study visit (see Section 9.1.14).

Rationale: A separate schedule of activities table was created for Cohort 2 of Part C to focus exclusively on the Cohort 2 population [redacted]

Vital signs, weight, growth parameters, and physical examination were added at Screening for participants in Part C to align with the baseline data collected for participants in Parts A and B.

This change also affects Section 1.3, Table 2: Schedule of Activities for Part B; Table 3: Schedule of Activities for Part C Cohort 1.

Section 1.3, Table 5: Schedule of Activities for Participants in Part B Who Discontinue Study Treatment but Agree to Remain in the Study

Change: A new table (Table 5) was added to the protocol for participants in Part B who discontinue study treatment but agree to remain in the study for follow-up.

Now reads:

Participants in Part B who discontinue treatment may remain in the study to continue the protocol-required tests and assessments described in Table 5 (unless the reason for discontinuation is to initiate treatment with a disallowed concomitant therapy per Section 7.6.1.2).

…

Table 5: Schedule of Activities for Participants in Part B Who Discontinue Study Treatment but Agree to Remain in the Study

Assessment[1]	Follow-Up Visits[2]
Weight	X
Growth Parameters	X
Physical Examination	X
Vital Signs (Temperature, Pulse Rate, Systolic and Diastolic Blood Pressure, Respiratory Rate, and Pulse Oximetry)	X
Neurological Examination[3]	X
Urine/Serum Pregnancy Test for Females of Childbearing Potential[4]	X
Safety Laboratory Tests	X
WHO Motor Milestones	X
HINE Section 2 Motor Milestones (as appropriate)	X
Motor Function Assessments (as appropriate, including CHOP INTEND, HFMSE, RULM, [redacted])	X
[redacted]	
Ventilator Use	X
Ventilator Use Diary (Participants with Infantile-Onset SMA)	----------X----------
Concomitant Therapy and Procedure Recording	----------X----------

Assessment[1]	Follow-Up Visits[2]
AE and SAE Recording	----------X----------

[redacted] AE = adverse event; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale – Expanded; RULM = Revised Upper Limb Module; SAE = serious adverse event; WHO = World Health Organization

Note: See Section 9 for additional details regarding efficacy, [redacted] assessments.

[1] Participants who initiate treatment with a disallowed concomitant therapy (see Section 7.6.1.2) must be withdrawn from Study 232SM203; they are not eligible to remain in the study for follow-up visits per Table 5.

[2] Participants should return to the clinic according to the original visit schedule per Table 2 (i.e., Days 1, 15, 29, 64, 135, 183, 279, 302) for follow-up visits after discontinuing treatment, but will follow a reduced schedule of assessments at these visits.

[3] 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.

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

Rationale: This new schedule of activities table provides Investigators and other site personnel with guidelines for which samples and assessments need to be collected and performed for any participants in Part B of the study who discontinue study treatment but agree to return to the clinic for regular follow-up visits. These guidelines are intended to streamline operation at the sites as well as ensure consistency in the data collected and reported.This change also affects Section 8.1, Discontinuation of Study Treatment.

Section 3.1.2, Rationale for Dosing Regimen

Change: Language on steady-state exposures for the 12 mg dose (~5 ng/mL) vs. the higher dose (~12 ng/mL) of nusinersen was updated based on the most recent PK modeling data available.

Now reads:

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.~~

Population PK modeling predicts that with increasing the nusinersen maintenance dose from 12 to 28 mg administered every 4 months, CSF C_{trough} should increase from 5 to 12 ng/mL at steady state. The exposure-response (PK/PD) relationship between steady-state CSF trough concentrations and CHOP INTEND response continuously increases as a function of PK, and is on an upward trajectory at concentrations consistent with the 12 mg maintenance dose. It is therefore predicted that additional clinical benefit (i.e., a 5-point increase in CHOP INTEND score) could be achieved by increasing CSF exposures to 12 ng/mL. 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~~**12** ng/mL as the clinical CSF C_{trough} target concentration and the predicted CSF PK profiles from ~~24~~**28** 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~~ **Based on the most recent PK modeling performed, relative to the approved 12-mg label regimen (CSF C_{trough} of approximately 5 ng/mL)**, ~~both~~ 28 mg administered as 3 loading doses (biweekly) ~~and~~ **or** 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~~**12** ng/mL) more rapidly **at the end of the loading dose period**. 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. **Moreover, the 28-mg maintenance dosing regimen adequately maintained the higher CSF C_{trough} target (approximately 12 ng/mL) during the maintenance dose period.** 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 **(see Section 3.3)**. 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 **dose** 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~~**12** 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.

Rationale: Recent PK modeling data have revealed updated predicted steady-state exposures with the 12 mg dose as compared with the higher dose, in contrast to what was presented in Protocol Version 4. Consequently, this section has been updated to align with the new data, as presented in the latest version of the Investigator's Brochure (Version 14). Importantly, the

PK/PD modeling continues to support that higher doses of nusinersen may lead to a clinically meaningful increase in efficacy. This change also affects Section 1.1, Synopsis.

Section 3.3, Benefit-Risk Assessment

Change: The summary of the toxicology studies of nusinersen in monkeys (Studies P058-17-03 and 396443-AS06) was streamlined and updated to include recent findings and interpretations of the results.

Now reads:

Nusinersen (Spinraza) **12 mg** has a positive benefit-risk profile, with more than ~~3~~**4** years of postmarketing experience and more than ~~10,000~~**11,000** patients treated. The safety profile to date does not preclude study of higher doses in any population.

Detailed information about the known and expected benefits and risks, reasonably expected AEs, and nonclinical toxicology studies supporting investigation of higher doses of nusinersen in the clinic are 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.

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~~**03**~~, with the dosing regimen matching with the most rigorous loading in Study 232SM203 (3 loading doses administered at 2-week intervals)~~. **In this study,** ~~T~~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~~ **As such, dosing for Study 232SM203 has** a safety margin of at least 4.5-fold for ~~the loading doses (based on~~ cumulative doses during the loading period~~)~~ **and a 3-fold margin for a single loading dose of 50 mg**.

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.~~ **Monkeys received a cumulative dose of 3.9, 13, and 52 mg at each dose level (0.3, 1, and 4 mg per dose, respectively) during the 52-week treatment duration.** ~~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.~~ **The overall NOAEL was determined to be 4 mg.** ~~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~~ **NOAEL** (~~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, t~~ **T**he exposure-based safety margin is at least ~~1.1-fold~~**1.4-fold based on exposure in the spinal cord (safety margins are higher for other tissues)**.

~~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.~~

Rationale: These changes were made to present the most recent data available on benefit-risk assessment relevant for this study and to align with the current version of the Investigator's Brochure (Version 14).This change also affects Sections 1.1, Synopsis.

Section 5.1, Study Overview

Change: The requirement for inpatient stays for participants enrolled in Part B was limited to Day 1 and Day 15 only, with the option for inpatient stays at other visits based on the Investigator's discretion.

Now reads:

Participants will remain at the clinic for at least 24 hours after ~~each~~ study treatment administration ~~or sham procedure~~ **on Days 1 and 15; inpatient stays at other visits may occur based on the Investigator's discretion. If the primary reason for the inpatient stay is due to an AE or SAE, reporting requirements per Section 11.3 must be followed**.

Rationale: Inpatient stays may be burdensome to study participants and their families. The current safety data available support removal of the required inpatient stays after the loading period for the higher dose (i.e., 50 mg administered on Days 1 and 15). Investigators are still able to use their clinical judgment on a case-by-case basis to determine whether an inpatient stay may be beneficial for participants following the Day 15 study visit. If an Investigator decides to keep a participant at the clinic for follow-up beyond what is required per protocol, it is important that

the site personnel continue to report AEs or SAEs that occur during that time period as required by the study protocol.This change also affects Section 1.1, Synopsis; Section 1.3, Schedule of Activities (Table 2).

Section 6.1, Inclusion Criteria

Change: The inclusion criterion for Part B regarding gestational age was revised to allow for additional flexibility if there are no complications due to prematurity and with approval by the Medical Monitor. The inclusion criteria for Part C were updated to specify the age and functional status requirements for enrollment into Cohort 2 of Part C.

Now reads:

Part B

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

…

13. Gestational age of 37 to 42 weeks for singleton births and 34 to 42 weeks for twins. **Infants with a lower gestational age may be considered for enrollment if there are no complications due to prematurity and approval by the Medical Monitor has been granted.**

…

Part C

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

~~3.~~ **2.** Currently on nusinersen treatment at the time of Screening, with the first dose being at least 1 year prior to Screening

…

Participants in Cohort 1

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

Participants in Cohort 2

11. Males and females ≥ 18 years of age at Screening (can be ambulatory or nonambulatory)

12. HFMSE total score ≥ 4 points at Screening

13. RULM entry item A score ≥ 3 points at Screening

Rationale: The gestational age requirements for participants in Part B were revised to enroll children without complications due to prematurity because some children with lower gestational age may still be eligible for the study. This is consistent with participants who were enrolled in Study CS3B, which may be used in some of the prespecified analyses to evaluate the higher dose.

The age and functional status requirements at Screening for Cohort 2 of Part C were added to inform Investigators of the eligibility criteria for Cohort 2 and ensure appropriate Screening of potential adult candidates. Participants may be ambulatory or nonambulatory to be representative of the real-world SMA patient population. An HFMSE total score of at least 4 and RULM entry item A score of at least 3 will enrich Cohort 2 with participants whose motor function abilities may enable greater potential to measure changes in efficacy with the higher dose.

Section 6.2, Exclusion Criteria

Change: The exclusion criteria for Part B were revised as follows: 1) to add a criterion related to history of systemic hypersensitivity reaction to the excipients contained in the study treatment formulation or to any diagnostic agents to be administered during the study; 2) to clarify that treatment with an investigational drug not specific for SMA is also exclusionary; and 3) to change the definition of "hypoxemia" for high-altitude study sites.

The exclusion criteria for Part C were revised as follows: 1) to add a criterion related to history of systemic hypersensitivity reaction to nusinersen, the excipients contained in the formulation, or to any diagnostic agents to be administered during the study; and 2) to exclude participants with severe scoliosis from Cohort 2.

Now reads:Part B

All ~~p~~**P**articipants

…

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

7. History of systemic hypersensitivity reaction to the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study

~~7.~~ **8.** Prior scoliosis surgery that would interfere with the LP injection procedure

…

~~10.~~ **11.** Treatment with an investigational drug ~~given for~~ **including but not limited to** 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 **(e.g., nusinersen)** or cell transplantation

…

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

~~15.~~ **16.** Hypoxemia (O_2 saturation [awake or asleep~~] <96%~~, without ventilation support**] < 96% at an altitude of < 1500 meters, < 92% at an altitude of 1500 to 2000 meters, or < 90% at an altitude > 2000 meters**) at Screening

…

Part C

All Participants

…

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

7. History of systemic hypersensitivity reaction to nusinersen, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study

~~7.~~ **8.** Prior scoliosis surgery that would interfere with the LP injection procedure

…

Participants in Cohort 2

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.**

Rationale: Exclusion criteria were added to Parts B and C to exclude participants who may have a history of systemic hypersensitivity to nusinersen (Part C only), to the excipients in the nusinersen injection formulation, or to any diagnostic agents that may be used as part of the study treatment administration procedure. Since Part B explicitly excludes prior exposure to nusinersen, it is impossible to identify a history of systemic hypersensitivity in those candidates.

The criterion in Part B that excludes participants who received treatment with an investigational drug for the treatment of SMA within 30 days or 5 half-lives of the agent was broadened to include other investigational drugs not given for the treatment of SMA as well. This aligns with changes made to Section 7.6.1.2, Disallowed Concomitant Therapy.

Lower oxygen levels at high-altitude study sites will drive down basal oxygen levels, so the original definition of hypoxemia in the protocol was not appropriate for high-altitude sites. The protocol was therefore updated to specify different definitions of hypoxemia based on altitude for participants with infantile onset SMA being screened for Part B of the study.

The exclusion criterion for severe scoliosis for participants in Cohort 2 of Part C was added to align with Parts A and B of the study.

This change also affects Section 1.3, Schedule of Activities (Table 4).

Section 6.3.2, Retesting and Rescreening

Change: The protocol was revised to allow a full rescreening of participants who originally failed Screening, at the discretion of the Investigator.

Now reads:

During the Screening period, participants who have an out-of-range result ~~that is not clinically significant can~~ **may** be retested 1 time only at the discretion of the Investigator **within the Screening process, without the need for a repeat full Screening**. 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.

Participants who fail Screening (see Section 6.3.3) may be rescreened once at the discretion of the Investigator. Participants who are rescreened will be assigned a new identification number.

Rationale: Potentially eligible study participants may have an acute ongoing medical condition that could lead to screen failure in the short-term, but after resolution could allow that participant to pass all Screening criteria. Protocol Version 4 does not specifically address rescreening; it only addresses retesting. The protocol has been updated to allow retesting of an out-of-range

result without repeating the full screening and has been revised to clarify that each candidate may be rescreened once at the discretion of the Investigator. It was also clarified that any participant who is rescreened will need to be assigned a new identification number.

Section 7.3.1, Nusinersen

Change: The study drug formulation language was revised to align with upcoming formulations that will be available for Study 232SM203.

Now reads:

Nusinersen will be supplied as specified in the DHA. The ~~proposed new~~ **study treatment is supplied as a** formulation **that** 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.~~ **Further details on drug preparation and administration may be found in the DHA.**

Rationale: New formulations (i.e., ready-to-use kits) will be available and may be used at clinical sites for Study 232SM203. The language in Protocol Version 4 was not consistent with use of the planned ready-to-use kits. Therefore, the protocol was revised to remove reference to dilution of the drug product and instead refers to the DHA for all information on drug supply, preparation, and administration. In addition, the concentrations of excipients were removed to align with the latest Investigator's Brochure template update by the Sponsor.

Section 7.6.1.2, Disallowed Concomitant Therapy

Change: The protocol was revised to prohibit participation in any other interventional clinical studies (including those for non-SMA treatments) while enrolled in Study 232SM203.

Now reads: Participants are prohibited from receiving other experimental or approved agents for the treatment of SMA, including gene therapy, **SMN2-splicing modifier,** 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.). **In addition, participants will not be allowed to enroll in other interventional studies during Study 232SM203.**

Rationale: Protocol Version 4 does not prohibit participants from enrolling in other interventional clinical studies for non-SMA treatments. Receiving treatment with other investigational therapies could interfere with the interpretation of the safety and efficacy findings for Study 232SM203. Therefore, the protocol was revised so that any participant who initiates treatment with an experimental or approved SMA therapy or enrolls in another interventional clinical study for any indication would need to be withdrawn from Study 232SM203. In addition, SMN2-splicing modifiers were added to the list of examples of treatments for SMA to align with the language in the exclusion criteria.This change also affects Section 1.3, Schedule of

Activities; Table 5, Schedule of Activities for Participants in Part B Who Discontinue Study Treatment but Agree to Remain in the Study; Section 8.1, Discontinuation of Study Treatment; Section 8.3, Withdrawal of Participants From the Study.

Section 9.1, Clinical Efficacy Assessments

Change: The protocol was revised [redacted] to update the information on PedsQL, and to add measures of [redacted] for the adult participants who will enroll in Cohort 2 of Part C.

[redacted]

…

9.1.10.1. 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~~ **Patient** self-report is measured in children and adolescents 5 to ~~18~~ **25** years of age, and parent proxy-report of child HRQOL is measured for children and adolescents 2 to ~~18~~ **25** years of age. **Patient self-report and parent proxy-report are available for participants who are ≥ 26 years of age for the Generic Core Scale.** 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 **Cohort 1**, the PedsQL (in addition to ACEND) will be evaluated in participants who are ≥ 2 years of age at Screening. **The PedsQL will not be evaluated for participants in Part C Cohort 2.**

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.

…

[redacted]

[redacted]

Rationale: [redacted]

The description of the PedsQL was updated to clarify that the adults in Cohort 1 of Part C will be assessed with this scale and to provide more details regarding the scales available for participants up to age 25 and aged 26 years or older. The text clarifies that participants in Cohort 2 of Part C will not be evaluated with the PedsQL.

With the increase in the number of adult participants as part of this protocol amendment, the following measures were added for Cohort 2 of Part C: [redacted]. These will enable collection of additional data that are important for adults with SMA, including [redacted].This change also affects Section 1.3, Schedule of Activities (Tables 2, 3, and 4); Section 4, Study Objectives and Endpoints; Section 16, References.

[redacted]

Change: [redacted]

Now reads:

[redacted]

[redacted]

Rationale: [redacted]

This change also affects Section 4, Study Objectives and Endpoints; [redacted]

Section 10.1, Clinical Safety Assessments

Change: Growth parameters were updated to allow for measurement of length for participants with later-onset SMA who are not able to have height measured. In addition, the requirements for measuring LP opening pressure were revised.

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

- AE and SAE recording
- Medical (including SMA) history. [redacted]
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry
- Growth parameters: body length/height (for all participants**; body length will be measured for participants who are not able to stand independently**), 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: ~~d~~**D**etails available in the DHA**. LP opening pressure will be evaluated for all participants in Parts A and C, but only for participants with later-onset SMA in Part B.**
- Concomitant therapy and procedure recording

Rationale: Protocol Version 4 required height and ulnar length to be measured for participants with later-onset SMA, but there are participants with later-onset SMA in Study 232SM203 who are unable to stand and cannot have height measured. Therefore, measurement of length is being offered as an alternative to height for these participants.

The requirement to evaluate LP opening pressure for the infantile-onset SMA population in Part B was removed. Measuring an accurate value for LP opening pressure is difficult in infants because the pressure can be elevated due to crying (increased intra-thoracic pressure increase) and posturing (intra-abdominal pressure increase) during the assessment. LP opening pressure values in this patient population would be varied and inconsistent. Furthermore, although sedation of infants could enable a more accurate reading of LP opening pressure, infants are not typically sedated for this procedure (either in clinical practice or the clinical study). Requiring sedation purely for this purpose does not justify the risks introduced. Therefore, the protocol has been revised to remove this assessment for the infantile-onset SMA participants in Part B, while retaining this assessment for all other participants in the study. This is aligned with the PSUR 05 PRAC recommendation and commitment to measure LP opening pressure in a clinical study with nusinersen to help further assess the important identified risk of hydrocephalus.

This change also affects Section 1.3, Schedule of Activities (Tables 2, 3, and 4).

Section 14.1.4, Central Laboratories for Laboratory Assessments

Change: The requirements for SMA genetic testing were clarified, noting that all laboratory samples collected from participants in China will be analyzed within China.

Now reads:

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. **Analysis of urine total protein, coagulation, pregnancy tests, and CSF protein/cell count/glucose will be conducted by local laboratories.** [redacted] will be analyzed at a laboratory selected by the Sponsor **(Appendix B)**.

~~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~~ **to evaluate** *SMN1* **gene status (**copy number**,** ~~and~~ deletion~~/~~**, and** mutation **where necessary to confirm 5q SMA)** and *SMN2* copy number by the central laboratory. **For participants without acceptable documentation of these genetic testing results before Screening, a blood sample must be collected during the Screening period to determine eligibility (preferably for analysis by the central laboratory, but may be determined by local lab genetic testing if needed). For participants with documentation of these genetic testing results before Screening or whose sample was analyzed locally during the Screening period (with documentation of these genetic testing results), a blood sample will be collected (preferably at Screening, but must be collected by the first maintenance dosing visit) for confirmatory testing through the central laboratory.**

Sample analysis for participants from China will be performed within China.

Rationale: The SMA genetic testing language was revised to further clarify for site personnel which samples need to be collected at specific times, as well as to further describe the different methods of determining study eligibility (i.e., through acceptable historical genetic documentation prior to Screening for Study 232SM203 or through collection and analysis of a blood sample at Screening). In addition, in order to simplify analysis of the samples collected in China, the protocol was updated so that those samples could be analyzed within China, removing the need to export genetic material out of the country.

This change also affects Section 1.3, Schedule of Activities (Tables 2, 3, and 4); [redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected throughout the protocol.
- Section numbers, eligibility criteria numbering, and footnote numbering were updated where applicable.
- The sample size was updated to "up to approximately 172 participants" throughout the protocol.
- The long-term extension study number (232SM302) was added throughout the protocol.
- Reference to the "high dosing regimen" was updated to "higher dosing regimen" throughout the protocol.
- The overall exposure of nusinersen worldwide was updated throughout the protocol with data available as of December 2020.
- In Section 1.3, Schedule of Activities for Parts B and C, several minor changes were made either to align with other changes made throughout the protocol or to clarify existing content:
  - Details on Screening were removed from the footnotes but are available in Section 6.3.1, Screening.
  - It was noted that if participants who meet the criteria for contraception use in Parts B and C enroll into the long-term extension study (232SM302) at the Day 302 visit, they do not need to return for the additional follow-up visit for Study 232SM203 at Day 399 (Part B) or Day 361 (Part C).
  - It was clarified that a local laboratory may be used for analysis of blood chemistry, hematology, and urinalysis samples for the Screening visit if needed for timely treatment at the Investigator's discretion.
  - It was clarified that coagulation testing results should be reviewed prior to dosing.
  - Removed the requirement for evaluating HFMSE and RULM prior to other motor function and motor milestone assessments because details on the order of assessments is provided in the scale manuals.

  - It was clarified that the 2 baseline assessments for CHOP INTEND, HFMSE, and RULM must occur on different days.

  - In the Part C Schedule of Activities tables, it was clarified that adult participants who do not require a caregiver during the study visits will only have the CGIC assessed by the Investigator.

  - In the Part C Schedule of Activities tables, it was clarified that the ACEND will not be collected for adult participants who do not require a caregiver.

  - In the Part C Cohort 2 Schedule of Activities table, the Day 241 timepoint for the ACEND assessment was removed.

- Section 2, List of Abbreviations, was updated.

- In Section 3.2.2, Current Therapies for SMA, language regarding the current therapies available for SMA was updated based on recent regulatory approvals.

- In Section 3.2.3, Profile of Previous Experience With Nusinersen, the information on regulatory approvals of nusinersen was simplified.

- In Section 6.2, Exclusion Criteria, it was clarified that nusinersen is an example of an antisense oligonucleotide treatment.

- In Section 7.1, Regimen, it was clarified that a protocol deviation should be recorded if a loading dose is delayed or missed (as per the schedule of activities) and that dosing should be continued according to the schedule of activities (rather than "the prescribed dosing frequency").

- In Section 7.3, Study Treatment Management, a statement was added clarifying that the DHA aligns with all other references, including the protocol.

- In Section 8.3, Withdrawal of Participants From the Study, it was clarified that participants who initiate treatment with a disallowed concomitant therapy as described in Section 7.6.1.2 must be withdrawn from the study. Similarly, in Table 5, it was clarified that these participants are not eligible to remain in the study for follow-up visits after discontinuing study treatment.

- In Section 9.1, Clinical Efficacy Assessments, several minor changes were made:

  - Information regarding the definitions of sitting without support and ambulatory were moved to the top of the section.

  - It was clarified that while videotaping of motor milestone and motor function assessments is optional, if the participant/caregiver provides consent to video recording, all assessments should be recorded.

  - The QoL questionnaires that apply for each part of the study were specified.

  - The appropriate patient populations for each assessment were clarified for Cohort 1 of Part C and added for Cohort 2 of Part C.

  - Assessment of the different efficacy measures was changed from "by the Investigator" to "by the clinical site evaluator."

  - Statements were added to clarify that, whenever possible, for each participant, the same clinical evaluator should conduct all motor milestone and motor function assessments across all study visits since the use of different raters can lead to variability in the data.

  - It was clarified that adult participants who do not require a caregiver may self-report WHO motor milestone achievement.

  - [redacted]

  - [redacted]

  - It was clarified that all participants with infantile-onset SMA in Part B need to record daily ventilator use in the ventilator use diary for the duration of the study, regardless of whether or not a ventilator is being used.

  - Some of the subsections were reordered to improve flow in the section.

- In Section 11.3, Monitoring and Recording Events, and Section 11.6, Safety Responsibilities, language regarding reporting requirements for SAEs was updated to include "or according to national law," in line with the latest protocol template update by the Sponsor to accommodate countries that may have different reporting requirements.

- In Section 12, Statistical Methods and Determination of Sample Size, subheading 12.1 was moved.

- Section 16, References, was updated.

LIST OF ABBREVIATIONS

[redacted]	[redacted]
[redacted]	[redacted]
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CSF	cerebrospinal fluid
C_{max}	maximum concentration
CNS	central nervous system
C_{trough}	trough concentration
DHA	Directions for Handling and Administration
EC_{50}	concentration at 50% of the maximum observed biological effect
ECG	electrocardiogram
[redacted]	[redacted]
EU	European Union
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
HRQOL	health-related quality of life
ICF	informed consent form
IDMC	independent data monitoring committee
[redacted]	[redacted]
LP	lumbar puncture
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory™
PK	pharmacokinetic(s)
[redacted]	[redacted]
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QoL	quality of life
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
[redacted]	[redacted]
SMN	survival motor neuron
SMN1	survival motor neuron-1 (gene)
SMN2	survival motor neuron-2 (gene)
US	United States
[redacted]	[redacted]
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 4

Date: 05 August 2020

EUDRA CT Number: 2019-002663-10

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 [redacted]

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

[redacted]

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.

[redacted]

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 15.3, Monitoring of the Study

Change: Language was added to the protocol regarding remote monitoring of study sites during the global COVID-19 pandemic.

Now reads:

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.

Rationale: This change was made to clarify that remote monitoring may be implemented only in the event that the COVID-19 pandemic precludes on-site monitoring.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Section 2, List of Abbreviations, was updated.

LIST OF ABBREVIATIONS

AE	adverse event
COVID-19	coronavirus disease 2019
IDMC	independent data monitoring committee
SAE	serious adverse event

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 3

Date: 05 June 2020

EUDRA CT Number: 2019-002663-10

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.2.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 [redacted].

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

[redacted]

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.

[redacted]

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 1.3, Schedule of Activities, Table 1: Schedule of Activities for Part A

Change: The optional postdose [redacted] on Day 1 and the corresponding footnote was removed from the study.

Now reads:

	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			

…

[redacted]

…

[redacted]

Rationale: The optional postdose [redacted] was removed to prevent potential for unblinding during the study.

This change also affects Table 2: Schedule of Activities for Part B; Table 3: Schedule of Activities for Part C; [redacted]

Section 1.3, Table 2: Schedule of Activities for Part B

Change: A footnote was added to Table 2 to specify that the LP opening pressure and CSF local lab sample can only be measured and collected on Days 1, 15, and 279 in Part B of Study 232SM203.

Now reads:

Table 2: Schedule of Activities for Part B

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

Rationale: In Part B, the Control Group (12/12 mg) will receive 4 loading doses of nusinersen on Days 1, 15, 29, and 64 followed by 2 maintenance doses of nusinersen on Days 183 and 279. The 50/28-mg Group will receive 2 loading doses of nusinersen on Days 1 and 15 followed by 2 maintenance doses of nusinersen on Days 135 and 279. In order to maintain the blinding in Part B of the study, both the LP opening pressure and the local CSF analysis will only be assessed at those visits where both groups are administered a dose of study treatment.

Section 1.3, Schedule of Activities

Change: The footnotes regarding study treatment injection in Tables 1, 2, and 3 were revised to clarify the potential anesthesia and/or sedation options that may be used for the LP procedure and to ensure that all participants in Part B would receive equivalent levels of anesthesia and/or sedation to maintain the blind.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote **4**~~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.

Table 2: Schedule of Activities for Part B

Footnote **4**~~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** ~~A~~**a**nesthesia (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~~ with later onset SMA~~, 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 with infantile-onset SMA will receive minimal sedation (i.e., a low dose of an anxiolytic) for the sham procedure, according to institutional procedures.~~ For participants with infantile-onset SMA, LP injections/sham procedures may not occur within 72 hours after an immunization.

Table 3: Schedule of Activities for Part C

Footnote **4**~~3~~: 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** ~~A~~**a**nesthesia (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. ~~For participants with infantile-onset SMA,~~ LP injections may not occur within 72 hours after an immunization.

Rationale: Although the benefit/risk ratio of general anesthesia in young participants does not justify use in this study, some forms of sedation to reduce anxiety may be indicated and the protocol was clarified to allow sites to use these methods at their discretion throughout the study as long as it is consistently used in an individual participant for all visits in Part B to maintain blinding to dosing regimen.

This change also affects Section 7.4, Blinding Procedures.

Section 1.3, Schedule of Activities

Change: The footnotes regarding ECG monitoring in Tables 1, 2, and 3 were revised to adjust the postdose ECG timing and address abnormal ECG results.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote ~~10~~**12**: ECG**s** will be performed predose, at ~~2~~**5** hours (~~±15 minutes~~**1 hour**) postdose**, and at 24 hours (±2 hours) postdose** on Day**s** 1, **15, and 29; at the Day 64 visit;** ~~,~~ at **45** hours (~~±30 minutes~~**1 hour**) postdose on Days ~~15 and 29~~**149 and 269;** ~~, at 24 hours (±2 hours) postdose at all dosing visits,~~ and at ~~EOS~~**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.**

Table 2: Schedule of Activities for Part B

Footnote ~~11~~**14**: ECG**s** will be performed predose, at ~~2~~**5** hours (~~±15 minutes~~**1 hour**) postdose**, and at 24 hours (±2 hours) postdose** on Day**s** 1, **15, 29, and 64;** at 4**5** hours (~~±30 minutes~~**1 hour**)

postdose on Days ~~15 and 29~~**135, 183, and 279;** ~~, at 24 hours (±2 hours) postdose at all dosing visits,~~ and at ~~EOS~~**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.**

Table 3: Schedule of Activities for Part C

Footnote ~~11~~**14**: ECG**s** will be performed predose, at ~~2~~**25** hours (~~±15 minutes~~**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** ~~and at 24 hours (±2 hours) after the Day 121 and 241 doses~~. 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.**

Rationale: The ECG monitoring schedule in the footnote was clarified to align with the content presented in the Schedule of Activities table. The postdose ECG assessments after each dosing visit were modified to align with the expected [redacted] (i.e., 4 to 6 hours postdose). Additional details were added to clarify that a clinically significant finding on a postdose ECG should prompt a repeat assessment within 2 hours of the initial abnormal finding.

Section 1.3, Schedule of Activities

Change: Additional text was added to allow the participants to complete the Safety Laboratory Tests prior to the dosing visit for Parts A, B, and C.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote ~~11~~**13**: …**These assessments may be performed up to 7 days prior to dosing/study visit, if necessary**…

Table 2: Schedule of Activities for Part B

Footnote ~~12~~**15**: …**These assessments may be performed up to 7 days prior to dosing/study visit, if necessary**…

Table 3: Schedule of Activities for Part C

Footnote ~~12~~**15**: …**These assessments may be performed up to 7 days prior to dosing/study visit, if necessary**…

Rationale: Allowing efficacy assessments to be conducted prior to the dosing visit days will reduce participant burden at those visits and increase flexibility for sites and study participants.

Section 1.3, Schedule of Activities

Change: A footnote for efficacy assessments was added and a portion of the text from the previous footnote was moved to the new footnote for Parts A, B, and C.

Now reads:

Table 1: Schedule of Activities for Part A

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

Footnote 19: **When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments.** [redacted]

Table 2: Schedule of Activities for Part B

Footnote ~~19~~**20: Videotaping of all motor milestone and motor function assessments is optional.** [redacted]

Footnote 23: When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments. [redacted]

Table 3: Schedule of Activities for Part C

Footnote ~~18~~20: **The Investigator will select the appropriate efficacy assessments for use based on criteria in Section 9.1.** Videotaping of all motor milestone and motor function assessments is optional. [redacted]

Footnote 21: **When assessing efficacy, HFMSE and RULM will be performed first, followed by remaining assessments.** [redacted]

Rationale: Additional guidance was provided to add clarity to the Schedule of Activities and to align with changes in Section 9.1, Clinical Efficacy Assessments.

Section 1.3, Schedule of Activities

Change: The loading dose visit windows for Parts A and B of Study 232SM203 were clarified and revised.

Now reads:

Table 1: Schedule of Activities for Part A

	Screening Visit[1]	Treatment				Follow-Up[2] EOS/~~ET~~	
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)

Table 2: Schedule of Activities for Part B

	Screening Visit[1]	Treatment	Follow-Up[2] EOS/~~ET~~

Assessments	D-21 to D-1	D1, D15 **(±1 day)**, D29 **(±1 day)**, D64 (±~~1~~7 day**s**)	D135 (±7 days), D183 (±7 days), D279 (±7 days)	2 to 14 Days After Each Maintenance Dose	D302/ET (±7 days)	D399 (+14 days)

Rationale: The 1-day visit windows for the Days 15 and 29 loading dose visits were clarified. For Part A, a 7-day window was added for the Day 64 visit, and in Part B, the Day 64 visit window was increased from 1 day to 7 days to offer greater visit scheduling flexibility for the sites and study participants with no anticipated impact on patient safety or quality of efficacy data collected.

This change also affects Section 1.1, Synopsis; and Section 5.2, Study Duration for Participants.

Section 1.3, Schedule of Activities

Change: A footnote was added to Tables 1, 2, and 3 in order to ensure that efficacy assessments (CHOP INTEND, HFMSE, and RULM) are conducted twice prior to the first dose of study treatment.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote 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.

Table 2: Schedule of Activities for Part B

Footnote 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.

Table 3: Schedule of Activities for Part C

Footnote 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.

Rationale: The requirement to assess efficacy twice prior to the first dose of study treatment was added to establish a more stable baseline and to be consistent with historical studies for nusinersen.

Section 1.3, Table 1: Schedule of Activities for Part A

Change: A footnote was added to Table 1 in order to specify that efficacy assessments are not required to be performed on Days 1 and 15 for Part A, except in cases when the Day 1 efficacy assessment is required for the second baseline measurement for HFSME and RULM.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote 21: During the loading period, the efficacy assessments will be performed on Day 29 predose only…

Rationale: A Day 1 predose motor assessment is unnecessary in cases where the baseline has been established during Screening. The schedule for capturing efficacy data during Part A of the study was modified to reduce participant burden by removing the need for assessments on Day 15.

Section 1.3, Schedule of Activities

Change: A footnote was added to Table 1 and an existing footnote was modified in Table 2 in order to add windows for the predose efficacy assessments required at the loading dose visits (i.e., Days 29 and 64, respectively) in Parts A and B of Study 232SM203.

Now reads:

Table 1: Schedule of Activities for Part A

Footnote 21: …The Day 29 efficacy assessments may be performed up to 3 days prior to dosing, if necessary.

Table 2: Schedule of Activities for Part B

Footnote ~~20~~**22**: During the loading period, the efficacy assessment**s** 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.**

Rationale: Allowing efficacy assessments to be conducted prior to the dosing visit days will reduce participant burden at those visits and increase flexibility for sites and study participants.

Section 4, Study Objectives and Endpoints

Change: [redacted]

Now reads:

…

Part B Secondary Objectives	Secondary Endpoints

…

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

…

Parts A and C Secondary Objectives	Secondary Endpoints

…

[redacted]	[redacted]
[redacted]	[redacted]

…

[redacted]	• [redacted] • [redacted]

…

Rationale: [redacted]

This change also affects Section 1.1, Synopsis.

Section 5.1, Study Overview

Change: The text describing the IDMC review for Part A of the study was revised in order to clarify the role of the IDMC, allow for additional participants to be enrolled at the discretion of the Sponsor, and refer to the IDMC charter.

Now reads:

…

Part A will enroll a ~~total~~**minimum** of 6 participants with later-onset SMA…

…

After ~~all~~ 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 ~~determine~~**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 ~~choose~~**recommend** to stop the study based on the safety findings.

…

Rationale: The protocol was clarified to allow additional participants to be enrolled in Part A if needed, to ensure sufficient data are available for the IDMC to evaluate safety prior to subsequent enrollment of participants in Part B of the study. The Sponsor will continue to monitor the study and retain accountability for study conduct. Furthermore, the protocol was clarified to note that further information will be provided in the IDMC charter.

This change also affects Section 1.1, Synopsis; Section 3.1, Study Rationale; Section 12.11, Sample Size Considerations; and Section 14.2.2, Independent Data Monitoring Committee.

Section 5.1, Study Overview

Change: Guidance was added on the number patients with scoliosis and/or severe contractures to be included in Part C of the study.

Now reads:

…**Up to 5 participants with severe scoliosis and/or severe contractures may be enrolled in Part C after consultation with the Medical Monitor**....

Rationale: Guidance describing the inclusion of participants with severe scoliosis and/or severe contractures was added to allow a representative population of participants currently taking Spinraza to qualify for Part C of this study.

This change also affects Section 1.1, Synopsis; and Section 1.3, Schedule of Activities.

Section 5.1, Study Overview

Change: Guidance was added to the date of first dose given to participants on study to assist investigators in scheduling participant enrollment in Part C.

Now reads:

…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...

Rationale: To clarify for sites that the schedule of the Day 1/first dose for participants in Part C of Study 232SM203 should be within 4 months ± 14 days from a participant's previous dose of nusinersen. Dose administration within this time frame is expected to produce nusinersen [redacted] consistent with those found in Parts A and B.

This change also affects Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3.1, Study Rationale; and Section 7.1, Regimen.

Section 5.2, Study Duration for Participants

Change: The study duration has been extended and an assessment has been added on Day 410, Day 420, and Day 382 for Part A, Part B, and Part C, respectively.

Now reads:

The total study duration for each participant will be up to ~~323~~**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 number of visits during the study:

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

Rationale: In order to align the requirements of contraception use and reporting, the follow-up period of the study was extended for those participants who require contraception use (as described in Section 11.5, Contraception Requirements). All participants requiring use of contraception will have last visit 120 days after the last dose. The 120-day follow-up interval after the last dose for subjects who are required to use contraception in the study is equivalent to approximately 5 half-lives of nusinersen in the target tissue. The Day 302 visit will remain the last visit for participants who do not meet the criteria for contraception use.

This change also affects Section 1.1, Synopsis; Section 1.2, Figure 1: Study Schematic; Section 1.3, Schedule of Activities; Section 5.1, Study Overview; Section 11.4.1, Pregnancy; and Section 11.5, Contraception Requirements.

Section 6, Study Population

Change: Inclusion criteria were added for Parts A, B, and C, and exclusion criteria were added for Parts A, B, and C relating to fertility status.

Now reads:

6.1. Inclusion Criteria

Part A

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

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

…

Part C

10. Post-menopausal 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

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

Rationale: The risk of nusinersen to women who are pregnant or currently breastfeeding is unknown; therefore, the inclusion and exclusion criteria were updated to only allow female participants in Part C who meet this inclusion criterion and participants in Parts A, B, and C who do not meet these exclusion criteria to enroll in this study.

Section 6.1, Inclusion Criteria

Change: Compliance with the study travel policy was added to the inclusion criteria in Parts A, B, and C.

Now Reads:

Part A

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

…

Part B

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

…

Part C

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

…

Rationale: As detailed in Section 15.4 in previously approved versions of the protocol, participants are required to adhere to the study travel policy in order to participate in the study. The ability to adhere to the travel policy was added to the inclusion criteria in order to fully evaluate participant eligibility during Screening.

Section 6.2, Exclusion Criteria

Change: Exclusion criteria in Part B were revised so that respiratory insufficiency and the medical necessity for a gastric feeding tube only apply to participants with later-onset SMA. Participants with infantile-onset SMA with those conditions may be enrolled.

Now reads:

All participants

~~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~~

…

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

Rationale: The exclusion criteria related to the need for respiratory support and gastric feeding tubes was clarified to specify that it only applies to participants with later-onset SMA. Previous data from nusinersen treatment in patients with early-onset SMA suggest that participants who need these supportive measures may still benefit from nusinersen treatment and are appropriate for inclusion in this trial. These criteria are consistent with the previous pivotal study of nusinersen in infantile-onset participants (CS3B, ENDEAR).

Section 6.2, Exclusion Criteria

Change: The participant's position for the Screening X-ray in Part B was changed from supine to sitting/supported sitting for participants with later-onset SMA. Physical assessment of scoliosis was added for regions where X-ray use is regulated.

Now reads:

Part A

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.**

…

Part B

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

~~18.~~**19.** Severe scoliosis evident on X-ray examination at Screening (with the participant ~~supine, not~~ 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.**

…

Rationale: The position of the Screening X-ray was modified in Part B for consistency with the historical study of nusinersen in later-onset participants (CS4, CHERISH). Parts A and B were updated to allow Investigators to perform a physical examination of scoliosis, in lieu of an X-ray examination, in regions with local regulations on use of X-ray.

This change also affects Section 1.3, Schedule of Activities.

Section 6.2, Exclusion Criteria

Change: An exclusion criterion to exclude participants who have had prior scoliosis surgery that may interfere with the LP injection procedure was added for Parts B and C.

Part B

All participants

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

…

Part C

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

…

Rationale: Investigators may be unable to administer nusinersen via the LP injection procedure to participants who have undergone scoliosis surgery.

Section 6.2, Exclusion Criteria

Change: The exclusion criteria regarding use of other investigational medications or participation in other clinical trials were revised.

Now reads:

Part A

~~12.~~**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 ~~risdiplam or branaplam;~~**any SMN2-splicing modifier** or ~~any history of~~ gene therapy~~,~~**; or** prior antisense oligonucleotide treatment~~,~~ or cell transplantation

…

Part B

~~11.~~**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 ~~risdiplam or branaplam;~~**any SMN2-splicing modifier** or ~~any history of~~ gene therapy~~,~~**; or** prior antisense oligonucleotide treatment~~,~~ or cell transplantation

…

Part C

~~9~~**11.** Concurrent **or previous** participation and/or administration of nusinersen in another clinical study. ~~Previous participation in a clinical trial of nusinersen is permitted, provided that the participant completed all study visits that have been scheduled prior to Screening in this 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.

~~10. Dosing with onasemnogene abeparvovec-xioi (Zolgensma) within 6 months prior to Screening. Prior use of onasemnogene abeparvovec-xioi is permitted in participants, as long as it has been at least 6 months since treatment; the corticosteroids administered concomitantly with this treatment must also have been stopped prior to Screening in this study.~~

Rationale: The exclusion criteria have been modified to minimize potentially confounding factors when interpreting safety.

Section 9.1, Clinical Efficacy Assessments

Change: [redacted] was modified to allow Investigators to use their clinical judgment to select which efficacy assessments will be used from a provided list, rather than defining this by onset type. A requirement to continue use of the scales selected at baseline was also added.

Now reads:

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

- ~~Infantile-onset SMA~~
  - ~~CHOP INTEND~~
  - ~~HINE Section 2 – motor milestones~~
  - ~~Daily ventilator or bilevel positive airway pressure (BiPAP) use (number of hours/day)~~
- ~~Later-onset SMA~~
  - ~~HFMSE~~
  - ~~Revised Upper Limb Module (RULM)~~
  - ~~[redacted]~~
  - ~~[redacted]~~
  - ~~World Health Organization (WHO) motor milestones~~
- ~~All participants~~
  - ~~Number of serious respiratory events~~
  - ~~Dysphagia assessments (Parent Assessment of Swallowing Ability [PASA], Parts A and B only)~~
  - ~~Number and duration of hospitalizations~~
  - ~~Growth parameters~~

- ~~Clinical Global Impression of Change (CGIC; physician and caregiver assessment)~~
- ~~Quality of life (QoL) questionnaires~~

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

<u>Participants with Later-Onset SMA:</u>

- **HFMSE**
- **RULM**
- **World Health Organization (WHO) Motor Milestones**
- [redacted]
- **QoL questionnaires**
- **Dysphagia assessments (Parent Assessment of Swallowing Ability [PASA])**

Part B

<u>Participants with Infantile-Onset SMA:</u>

- **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**
- [redacted]
- [redacted]
- **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.**

- [redacted]
- [redacted]
- **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.

Rationale for [redacted] addition to Parts A and B: The [redacted] was added to Parts A and B to be [redacted] in order to gather additional motor efficacy data.

Rationale for the modified assessment list in Part C: Participants in Part C will only enter Study 232SM203 after having received nusinersen treatment for at least 1 year. Thus classification for assessment by age at SMA onset prior to this treatment period alone is not appropriate for this study. The revised list is based on age and clinical status at Screening in this study as the determining factors for which clinical efficacy assessments will be administered to Part C participants. In addition, the scales used at baseline are required to be continued throughout the study to aid interpretation of the results.

This change also affects Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 4, Study Objectives and Endpoints; Section 9.1.1, Motor Milestones; Section 9.1.2, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; [redacted]; and Section 10.1, Clinical Safety Assessments.

Section 9.1.8, Quality-of-Life Questionnaires

Change: The SMA-HI assessment was removed from Study 232SM203 (Part C).

Now reads:

~~9.1.9.3. Spinal Muscular Atrophy – Health Index~~

~~Participants in Part C who are ≥ 8 years of age at Screening will complete the SMA-HI, a patient-reported outcome measure specific to SMA. The SMA-HI was developed and validated using Food and Drug Administration guidelines for patients with SMA who are 8 to 85 years of~~

~~age and is currently being used to measure therapeutic response in clinical trials. The SMA-HI measures a patient's perception of total disease burden and 15 additional areas of SMA-specific symptomatic health. Fifteen scores are generated (one for each of the subscales) in addition to a total SMA-HI score (measuring overall disease burden).~~

Rationale: This scale is not anticipated to provide data essential to the evaluation of the benefit/risk of patients transitioning from the 12/12-mg dosing regimen of nusinersen to the 28 mg maintenance dosing regimen in this study beyond what is provided by the PedsQL which will now be administered to all participants with later-onset SMA who are ≥ 2 years of age.

This change also affects Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 2, List of Abbreviations; Section 4, Study Objectives and Endpoints; and Section 12.4.3, Analysis of the Remaining Endpoints.

Section 9.1.10, Ventilator Use

Change: A new section was added to the protocol to provide additional details on ventilation use.

Now reads:

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.

Rationale: To clarify that ventilator use will be assessed for all study participants and to provide additional details on the daily ventilation diary that is required for participants with infantile-onset SMA who are enrolled in Part B of the study.

This change also affects Section 1.1, Synopsis; Section 1.3, Schedule of Activities; and Section 4, Study Objectives and Endpoints.

Section 10.1, Clinical Safety Assessments

[redacted].

Now reads:

…

[redacted]

…

[redacted]

Section 10.2, Laboratory Safety Assessments

Change: CK isoenzyme analysis was removed from Study 232SM203.

Now reads:

- 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 ~~isoenzymes (expressed in the brain, myocardium, and skeletal muscle)~~

Rationale: Specific CK isoenzyme analysis is not required for the safety or efficacy assessment of nusinersen in Study 232SM203; however, CK enzyme will still be analyzed.

This change also affects Appendix B, Laboratory Analytes.

Section 11.4.1, Pregnancy and Section 11.5, Contraception Requirements

Change: The language on pregnancy, contraception requirements, and sperm/egg donation was modified.

Now reads:

11.4.1. Pregnancy

Participants should not become pregnant or impregnate their partners ~~during the study and for at least 90 days after their last dose of study treatment~~**for the duration of the study**.

…

11.5. Contraception Requirements

All female participants of childbearing potential and all male participants of reproductive age must ensure that ~~highly~~ 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 ~~and for at least 90 days after their last dose of study treatment.~~

…

- ~~Female surgical sterilization (e.g., bilateral tubal ligation), where applicable, according to local guidelines.~~

For the purposes of the study, ~~highly~~ 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, injected, or implanted ~~progestogen-only~~ hormonal methods of contraception ~~associated with the inhibition of ovulation~~

…

Rationale: Current safety data on nusinersen do not suggest a risk to the fetus; however, there are no data in humans. Because of the long half-life of nusinersen, a longer requirement for contraception, equivalent to 5 half-lives of nusinersen, was included in the study by increasing the study duration for those participants who meet these criteria.

Section 12.10, Interim Analyses

Change: The interim analyses section was modified to add text describing the potential for interim analyses of Parts A and C data.

Now reads:

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. [redacted] **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 ~~analysis~~**analyses** and controlled access to the unblinded data will be documented in the Statistical Analysis Plan, the unblinding plan, and the IDMC charter.

Rationale: The Sponsor may perform interim analyses on the open-label portions of the study (Parts A and C) prior to the completion of the double-blind portion (Part B).

This change also affects Section 12.4, Methods of Analysis for Efficacy Endpoints; and Section 12.4.1, Analysis of the Primary Endpoint in Part B.

Section 15.3, Monitoring of the Study

Change: The option for remote monitoring/remote data verification was added.

Now reads:

...

The ~~Medical~~**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)**. 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.

~~During these visits,~~ 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 ~~(centralized monitoring)~~ may also be conducted and reported as defined in the monitoring plan.

Monitoring ~~visits~~ 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.

Rationale: In response to the global COVID-19 pandemic, the protocol was modified to allow for remote monitoring of the sites in order to reduce the amount of direct human contact required per protocol, thereby improving safety for both study participants and staff.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.
- Minor editorial changes were made throughout the protocol.
- On the Sponsor Signature Page, the signatory's name and role were updated.
- Text was revised throughout the protocol to clarify that Part A will enroll participants aged 2 to ≤ 15 years, inclusive.
- In Section 1.3, Schedule of Activities (Tables 1, 2, and 3), the placement of several footnotes was changed. In addition, the footnotes regarding predose [redacted] were deleted because that information was already presented within the Schedule of Activities tables.
- In Section 1.3, Schedule of Activities (Tables 1, 2 and 3), an additional pregnancy test was added to the Day 302 follow-up visit for Parts A, B and C to align with changes in Section 5.2, Study Duration for Participants, and a footnote was added to the assessment to provide clarity.
- In Section 1.3, Schedule of Activities, Tables 1, 2, and 3 were updated to clarify that pregnancy tests, X-ray examinations to confirm eligibility at Screening, and CSF cell count/protein/glucose are to be analyzed locally. This change also affects Section 10.2, Laboratory Safety Assessments; Section 14.1.4, Central Laboratories for Laboratory Assessments; and Appendix B, Laboratory Analytes.
- In Section 3.1, Study Rationale, the phrase "with less frequent dosing during the loading period" was removed. This change also affects Section 1.1, Synopsis.
- In Section 3.1.2, Rationale for Dosing Regimen, the number of subjects in Study CS3A was corrected and the age range of participants was included. Study CS3B was also updated to include the number of subjects and age range of participants. This change also affects Section 1.1, Synopsis.
- In Section 3.1.2, Overview of SMA, the phrase "at the end of the loading dose period" was removed. This change also affects Section 1.1, Synopsis.
- In Section 3.2.2, Current Therapies for SMA, the countries where Zolgensma® has been approved were updated.

- In Section 3.2.3, Profile of Previous Experience With Nusinersen, the list of global marketing authorizations for Spinraza and the number of patients treated with nusinersen were updated. This change also affects Section 1.1, Synopsis, and Section 3.3, Benefit-Risk Assessment.

- In Section 4, Study Objectives and Endpoints, the Quality of Life and Swallowing headers were removed from the endpoints. Headers for assessments specifying Parts A and C were added or removed as necessary to reflect other changes protocol. This change also affects Section 1.1, Synopsis.

- In Section 4, Study Objectives and Endpoints, [redacted] in order to align with the Schedule of Activities tables.

- In Section 4, Study Objectives and Endpoints, [redacted]

- In Section 5.1, Study Overview, the number of sites where the study will be conducted was changed from 50 to 65. This change also affects Section 1.1, Synopsis.

- In Section 5.1, Study Overview, the text was modified to clarify that participants enrolled in Parts A and B will be required to stay in the clinic for at least 24 hours after each study treatment administration, and participants in Part C will remain at the clinic for at least 24 hours after the first treatment administration only, as described in the schedule of activities. This change also affects Section 1.1, Synopsis.

- In Section 5.4, Unscheduled Visits, additional guidance was added to clarify that laboratory assessments collected locally should be included in the CRF.

- In Section 6.2, Exclusion Criteria, the text was revised to clarify that exclusion of a participant based on the parent or legal guardian being unwilling or unable to meet the guidelines in the consensus statement for standard of care in SMA or provide nutritional and respiratory support throughout the study will be per the Investigator's judgment.

- In Section 7.1, Regimen, the text regarding the participants enrolled in Part A was revised to clarify that only 1 participant can receive their first dose of study treatment on a given day, as was originally intended. This change also affects Section 1.1, Synopsis, and Section 5.1, Study Overview.

- In Section 7.1, Regimen, Table 4: Part B Blinded Dosing Schedule, the EOS column was removed for clarity and no dose will be administered on that day.

- In Section 7.4, Blinding Procedures, the text regarding artificial CSF was revised for clarity and to align with the DHA, as was originally intended.

- In Section 7.7, Continuation of Treatment, "open-label" was removed as a qualifier before the long-term extension study. This change also affects Section 1.1, Synopsis, and Section 5.1, Study Overview.

- In Section 9.1, Clinical Efficacy Assessments, BiPAP was removed because is already included as time on a ventilator. This change also affects Section 1.3, Schedule of Activities; Section 2, List of Abbreviations; Section 10.3, Telephone Assessments; Section 12.4.3, Analysis of the Remaining Endpoints.

- In Section 9.1, Clinical Efficacy Assessments, the text was modified to clarify that quality-of-life questionnaires only apply to the later-onset participants for alignment with other sections of the protocol.

- Section 9.1.1, Growth Parameters, was deleted and its text was moved to Section 10.1, Clinical Safety Assessments, replacing the previous text for growth parameters.

- In Section 9.1.2, Motor Milestones, Section 9.1.7, Clinical Global Impression of Change, and Section 9.1.8.2, Assessment of Caregiver Experience With Neuromuscular Disease, additional guidance was provided for adult participants who do not require a caregiver during the study visits.

- [redacted] Also, the text about SMA type was removed to align with Section 9.1, Clinical Efficacy Assessments.

- In Section 9.1.8.1, Pediatric Quality of Life Inventory (Generic Core Scales and Neuromuscular Module), the upper age limit and SMA type for use of PedsQL for participants enrolled in Part C of Study 232SM203 were removed. This change also affects Section 1.3, Schedule of Activities.

- [redacted]

- In Section 10.1, Clinical Safety Assessments, LP opening pressure was added to the list of safety assessments with a reference to the DHA for additional details.

- In Section 11.2.2, Relationship of Events to Study Treatment, "LP" was changed to "LP/sham" for clarity. Additional text was provided to clarify that the relationship to study treatment and LP/sham procedure will be documented separately.

- In Section 11.3.1, Adverse Events, "Screening" was changed to "the time of signing of the ICF" to align with other parts of the protocol.

- In Section 12.4, Methods of Analysis for Efficacy Endpoints, the text was modified to correct the details regarding the feasibility of borrowing data from Study CS3B for the analysis of Part B in Study 232SM203.

- In Section 12.4.2, Analysis of the Secondary [redacted] Endpoints in Part B, "total" was added to the HINE Section 2 motor milestone score at Day 302 in Table 7 as was originally intended and to align with Section 4, Study Objectives and Endpoints.

- In Section 12.11, Sample Size Considerations, the text was revised to correct the loading dose of nusinersen that will be administered to participants in Part A and the loading and maintenance dose that will be administered to participants in Part B. This change also affects Section 1.1, Synopsis.

- In Appendix A, Permanent Ventilation Definition Criteria: Acute Reversible Event, the requirement to document the reason for determination of an acute reversible event in the CRF was removed because other sources besides the CRF (e.g., patient notes) may contain this information as well.

LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
BiPAP	bilevel positive airway pressure
CGIC	Clinical Global Impression of Change
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK	creatine kinase
C_{max}	maximum concentration
COVID-19	coronavirus disease
CRF	case report form
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
ECG	electrocardiogram
EOS	end of study
ET	early termination
GCP	Good Clinical Practice
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
LP	lumbar puncture
PASA	Parent Assessment of Swallowing Ability
PedsQL	Pediatric Quality of Life Inventory™
[redacted]	[redacted]
QoL	quality-of-life
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMA-HI	Spinal Muscular Atrophy – Health Index
SMN2	survival motor neuron-2
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 232SM203

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

Version 2

Date: 04 December 2019

EUDRA CT Number: 2019-002663-10

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM203 is to clarify the objectives and endpoints for the different parts of the study (Parts A, B, and C).

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

Section 4, Study Objectives and Endpoints

Now reads:

Part B Primary Objective	**Primary** Endpoint~~s~~
To examine the clinical efficacy of nusinersen administered intrathecally at higher ~~and less frequent~~ doses to participants with SMA**, as measured by change in CHOP INTEND total score**	~~The primary endpoint that relates to this objective is as follows:~~ ~~Part B:~~ 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	~~The secondary endpoints that relate to the primary objective are as follows:~~ ~~Part B:~~ 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 (≥ 16 hours of ventilation/day continuously for

	> 21 days in the absence of an acute reversible event [Appendix A] or tracheostomy) • Time to death (overall survival) ~~Parts A, B, and C:~~ 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 ~~Part C: Infantile-Onset SMA~~ ~~• Change from baseline in CHOP INTEND~~ ~~• Change from baseline in HINE Section 2 motor milestones~~ ~~Part C: Later-Onset SMA~~ ~~•~~ [redacted] ~~• Change from baseline in SMA-HI (participants ≥ 8 years of age only)~~
~~Secondary Objectives~~	~~Secondary Endpoints~~
To examine the safety and tolerability of nusinersen administered intrathecally at higher ~~and less frequent~~ doses to participants with SMA	~~The endpoints that relate to this objective are as follows:~~ ~~Parts A, B, and C:~~ • 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 ~~and less frequent~~ doses compared to the currently approved dose in participants with SMA	~~Parts A, B, and C:~~ Quality of Life • Number and duration of hospitalizations • ~~Change in PedsQL from baseline to Day 302 (later-onset SMA population)~~ • ~~Change in ACEND from baseline to Day 302 (later-onset SMA population)~~ • CGIC (physician, caregiver) at Day 302 • Number of serious respiratory

	events • Proportion of time on ventilation (infantile-onset SMA population) Swallowing • Change in the PASA scale ~~(Parts A and B only)~~
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]-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™; [redacted] PT = prothrombin time; QTcF = corrected QT interval using Fridericia's formula; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; ~~SMA-HI = Spinal Muscular Atrophy Health Index;~~ 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: 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** **Part C only: Infantile-Onset SMA** • **Change from baseline in CHOP INTEND** • **Change from baseline in HINE Section 2 motor milestones** **Part C only: Later-Onset SMA** [redacted]
To examine the effect of nusinersen administered intrathecally at higher doses to participants with SMA	**Quality of Life** • **Number and duration of hospitalizations** • **CGIC (physician, caregiver) at Day 302** • **Number of serious respiratory events** • **Ventilator use (infantile-onset SMA population)** **Swallowing** • **Change in the PASA scale (Part A only)**
[redacted]	

[redacted] 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™; [redacted]; PT = prothrombin time; QTcF = corrected QT interval using Fridericia's formula; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMA-HI = Spinal Muscular Atrophy Health Index; WHO = World Health Organization

Rationale: These changes were made to clarify that the primary objective for Part B is to examine efficacy, as measured by the change from baseline in CHOP INTEND total score. The remaining assessments that will be used to evaluate the clinical efficacy of nusinersen for participants in Part B are secondary endpoints related to a secondary objective, which also has been clarified. A separate table containing the objectives and endpoints for Parts A and C of the study is added to emphasize the differences between Part B and Parts A and C, and to clarify that safety is the primary objective for Parts A and C.

This change also affects Section 12, Statistical Methods and Determination of Sample Size; and Appendix A, Permanent Ventilation Definition Criteria: Acute Reversible Event.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 5, Study Design

Change: Text regarding the Independent Data Monitoring Committee (IDMC) review of Part B safety data was revised.

Now reads:

Continued enrollment into Part B and ~~E~~**e**nrollment into Part C will ~~begin~~**occur** after a ~~safety~~ review by the IDMC of 15 participants in Part B who have available safety **and** [redacted] data through Day 29 (in order to achieve 6 participants who have received 50 mg in the 50/28-mg Group, while maintaining the blind), provided that no safety concerns are identified.

Rationale: While it was originally intended that the IDMC review of the first 15 participants in Part B with Day 29 safety and [redacted] data would determine whether enrollment in this part of the study could continue, this has now been clarified in the protocol.

This change also affects Section 14.2.2, Independent Data Monitoring Committee.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- On the Sponsor Signature Page, the signatory's role was updated.
- In Section 7.3.1, Nusinersen, a reference to the Directions for Handling and Administration (DHA) was added with respect to details on diluting the drug product to the appropriate dosage.
- Typographical errors and formatting were corrected.