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1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec	
Protocol Number:	232SM404	
Version Number:	4.0	
Name of Study Treatment:	Research Name:	BIIB058
	Generic Name:	Nusinersen
	Trade Name:	Spinraza™
Study Phase:	4	
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 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. This study will be conducted in participants with suboptimal clinical status following treatment with onasemnogene abeparvovec (known as onasemnogene abeparvovec-xioi in the US). The study will have a single-arm open-label design and will provide data on clinical outcomes with nusinersen treatment in participants who previously received onasemnogene abeparvovec. The anticipation of additional clinical benefit is based on the possibility for nusinersen to rescue motor neurons that were not transduced by onasemnogene abeparvovec treatment.	

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Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Total HINE Section 2 motor milestones score
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Incidence of AEs and SAEs during the treatment period Change from baseline in clinical laboratory parameters, ECGs, and vital signs
To evaluate clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	WHO motor milestones Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, and RULM Time to death or permanent ventilation (tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event; Appendix A)
To evaluate the PD of nusinersen in participants who previously received onasemnogene abeparvovec	Change from baseline in CSF and plasma levels of NF-L

[redacted]

Study Design:	This is a Phase 4, open-label, multicenter, single-arm study to assess the clinical outcomes, safety, and tolerability of multiple doses of nusinersen administered by IT injection to participants who previously received IV onasemnogene abeparvovec. Participants must not have previously received nusinersen. All participants will undergo a loading period during which they will receive 12 mg nusinersen administered IT by LP on Days 1, 15, 29, and 64, followed by a maintenance period during which the participants will receive 12 mg nusinersen IT by LP approximately every 4 months.

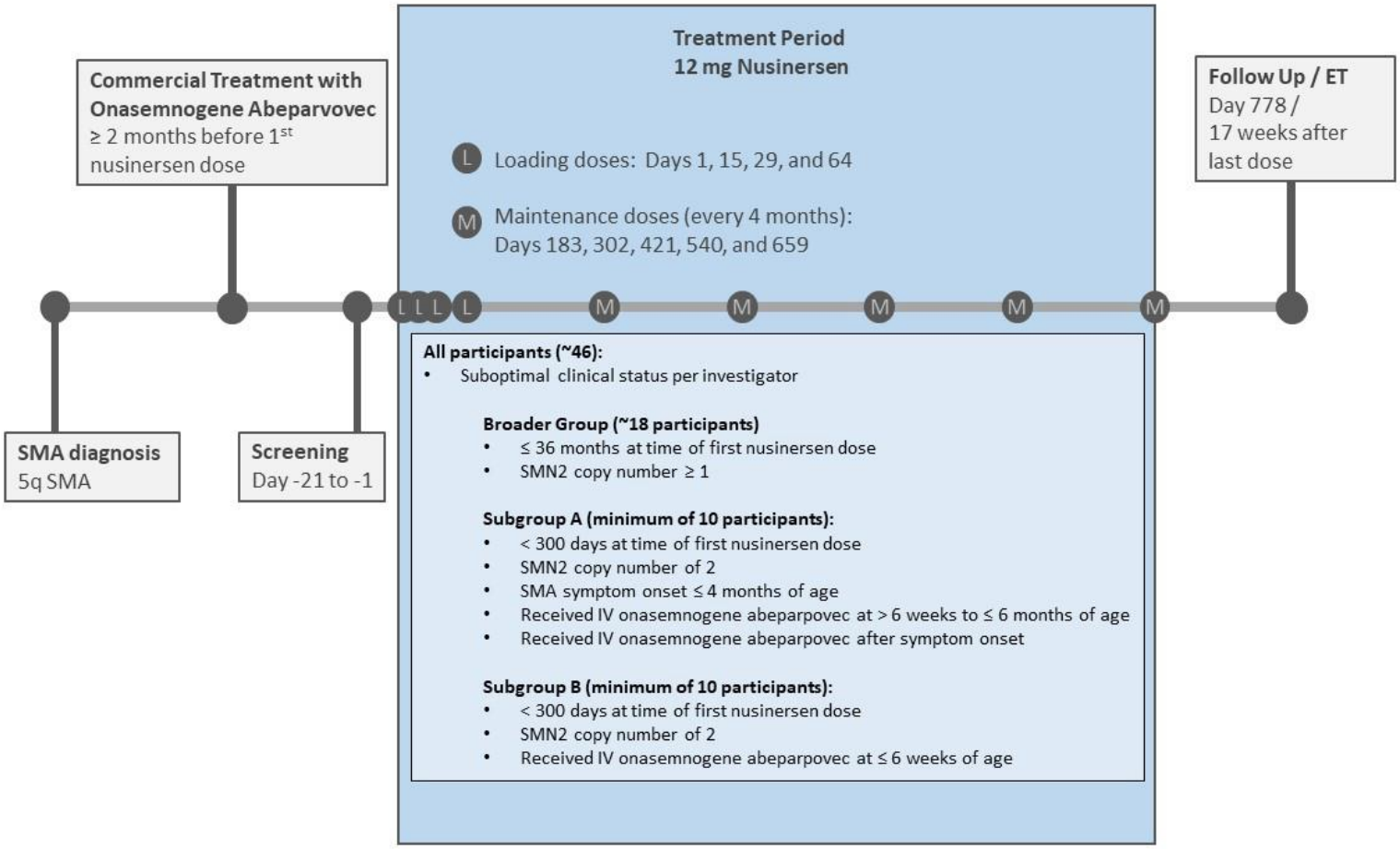
	A total of approximately 46 participants are planned for enrollment. Participants with the broadest entry criteria are herein referred to as the Broader Group and will contribute approximately 18 participants to the overall study population. A total of approximately 28 participants will receive an initial dose of nusinersen at < 300 days of age (Subgroups A and B). Subgroups A and B will each enroll at least 10 participants.
Study Location:	Approximately 20 sites are planned globally.
Study Population:	This study will be conducted in participants with SMA who meet the following criteria: • aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1 • have received onasemnogene abeparvovec (at least 2 months prior to the first nusinersen dose) • who are determined by the Investigator to have suboptimal clinical status Detailed criteria are described in Section 6.
Number of Planned Participants:	Approximately 46 participants will be treated with nusinersen.
Treatment Groups:	All participants will receive open-label nusinersen 12 mg administered IT.
Sample Size Determination:	A total sample size of approximately 46 participants is planned for this study, which is considered sufficient to characterize the clinical response, safety, tolerability, [redacted] of 12 mg nusinersen in participants previously dosed with onasemnogene abeparvovec. A formal sample size calculation was not performed.
Visit Schedule:	Participants will have up to 14 visits during the study. Visit days are calculated with respect to the date of first dose of nusinersen, which is designated as Day 1. Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1). Telephone contact for safety monitoring will occur 1 to 14 days after nusinersen dose as indicated in the Schedule of Activities (Table 1).

Duration of Study Participation:	Study duration for each participant will be approximately 115 weeks: • 3-week screening period (Day -21 to -1) • 95-week treatment period (Day 1 to 659) • 17-week follow-up period (Day 660 to 778)
Diagnostic and Monitoring Procedures:	Genetic testing for SMA is done in this study. Monitoring includes assessments specified in the Schedule of Activities (Table 1).
Benefit-Risk Analysis:	Nusinersen (Spinraza) has a positive benefit-risk profile, with more than 5 years of postmarketing experience and more than 13,000 patients treated. It has been effective in all subgroups tested and has been well tolerated without new or unexpected safety issues identified in any of the subpopulations. However, there are no clinical trial data of nusinersen in patients who have previously been treated with onasemnogene abeparvovec. Risks of participation in the study include clinical assessments of motor function, [redacted], phlebotomy, and LP. These procedural risks are described in Section 3.3.

1.2. Study Design Schematic

See Figure 1 for a schematic of the study design.

Figure 1: Study Design



ET = Early Termination; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.
Note: One month is defined as 30 days in this protocol.

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1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Period	Screening	Treatment										Follow-Up	Visits by Participant Age in Months (±14D)[1]		
Study Day/ Participant Age	D -21 to D -1	D1[2]			D15, D29 (±1D)			D64 (±7D), D183, D302, D421, D540, D659 (±14D)			1 to 14 Days After Each Dose[3]	D778 (±14D) /ET	15	18	24
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose					
Informed Consent[4]	X														
Inclusion/Exclusion Criteria	X	X													
Medical History[5]	X														
SMA Genetic Testing[6]	X							X[7]							
Vital Signs and Pulse Oximetry[8, 9]	X	X		X	X		X	X		X		X			
Weight[9]	X	X			X			X				X		X	
Growth Parameters[9]	X							X[10]				X[10]		X[10]	
Physical Examination[11]	X	X			X			X				X			
Neurological Examination[12]	X	X		X	X		X	X		X		X			
[redacted]															
ECG[9, 13]	X	X						X				X			
SNAP[10, 14]	X							X				X			
Laboratory Safety Tests[9, 10, 15]	X	X			X			X				X			

Study Period	**Screening**	**Treatment**										**Follow-Up**	**Visits by Participant Age in Months (±14D)[1]**		
Study Day/ Participant Age	**D -21 to D -1**	**D1[2]**			**D15, D29 (±1D)**			**D64 (±7D), D183, D302, D421, D540, D659 (±14D)**			**1 to 14 Days After Each Dose[3]**	**D778 (±14D) /ET**	**15**	**18**	**24**
		Pre dose	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**					
Local Coagulation Laboratory Tests[10, 16, 17]	X	X			X			X				X			
Immunogenicity		X						X				X			
[redacted]															
Study Treatment Injection			X			X			X						
Telephone Contact[3]											X				
Ventilator or BiPAP Use Data Recording		X			X			X			X	X			
Ventilator Use Diary[9, 20]	X----------X														
Concomitant Medication and Ancillary Procedure Recording	X----------X														
AE Collection	X----------X														
Efficacy Assessments: Motor Assessments[21]															
CHOP INTEND[11]	X	X						X[10]				X		X	

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Study Period	**Screening**	**Treatment**									**Follow-Up**	**Visits by Participant Age in Months (±14D)[1]**		
Study Day/ Participant Age	**D -21 to D -1**	**D1[2]**			**D15, D29 (±1D)**			**D64 (±7D), D183, D302, D421, D540, D659 (±14D)**			**1 to 14 Days After Each Dose[3]**	**D778 (±14D) /ET**	**15**	**18**	**24**
		Pre dose	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**					
HFMSE[11]	X	X						X[10]				X			
Total HINE Section 2 Motor Milestones[11]	X	X						X[10]				X	X	X	X
WHO Motor Milestones[11, 22]	X	X						X[10]				X	X	X	X
RULM[11]	X	X						X[10]				X			
[redacted]															
Efficacy Assessments: Other															
[redacted]															

Study Period	Screening	Treatment										Follow-Up	Visits by Participant Age in Months (±14D)[1]		
Study Day/ Participant Age	D -21 to D -1	D1[2]			D15, D29 (±1D)			D64 (±7D), D183, D302, D421, D540, D659 (±14D)			1 to 14 Days After Each Dose[3]	D778 (±14D) /ET	15	18	24
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose					
[redacted]															

Note: For RULM, [redacted] if an assessment is not performed at a visit, it may be performed at the next dosing visit but should be recorded as a deviation from the protocol.

[1] Age-based visits are required only for participants < 300 days of age at the time of first nusinersen dose. If the window for an age-based visit overlaps with another scheduled visit, the visits may be combined. One month is defined as 30 days in this protocol.

[2] Assessments (with the exception of coagulation testing) that were performed at Screening within 7 days of the Day 1 dosing visit do not need to be repeated on Day 1 unless results at Screening require reassessment (e.g., abnormal ECG, physical examination findings, out of range laboratory results, etc.). Coagulation testing must be performed at the Day 1 visit regardless of when it was performed prior to Day 1. (See footnote 17 for more details.)

[3] Telephone contact for safety monitoring must occur 1 to 14 days after treatment administration on Days 64, 183, 302, 421, 540, and 659 and every other month during the maintenance period when no treatment administration is planned.

[4] Including any optional consents.

[5] [redacted]

[6] A blood sample will be collected at Screening for SMN2 copy number analysis only from those participants without acceptable genetic documentation of SMN2 copy number.

[7] For all other participants, a blood sample will be collected during the study (preferably before or on the first maintenance dosing visit) for the analysis of both SMN1 copy number and deletion/mutation and SMN2 copy number by the central laboratory.

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

[9] Vital signs, ECG, weight, growth parameters, laboratory safety tests, urine samples, and ventilator use diaries may be collected/assessed in the home setting by qualified personnel within the prespecified visit window, where local regulations allow.

[10] These assessments may be performed up to 7 days prior to dosing, if necessary. Predose safety assessments (laboratory safety tests, SNAP, growth parameters, and coagulation tests) should be repeated if dosing does not occur within the 7-day window. The laboratory safety assessments may be repeated at a local laboratory, if necessary, except at Screening when a central laboratory is required.

[11] Videotaping of motor milestone and function assessments and physical examinations is optional.

[12] HINE Sections 1 and 3 will be administered by the Investigator to participants ≤ 24 months of age, and a standard neurological examination will be performed in participants > 24 months of age. On dosing visits, neurological examination will be performed at 2 timepoints: predose and at approximately 1 hour postdose (or when sedation has worn off, if it was used). Predose neurological examinations should be repeated if the LP does not occur on the same day.

[13] ECG will be assessed at Screening and on Days 1, 302, and 778/ET only.

[14] [redacted] and SNAP will be assessed at Screening and on Days 302 and 778/ET only.

[15] Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. Urine samples may be collected during LP if necessary. Plasma and urine samples (as well as vital signs, ECG, weight, growth parameters, and ventilator use diaries) may be collected in the home setting by qualified personnel within the prespecified visit window, where local regulations allow. 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 at each dosing visit. Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing. See also footnotes 2, 15, and 17.

[17] Predose review of coagulation results must be completed on Day 1 prior to administering nusinersen dose for participants who received onasemnogene abeparvovec ≤3 months prior to the first nusinersen dose. Refer to Section 11.4 for guidance on suspension of dosing beyond the specified INR threshold.

[redacted]

[20] Completion of the daily ventilator use diary is required for the duration of the study only for participants who initiated ventilator use during the study.

[21] Efficacy assessments will be selected by the Investigator according to the criteria in Table 2.

[22] WHO motor milestone assessments will be performed by appropriately trained site personnel, including a physical therapist. During the study period, caregivers will be asked to record the date a participant achieves new milestones.

[redacted]

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[redacted]
[redacted]
[redacted]
[redacted].
[redacted] Ability weekly survey.
[redacted]

2. LIST OF ABBREVIATIONS

[redacted]	[redacted]
[redacted]	[redacted]
AAV	adeno-associated virus
[redacted]	[redacted]
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
anti-HBs	anti-hepatitis B surface antibody
[redacted]	[redacted]
BiPAP	bilevel positive airway pressure
[redacted]	[redacted]
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	confidence interval
[redacted]	[redacted]
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
D	Day
DHA	Directions for Handling and Administration
DILI	drug-induced liver injury
[redacted]	[redacted]
ECG	electrocardiogram
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBc	hepatitis B core antibody
HBs	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	international normalized ratio

IRT	interactive response technology
ISO	international organization for standardization
IT	intrathecal(ly)
IV	intravenous(ly)
LFT	liver function test
LP	lumbar puncture
mRNA	messenger ribonucleic acid
NF-L	neurofilament light subunit
NIST SP	National Institute of Standards and Technology Special Publication
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SNAP	sensory nerve action potential
SUSARs	suspected unexpected serious adverse reactions
UK	United Kingdom
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization

3. INTRODUCTION

Nusinersen is an antisense oligonucleotide administered IT via LP; it increases SMN protein 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 other countries. The population for this study includes participants with SMA who received onasemnogene abeparvovec (known as onasemnogene abeparvovec-xioi in the US).

Onasemnogene abeparvovec (Zolgensma®) is a one-time gene replacement therapy with an AAV vector containing a transgene that encodes human SMN protein. It was approved by the FDA in May 2019 for children under the age of 2 with SMA with bi-allelic mutations in the SMN1 gene and approved by the Japanese Ministry of Health, Labour and Welfare in March 2020. It was also granted conditional approval by the European Medicines Agency in May 2020 for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and either a clinical diagnosis of SMA Type I or up to 3 copies of the SMN2 gene.

3.1. Study Rationale

Nusinersen has demonstrated efficacy and safety across a broad range of SMA phenotypes and patient populations. It is delivered IT and acts by binding to the SMN2 pre-mRNA transcript. This leads to inclusion of exon 7 in the SMN2 mRNA transcripts with resulting increased production of full-length SMN protein. Since receiving FDA approval in December 2016, more than 13,000 patients have been treated with nusinersen.

This study will evaluate nusinersen in participants with SMA who have previously received onasemnogene abeparvovec and have suboptimal clinical status as determined by the Investigator. Preclinical animal models and limited human postmortem studies have demonstrated that onasemnogene abeparvovec transduces only a subpopulation of motor neurons [Foust 2009; Meyer 2015; Thomsen 2021]. Nusinersen has the potential to increase SMN protein in untransduced motor neurons and rescue these motor neurons.

There is emerging real-world evidence of nusinersen being administered to patients who have previously received onasemnogene abeparvovec in clinical trials or commercially. Other than case reports of treatment with onasemnogene abeparvovec and nusinersen [Feldman 2020; Lee 2019], however, there has been no systematic assessment of the clinical outcomes or safety of treatment with nusinersen after onasemnogene abeparvovec. The primary objective of the study is to assess the clinical outcomes of treatment with nusinersen following onasemnogene abeparvovec. Clinical outcomes will be assessed using the total HINE Section 2 motor milestones score.

The secondary objective of this study is to evaluate the safety, tolerability, additional clinical outcomes, and PD of nusinersen treatment in participants with SMA who have previously received onasemnogene abeparvovec.

3.1.1. Rationale for Study Population

Pediatric participants are included in this study as earlier treatment with nusinersen in symptomatic and presymptomatic infants with SMA has been associated with greater clinical benefit. See the Investigator's Brochure for more details.

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It is hypothesized that younger participants who receive onasemnogene abeparvovec and then nusinersen may derive the most benefit compared to onasemnogene abeparvovec alone. See Section 3.2.1 and Section 3.2.2 for additional details.

Participants who have the capacity should provide their assent to participate in the study. See Section 13.4 for additional details.

3.1.2. Rationale for Dosing Regimen

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.

See the Investigator's Brochure for related background data and risk mitigation strategies.

3.1.3. Rationale for the Use of Authorized and/or Unauthorized Auxiliary Medicinal Products

This study does not include the use of auxiliary medicinal products.

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 gene (0 to 8 copies) [Wirth 2006]. The number of SMN*2* copies and the resulting amount of full-length SMN expressed in patients with SMA (10% to 40% of normal SMN protein levels) correlate with SMA disease severity; thus, SMN2 is a key modifier of disease phenotype [Coovert 1997; Feldkötter 2002; Lefebvre 1997; Prior 2004].

3.2.2. Current Therapies for SMA

There are several therapies available for the treatment of SMA. Nusinersen, also referred to as ISIS 396443, BIIB058, or Spinraza™, developed by Biogen is approved for the treatment of SMA in the US (December 2016), EU (5q SMA) [May 2017], and other major markets (5q SMA, infantile SMA, and all other SMAs). The gene transfer agent onasemnogene abeparvovec-xioi (Zolgensma), developed by AveXis and Novartis, is an AAV9 vector expressing

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an SMN1 gene delivered IV. Zolgensma is approved in the US (May 2019) and Japan (March 2020) for the treatment of SMA Type I in patients < 2 years old and in the EU (May 2020) for the treatment of 5q SMA in patients who weigh up to 21 kg. Risdiplam [EVRYSDI® USPI 2022], developed by Genentech, is an oral SMN2-directed splicing modifier approved for the treatment of SMA in pediatrics and adults. It was first approved in the US (August 2020) and has since received approval in other markets.

3.2.3. Profile of Previous Experience With Nusinersen

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

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

Nusinersen was approved for the treatment of SMA under the tradename Spinraza™ in the US, EU, and other countries.

More than 13,000 patients have been treated with nusinersen in the postmarketing setting, expanded access program, and clinical trials worldwide.

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

3.3. Benefit-Risk Assessment

Nusinersen (Spinraza) has a positive benefit-risk profile, with more than 5 years of postmarketing experience and more than 13,000 patients treated. It has been effective in all subgroups tested and has been well tolerated without new or unexpected safety issues identified in any of the subpopulations. However, there are no clinical trial data of nusinersen in patients who have previously been treated with onasemnogene abeparvovec.

Translation of the transgene is not expected to be affected by nusinersen as the transgene does not contain introns.

Risk of Liver Injury

Onasemnogene abeparvovec has high tropism for the liver and can induce an immune response to the viral capsid resulting in elevated liver transaminases, elevated troponin I, or decreased platelet counts. To reduce this reaction, corticosteroids are initiated 1 day before the infusion, continued for at least 30 days, and then tapered off over a period of 28 further days beginning

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once the liver transaminase levels are < 2 × ULN [Zolgensma solution for infusion 2020/SmPC ; Zolgensma USPI 2019].

Nusinersen is metabolized via exonuclease (3'- and 5')-mediated hydrolysis and is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes. Nusinersen administered via IT injection (single and multiple dose) rapidly distributes throughout the CSF space with uptake into CNS tissues followed by transfer via CSF bulk flow to systemic circulation, resulting in drug distribution within peripheral tissues such as skeletal muscle, liver and kidney. The primary route of elimination is likely by urinary excretion. No liver-related effects (including no evidence of hepatic inflammation) were seen in preclinical studies of nusinersen, despite hepatic concentrations of the drug in these animals that were 4- to 21-fold higher than those seen in humans. Considerably higher doses in mice, administered systemically (with liver concentration over 80-fold greater than those in humans) led to only mild elevation in AST (approximately 50%) and ALT (approximately 2-fold or less). Based on these findings, there is no concern for IT-administered nusinersen causing hepatotoxicity in contrast to IV onasemnogene abeparvovec.

Two cases of acute serious liver injury have been reported in patients who had nusinersen as the initial therapy, followed by onasemnogene abeparvovec, followed by the resumption of nusinersen < 2 months later [Feldman 2020]. In the first case, the patient had liver transaminase elevations 3 × ULN prior to obtaining onasemnogene abeparvovec. Maintenance nusinersen was resumed 3 weeks after onasemnogene abeparvovec infusion, and liver failure developed 4 weeks later. An additional patient was reported as presenting with acute liver failure 8 weeks after receiving onasemnogene abeparvovec. Based on the time course and hepatic inflammatory infiltrate, AAV vector-induced immune response as a consequence of onasemnogene abeparvovec treatment was concluded to be the most likely etiology of liver injury in both cases. Both patients had hepatic recovery with steroid therapy.

Amelioration of potential for ongoing or new onasemnogene abeparvovec-induced liver effects (AST and/or ALT levels ≤ 2 × ULN) arising within the dose-shortened interval will be mitigated by patients continuing to receive steroids as specified in the onasemnogene abeparvovec label throughout this period. Furthermore, onasemnogene abeparvovec label-specific monitoring will also be ongoing over the duration of the dose-shortened interval, allowing early detection of any deleterious changes in LFTs. This should permit immediate application of appropriate medical management steps in the event of laboratory signs of liver injury.

Prior to initial nusinersen dosing, participants must have AST and ALT levels that are ≤ 2 × ULN and be naïve to nusinersen. Past history of DILI or hepatic failure are exclusion criteria as well for receiving study treatment with nusinersen. Coagulation assessments will be undertaken predose at each study visit, and test results will be reviewed prior to dosing with nusinersen. Within the dose-shortened interval, where patients may still be at risk for onasemnogene abeparvovec-induced liver injury, the requirement for review of coagulation assessments precludes dosing of patients with nusinersen in situations where coagulation assessments show an INR ratio of > 1.5. Investigators are also advised to maintain a low threshold for consulting hepatologists/gastroenterologists when dosing nusinersen during the dose-shortened interval.

Risk of Coagulation Abnormalities and Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, have been observed after infusion of onasemnogene abeparvovec in clinical trials. In the Phase 1 study [Mendell 2017], a minority of participants reported nonclinically significant platelet decreases that reached a nadir 1 week after dosing. The current recommendations per label are to monitor platelet counts weekly for the first month after infusion and then every other week for the second and third month until platelet counts return to baseline [Al-Zaidy and Mendell 2019; Zolgensma USPI 2019].

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. For example, in sham-controlled nusinersen studies for patients with infantile-onset and later-onset SMA (CS3B and CS4), 24 of 146 (16%) nusinersen-treated patients with high, normal, or unknown platelet count at baseline developed platelet levels < lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients [Spinraza USPI 2017].

In this study, platelet count and coagulation laboratory testing will be performed at baseline, prior to each administration of nusinersen, and as clinically needed. Furthermore, nusinersen will be dosed a minimum of 2 months after onasemnogene abeparvovec, and so any theoretical additive effects on platelet counts are not expected.

Procedural Risks

Participants in this study will be subjected to the known risks of certain procedures, including the following:

- Clinical Assessments of Motor Function: the main risk of the functional clinical measures will be fatigue. Participant's parent or legal guardian will be made aware that the participant may feel tired after these assessments and should be given adequate rest to recover from each measure.
- [redacted] SNAP studies are of minimal risk but can cause some discomfort due to the application of current to generate a motor or sensory response. Participant's parent(s)/legal guardian(s) will be made aware of this potential for transient discomfort.
- Phlebotomy: there will be multiple blood draws involved in this study that could cause bruising and/or pain. There is also a small risk of infection, lightheadedness, and/or fainting.
- LP: this is a standard procedure used in medical practice. The side effects of an LP may include back discomfort, bleeding, headache, pain at the LP site, and infection (including serious infection, such as meningitis). Pain during the LP procedure will be prevented or minimized by using local anesthesia (lidocaine) or IV sedation, if necessary. Infection after an LP is very rare, but serious, and would be treated with antibiotics. Post-LP headaches can be mild to severe and will be managed with analgesics as needed. If the headache is prolonged, a blood patch may be performed. This procedure involves taking blood from the participant and injecting it in the same place where the spinal needle was put in during the LP. The clotting of the blood in this space should stop further fluid

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leaking and stop the headache. Nausea, dizziness, and ringing in the ears may accompany the headache.

All feasible measures will be taken to minimize the risk to the study participants.

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 are provided in the Investigator's Brochure and ICF. A high-level summary of those benefits and risks known during study design is provided here.

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4. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To evaluate the clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Total HINE Section 2 motor milestones score
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Incidence of AEs and SAEs during the treatment period Change from baseline in clinical laboratory parameters, ECGs, vital signs, and other safety assessments
To evaluate clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	WHO motor milestones
	Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, and RULM
	Time to death or permanent ventilation (tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event; Appendix A)
To evaluate the PD of nusinersen in participants who previously received onasemnogene abeparvovec	Change from baseline in CSF and plasma levels of NF-L
[redacted]	



5. STUDY DESIGN

5.1. Study Overview

This open-label, single-arm, interventional study will evaluate the efficacy and safety of nusinersen in approximately 46 participants who previously received IV onasemnogene abeparvovec in a clinical practice setting. The study will be conducted at approximately 20 sites globally.

This study will be conducted in participants with SMA who have previously received onasemnogene abeparvovec treatment and who are determined by the Investigator to have suboptimal clinical status. Participants must have received onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. All participants will be aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1, and have received IV onasemnogene abeparvovec either before or after symptom onset of SMA. One month is defined as 30 days in this protocol.

Of the approximately 46 participants to be recruited in total, approximately 28 will be recruited into Subgroup A or Subgroup B. Approximately 18 participants will be recruited into the Broader Group.

It is hypothesized that younger participants who receive onasemnogene abeparvovec and then nusinersen may derive the most benefit compared to onasemnogene abeparvovec alone. In order to optimize the evaluation of the benefit of nusinersen after receiving onasemnogene abeparvovec, participants with an SMN2 copy number of 2 and first dose of nusinersen at < 300 days of age will be enrolled in Subgroup A or Subgroup B. The maximum age of < 300 days at first nusinersen dose for participants in these subgroups will ensure adequate time to assess suboptimal clinical status after onasemnogene abeparvovec and ensure sufficient time on nusinersen to evaluate the benefit during the critical window for motor milestone achievement.

Subgroup A

Participants who meet the following additional criteria may enroll in Subgroup A:

- Received IV onasemnogene abeparvovec at > 6 weeks to ≤ 6 months (43 days to 180 days) of age.
- < 300 days of age at the time of first nusinersen dose.
- SMN2 copy number of 2.
- SMA symptom onset ≤ 4 months (120 days) of age.
- Must have received IV onasemnogene abeparvovec after SMA symptom onset.

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Subgroup B

Participants who meet the following additional criteria may enroll in Subgroup B:

- Received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age.
- < 300 days of age at the time of first nusinersen dose.
- SMN2 copy number of 2.

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 up to 115 weeks:

- Screening period of up to 21 days
- Treatment period of 95 weeks
- Follow-up period of 17 weeks (approximately 4 months)

Participants will have up to 14 visits during the study. Visits up to Day 29 should be performed ± 1 day from the nominal visit day, the visit on Day 64 should be performed ± 7 days from the nominal visit day, and visits from Day 183 onward and visits based on participant age should be performed ± 14 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, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed, the date may be the date of AE resolution.

5.3. Study Stopping Rules

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. Visits, when occurring on non-visit days, are considered unscheduled visits. The reason for an unscheduled visit should be documented on the CRF.

5.5. Start of Study

The start of the study is the date the first participant signs the ICF.

5.6. End of Study

The end of study is last participant, last visit for final collection of data.

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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. One month is defined as 30 days in this protocol.

6.1. Inclusion Criteria

Inclusion criteria 1 through 10 must be met by all participants:

1. Signed informed consent of parent or guardian. Ability of the participant's legally authorized representative (e.g., parent 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.
2. Genetic documentation of 5q SMA homozygous SMN1 gene deletion or mutation or compound heterozygous mutation.
3. SMN2 copy number of ≥ 1.
4. ≤ 36 months of age (1080 days) at the time of first nusinersen dose.
5. Must have received IV onasemnogene abeparvovec per the approved label or per local/regional regulations, including the steroid regimen and monitoring specified therein.
6. Must have received IV onasemnogene abeparvovec ≥ 2 months prior to first nusinersen dose.
7. Suboptimal clinical status, including meeting ≥ 1 of the following conditions at Screening and Day 1 (see Section 9.1.11):
    a. Suboptimal motor function as determined by the Investigator
    b. Respiratory support as determined by the Investigator
    c. Abnormal swallowing or feeding ability for age as determined by the Investigator
    d. Any other suboptimal clinical status as determined by the Investigator
8. 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.
9. 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).
10. ALT and AST ≤ 2 × ULN at Screening and within 7 days prior to dosing. Repeat testing may be performed if needed (see Section 6.3.2).

The following are additional inclusion criteria that must be met **only** by participants recruited into Subgroups A and B:

11. < 300 days of age at the time of first nusinersen dose.
12. SMN2 copy number of 2.

The following are additional inclusion criteria that must be met **only** by participants recruited into Subgroup A:

13. SMA symptom onset ≤ 4 months (120 days) of age.
14. Must have received IV onasemnogene abeparvovec at > 6 weeks to ≤ 6 months (43 days to 180 days) of age.
15. Must have received IV onasemnogene abeparvovec after SMA symptom onset.

The following are additional inclusion criteria that must be met **only** by participants recruited into Subgroup B:

16. Must have received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age.

6.2. Exclusion Criteria

The following exclusion criteria apply to all participants:

Medical History and Current Health Status

1. Severe or serious AEs related to onasemnogene abeparvovec therapy that were ongoing during Screening.
2. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments, including a history of hydrocephalus or implanted shunt for CSF drainage.
3. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA).
4. History of or current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.
5. Serious infection (e.g., pneumonia, septicemia) that has not completely resolved, as indicated by the absence of signs, symptoms, or ongoing investigations, or remained resolved within 30 days prior to nusinersen dosing.
6. Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection), which have not resolved within 14 days prior to nusinersen dosing. Participants are eligible to be rescreened after successful treatment or resolution of the infection.
7. History of any clinically significant abnormalities that would render the participant unsuitable for inclusion, as determined by the Investigator.
8. Clinically significant abnormal laboratory test (such as thrombocytopenia) at Screening (as determined by the Investigator) that would render the participant unsuitable for inclusion.
9. History of DILI or liver failure.
10. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities.

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11. Permanent ventilation, defined as tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event.
12. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia, and respiratory parameters) that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.
13. Participant's parent or legal guardian is not willing to meet standard-of-care guidelines for care (including vaccinations and RSV prophylaxis if available) nor provide nutritional and respiratory support throughout the study. 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.

Medications

14. Prior exposure to nusinersen
15. Treatment with an investigational drug, 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-directed splicing modifier; prior antisense oligonucleotide treatment or cell transplantation; gene therapy for the treatment of SMA other than onasemnogene abeparvovec. Note: treatment with onasemnogene abeparvovec as part of an investigational study is allowed (per inclusion criterion 5).

Others

16. Plans to undergo elective procedures or surgeries at any time after signing the ICF through the end of the study.
17. Inability to comply with study requirements.
18. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

The following additional exclusion criterion applies **only** to participants recruited into Subgroups A and B:

19. Weight-for-age is below the third percentile, based on WHO Child Growth Standards at the time of receiving onasemnogene abeparvovec. Adjustments for the gestational weight of premature babies enrolled in Subgroups A and B are allowed provided IV onasemnogene abeparvovec was dosed per the approved label or per local/regional regulations.

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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 or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

6.3.2. Retesting

Participants who fail the screening criteria can be retested once. 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.

If ALT and/or AST are > 2 and ≤ 2.5 × ULN during the Screening period, repeat testing may be performed once and ALT and AST must be ≤ 2 × ULN at Screening and within 7 days prior to dosing. Repeat testing may be performed at a local laboratory if necessary.

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently dosed. 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.

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7. STUDY TREATMENT

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

7.1. Regimen

Refer to and follow the DHA for details.

Each participant will receive 4 loading doses of 12 mg of nusinersen administered IT by LP on Days 1, 15, 29, and 64. Maintenance dosing of 12 mg of nusinersen will be administered IT by LP on Days 183, 302, 421, 540, and 659.

All participants will be dosed with 12 mg (5 mL) regardless of age.

Note that injections should not occur within 72 hours after an immunization.

If a loading dose is delayed or missed, nusinersen should be administered as soon as possible, with at least 14 days between doses, and dosing continued at the prescribed dosing frequency. In the maintenance phase, if a planned dose is delayed or missed, nusinersen should be administered as soon as possible and dosing continued at the prescribed dosing frequency. In case of missed dose(s), continuation of the participant in the study should be discussed with the Medical Monitor, and an adjustment in the dose schedule may be permitted per Sponsor discretion.

7.2. 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 vials are for one-time use only; do not use any study treatment remaining in the vial for another participant.

7.2.1. Nusinersen

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

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

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7.2.1.1. Preparation

The individual preparing nusinersen should first 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.

7.2.1.2. Storage

Study treatment must be stored in a secure location.

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

7.2.1.3. Handling and Disposal

The Investigator must return all used and unused vials of nusinersen as instructed by the Sponsor unless approved for on-site destruction.

If any nusinersen supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval by the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor 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.

7.2.1.4. 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 (subject-by-subject 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. By the end of the study, reconciliation must be made between the amount of nusinersen supplied, dispensed, and subsequently destroyed or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3. Precautions

There are no protocol-required treatment precautions.

7.4. Auxiliary Medicinal Products

This study does not use auxiliary medicinal products.

7.5. Compliance

Study treatment will be administered by the site staff.

7.6. Concomitant Therapies 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-directed 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 232SM404.

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 the time the participant is enrolled in the study and the final study visit/telephone call.

7.7. Continuation of Treatment

Nusinersen is an approved treatment, and continued use after completing study requirements will be at the discretion of the participant and Investigator through prescription/commercial sources.

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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'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 experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.
- The participant receives a disallowed concomitant therapy (Section 7.6.1.2).

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

Participants who discontinue treatment will continue follow-up (i.e., regular study visits, but with no postdose safety monitoring visits) unless consent is withdrawn (see Section 8.3) or a participant initiates treatment with a disallowed concomitant therapy. If participants or their caregiver(s) are unable to come for study visits, the minimum requirement for follow-up will be telephone calls on a monthly basis. The methods used to continue follow-up (i.e., site visits or telephone calls to the participant's caregiver) should be documented in the source document.

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 site must attempt to contact the participant's parent(s)/legal guardian(s) and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant's parent(s)/legal guardian(s) 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's parent(s)/legal guardian(s). These contact attempts should be documented in the participant's medical record.

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- Should the participant's parent(s)/legal guardian(s) continue to be unreachable, that participant will be considered to have withdrawn from the study with a 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's parent(s)/legal guardian(s) withdraws consent for participation in the study.
- The participant receives a disallowed concomitant therapy or enrolls in another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered (Section 7.6.1.2).
- The parent(s)/legal guardian(s) are 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.

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9. EFFICACY, [redacted] AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the Schedule of Activities (Table 1).

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:

- Total HINE Section 2 motor milestones
- WHO motor milestones
- CHOP INTEND
- HFMSE
- RULM
- [redacted]
- Daily ventilator use
- [redacted]

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

The Investigator will conduct efficacy assessments based on the criteria described in Table 2.

Table 2: Efficacy Assessment Criteria

Assessment	Criteria
Total HINE Section 2 motor milestones	All participants through end of study.
WHO motor milestones[1] [redacted]	All participants.
[redacted]	[redacted]
CHOP INTEND	Participants < 2 years of age at the time of informed consent Participants 2 to ≤ 3 years of age at the time of informed consent if they did not achieve independent sitting prior to Screening[2]. Participants may discontinue these assessments after Day 421 once they have demonstrated a maximum score at one visit.
HFMSE RULM [redacted]	Participants ≥ 2 years of age (Note: The HFMSE and RULM will be performed in addition to the CHOP INTEND and HINE Section 2 motor milestones if those assessments are continued beyond 2 years of age [see above]).
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[1] WHO motor milestone assessments will be performed by appropriately trained site personnel, including a physical therapist.

[2] Sitting independently is defined as able to sit without support per WHO motor milestones (Test Item No. 1 – Sitting Without Support).

[redacted]

9.1.1. Motor Milestones

The WHO and HINE Section 2 motor milestones will be assessed for all participants through the end of the study. The Investigator must assess the total HINE Section 2 motor milestones. Appropriately trained site personnel, including a physical therapist can assess the WHO motor milestones. Videotaping of the WHO and/or HINE Section 2 motor milestone assessments will be optional. During the study period, caregivers will be asked to record the date a participant achieves a new milestone.

WHO motor milestones will be assessed using the WHO motor milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004].

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 3 to the right side of the table, as denoted by the Milestone Level Progression arrow in the table [Haataja 1999].

Table 3: 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]

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

The CHOP INTEND will be assessed in participants who are < 2 years of age at the time of informed consent or who are 2 to ≤ 3 years of age at the time of informed consent if they did not achieve independent sitting prior to Screening. Participants may discontinue this assessment after Day 421 if they demonstrate a maximum score at one visit. Sitting independently will be defined as able to sit without support per WHO motor milestones (Test Item No. 1 – Sitting Without Support).

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

9.1.3. Hammersmith Functional Motor Scale – Expanded

The HFMSE will be assessed in participants ≥ 2 years of age.

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

9.1.4. Revised Upper Limb Module

The RULM will be assessed in participants ≥ 2 years of age.

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

The purpose of an upper limb scale for use in SMA is to assess the change that occurs in the motor performance of the upper limb over time. Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be impacted by muscle strength, contractures, and maturational development (puberty), and the RULM aims to incorporate the performance of the shoulder, elbow, wrist, and hand. If an assessment is not performed at a visit, it may be performed at the next dosing visit but should be recorded as a deviation from the protocol.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.17. Ventilator Use

Ventilator use will be assessed for all participants who initiate ventilator use.

The participant's ventilator use (number of hours per day, in participants who require ventilatory support) 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.

[redacted]

[redacted]

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 history should include SMA history, onasemnogene abeparvovec dosing history, primary reason for participation in the study (as indicated by the caregiver), and steroid use history. [redacted]
- Physical examinations (videotaping of physical examinations is optional).
- Vital sign measurements: temperature, heart rate, systolic and diastolic blood pressure, respiratory rate, and pulse oximetry.
- ECGs.
- Growth parameters: WHO growth parameters of body length or height (for all participants), head circumference (for participants up to 36 months of age), chest circumference (for participants up to 36 months of age), and arm circumference (for participants up to 36 months of age) will be measured. In participants with scoliosis, arm span may be measured in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. If arm span cannot be measured due to contractures, the Investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist. 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 by the Investigator to participants ≤ 24 months of age at the time of informed consent. A standard neurological examination will be performed in participants > 24 months of age at the time of informed consent and for participants who reach > 24 months of age during their study participation.
- SNAP amplitudes (radial and sural). Sensory nerve conduction studies will be performed to assess the function of sensory nerves/neurons. SNAP will be assessed in the sural and radial nerves unilaterally, in which the amplitude (onset to peak) of the response will be measured at the clinic by the Investigator or designee.

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- Immunogenicity.
- Use of concomitant medications and ancillary procedures.

10.2. Laboratory Safety Assessments

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

The following laboratory tests will be performed to assess the safety profile of nusinersen:

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

AST and ALT samples collected at Screening must be taken at least 72 hours prior to the first dose of nusinersen to allow for laboratory processing timelines. A complete list of laboratory analytes is provided in Appendix B.

10.3. Telephone Assessments

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 1 to 14 days after each nusinersen dose administration on Days 64, 183, 302, 421, 540, and 659. Participants will also be contacted via telephone every other month during the maintenance period when no treatment administration is planned.

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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 the site staff for reporting SAEs, 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 finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal 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 participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the participant's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a 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 of an SAE as defined in Section 11.1.2.
- The relationship of the event to study treatment as defined in Section 11.2.2.
- The severity of the event as defined in Section 11.2.3.

11.2.2. Relationship of Events to Study Treatment

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

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Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug (nusinersen) or the LP procedure if there is not a reasonable possibility that the event has been caused by the product under investigation or LP procedure. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the product or the LP procedure and the AE, the presence of a biologically implausible relationship between the product or the LP 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 drug (nusinersen) or the LP procedure if there is a reasonable possibility that the event may have been caused by the product under investigation or the LP 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 drug or the LP procedure and the AE, a known response pattern of the suspected drug or the LP procedure, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug or the LP 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 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.

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AEs that are 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. 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 must also 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 ongoing when the participant completes the study or discontinues from 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.

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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.

11.4. Procedures for Handling Special Situations

11.4.1. Liver Injury

The risk of liver injury following onasemnogene abeparvovec treatment is discussed in Section 3.3. Investigators should therefore bear in mind the possibility of liver injury with all AEs and consider further investigation at their discretion as needed within the clinical context.

Nusinersen dosing for individual participants should be suspended until discussion with the Sponsor if any of the following circumstances are met:

- platelets are $< 50 \times 10^9$/L.
  - The American Association of Blood Banks guidelines recommend a minimum platelet count for 50×10^9/L for LP. However, Investigators may use their discretion in considering dose suspension for participants with platelet counts $< 75 \times 10^9$/L to $< 100 \times 10^9$/L, if desired.
- INR is > 1.5 (see Table 1 and footnotes for coagulation testing requirements).
- participant experiences a liver-related SAE.

Investigators should have a low threshold for consulting hepatologists/gastroenterologists, particularly when dosing nusinersen < 3 months after receiving onasemnogene abeparvovec.

11.4.2. Overdose

An overdose is any dose of study treatment administered to 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 it 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. Abuse, Misuse, Medication Error, and Accidental or Occupational Exposure

Abuse, misuse, medication error, and accidental or occupational exposure events (defined below) are not considered AEs and should not be recorded as an AE on the CRF; however, all occurrences of abuse, misuse, medication error, and accidental or occupational exposure with study treatment administered must be recorded on a Clinical Trial Special Situation(s) Report form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the event. Abuse, misuse, medication error, and accidental or occupational exposure must be

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reported to the Sponsor from first dose of study treatment to last study visit or telephone contact, even if the event does not result in an AE. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an AE, the AE must be recorded on the CRF. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an SAE, both the SAE and the Clinical Trial Special Situation(s) Report forms must be completed and faxed or emailed to the Sponsor within 24 hours of awareness. All study treatment-related dosing information must be recorded on the dosing CRF.

These events are defined as follows:

Abuse: persistent or sporadic, intentional excessive use of the study treatment that is accompanied by harmful physical or psychological effects.

Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

Medication error: any preventable incident that may cause or lead to inappropriate study treatment use or participant harm while the study treatment is in the control of the healthcare professionals or participants. Such incident may be due to healthcare professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Accidental or occupational exposure: the unintentional exposure to study treatment as a result of the participant's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (i.e., study product administered to the wrong participant).

11.4.4. Medical Emergency

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

11.5. Safety Responsibilities

11.5.1. 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 cases of abuse, misuse, medication error, and accidental or occupational exposure with study treatment administered, and record on a Clinical

Trial Special Situation(s) Report form and fax or email to the Sponsor within 24 hours of the site becoming aware of the event.

- 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.

11.5.2. The Sponsor

Biogen's responsibilities include the following:

- Before a site can enroll any participants, the Site 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, EudraVigilance Database, central ethics committees, and Investigators of SAEs, as required by local law, within the required time frames.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

12.1. General Considerations

12.2. Analysis Sets

The Safety Set will be defined as all participants who received at least 1 dose of nusinersen.

The analysis for efficacy will be performed on the Evaluable Set. The Evaluable Set will be defined as the participants in the Safety Set who also satisfy one of the following conditions:

- Have ⩾ 1 postbaseline efficacy assessment on Day 64 or later after removing any data impacted by the use of any disallowed concomitant therapy, OR
- Discontinued due to AE or death

12.3. Definition of Baseline

Baseline will be defined as the closest available assessment prior to the first dose of nusinersen. For endpoints that are introduced based on age or ability during the study, it may be necessary to define a different baseline as the first evaluable assessment in order to allow summaries over time to be presented.

12.4. Methods of Analysis for Efficacy Endpoints

In general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category. Ninety-five percent CIs will be reported for point estimates as appropriate, such as means or proportions.

12.4.1. Analysis of the Primary Endpoint

The main analysis for efficacy will be performed on the Evaluable Set. Total HINE Section 2 motor milestones score and change from baseline by visit will be presented.

12.4.2. Analysis of the Secondary Endpoints

The main analysis of the secondary endpoints will be performed using the Evaluable Set. Summaries will also be made using the Safety Set. Depending on the number of participants evaluated on each scale, summary statistics or individual participant data may be presented.

The proportion of participants achieving WHO motor milestones will be reported. In addition, for the Evaluable Set, the proportion of participants achieving sitting without support as defined by the WHO motor milestones criteria by 15, 18, and 24 months of age will be reported. This will be repeated for the remaining WHO motor milestones.

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CHOP INTEND score over time and change from baseline will be presented. Total score and changes from baseline to each visit in applicable motor function assessments, HFMSE and RULM, will be presented over time.

A Kaplan-Meier survival curve of the time to death or permanent ventilation will be presented and used to estimate the median time to event and corresponding 95% CI. An event of permanent ventilation will be defined as tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event (Appendix A). The Investigator will determine the date at which a participant is considered to have met the endpoint and enter this date in the CRF. Guidance on how the endpoint will be assessed will be provided in a separate document.

[redacted]

12.6. Methods of Analysis for Pharmacodynamic Endpoints

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

Change from baseline in CSF and plasma levels of NF-L will be summarized at each visit.

[redacted]

12.8. Methods of Analysis for Safety Endpoints

The Safety Set will be used for the analysis of safety.

12.8.1. Adverse Events

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

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 incidence of treatment-emergent AEs will be summarized overall, by severity, and by 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.

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.

12.8.2.1. Electrocardiograms

The number and percentage of participants with ECG shifts from baseline normal to each of the categorical values (normal, abnormal, and abnormal [not AE]) will be summarized.

12.8.2.2. Vital Signs and Pulse Oximetry

The analysis of vital signs and pulse oximetry will focus on clinically significant abnormalities. The number and percentage of participants with clinically relevant postbaseline abnormalities

will be presented. Summary statistics for actual values and change from baseline will also be presented.

12.8.3. SNAP Amplitudes

Changes from baseline to each visit in SNAP amplitudes in the sural and radial nerves will be presented over time using descriptive statistics.

12.9. Methods of Analysis for Immunogenicity Data

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

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

12.10. Interim Analyses

Interim data analyses may be performed to allow for the planning of future studies. Further details of the scope of these analyses will be defined in the statistical analysis plan.

12.11. Sample Size Considerations

It is planned that approximately 46 participants will be dosed, which is considered sufficient to characterize the safety, tolerability, [redacted] of 12 mg nusinersen in participants previously dosed with onasemnogene abeparvovec.

A formal sample size calculation was not performed.

13. ETHICAL REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must conduct the clinical trial in compliance with the protocol, the principles of applicable ICH and GCP guidelines, and the requirements of Clinical Trials Regulation (EU) No. 536/2014 or, if applicable, Clinical Trials Directive 2001/20/EC.

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 re-lock. 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 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 governmental 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, the study site must submit a close-out letter to the ethics committee and the Sponsor.

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13.3. Changes to 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, at any time, may 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.

The Investigator must reassess the participant's capacity to provide informed consent periodically over the course of the study. In the event the participant is no longer cognitively intact and loses capacity to provide informed consent, the Investigator must obtain participant consent of the participant's legally authorized representative (in accordance with local laws and regulations) or withdraw the participant from the study.

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13.5. Participant Data Protection

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

The sponsor for all EU sites is Biogen Idec Research Limited in the UK. The UK is a third country recognized by the European Commission as having an adequate level of data protection under Article 45(3) GDPR; therefore, no further arrangements are necessary for a transfer of pseudonymized trial data between the EU trial sites and Biogen Idec Research Limited. Biogen Idec Research Limited transfers pseudonymized trial data it receives for further research to its affiliates in the US on the basis of EU- and UK-approved Standard Contractual Clauses per Article 46(2)© GDPR.

During the study, participants' race and ethnicity and full date of birth will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). [redacted]

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

The Sponsor will conduct this study and process all personal data according to the Sponsor policies related to data privacy, records retention and disposition, and information security. The Sponsor has developed, implemented, and will maintain a comprehensive, documented information security program that requires the implementation of administrative, physical, and technical safeguards to protect personal data against unauthorized or inappropriate use, access, or transmission. Such technical and organizational measures (including organizational processes and procedures) are designed to protect personal data from unauthorized use or access, accidental loss, damage, destruction, theft, or disclosure, and to ensure that such measures are commensurate with the harm that may result from this. The Sponsor's information security controls are compliant with the NIST SP 800-53 (or the ISO equivalent) framework to protect the confidentiality of personal data.

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In case of a suspected data security breach, the Sponsor will follow the procedure outlined in its data privacy and information security policies, which require immediate reporting to the Sponsor's Global Privacy Office so that risk and next steps (including reporting to data protection authorities and/or data subjects) can be assessed.

13.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials 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 by 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 poststudy 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 off-site facility or transfer of ownership if the Investigator leaves the site.

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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 administrative aspects of the study, including but not limited to, study initiation, management of SAE reports, and monitoring.

14.1.2. Interactive Response Technology

IRT will be used in this study. 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 Sponsor and hosted by Medidata.

14.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by the Sponsor to analyze all hematology, blood chemistry, urinalysis, and CSF samples collected for this study. [redacted]

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

14.2. Study Committees

14.2.1. Independent Data Monitoring Committee

Safety data will be reviewed on an ongoing basis by the Sponsor. Safety data will also be reviewed on an ongoing basis by an IDMC, and the IDMC may provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

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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 on-site 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 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 (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 participant 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 study site and its facilities.

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15.4. Study Funding

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

15.5. 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, "A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec," 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 (*DD MMM YYYY*)

_____

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 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.

One of the secondary endpoints 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) meets 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 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 HBsAg)
    - 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), 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.

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APPENDIX B. LABORATORY ANALYTES

Clinical Safety Assessments (Minimum Requirements)		Other Assessments
Blood Chemistry Sodium Potassium Chloride Total protein Albumin Calcium Phosphorus Bicarbonate Glucose Blood urea nitrogen Creatinine Creatine phosphokinase and/or Creatine kinase Cystatin C Total serum bilirubin (direct and indirect) Alkaline phosphatase AST ALT GGT	Urinalysis Specific gravity pH Protein Glucose Ketones Bilirubin Blood RBC WBC Epithelial cells Bacteria Casts Crystals Hematology Red blood cells Hemoglobin Hematocrit Platelets WBCs WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	[redacted] Immunogenicity Evaluation Plasma anti-nusinersen antibodies **The following are to be assessed by local laboratory only:** Urine total protein (quantitative) Coagulation (activated partial thromboplastin time, prothrombin time, and international normalized ratio)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted]; [redacted]; GGT = gamma glutamyl transferase; [redacted]; [redacted]; RBC = red blood cell; [redacted]; WBC = white blood cell.

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AMENDMENT SUMMARY

Biogen Protocol 232SM404

A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec

Version 4.0

Date: 08 November 2023

EU TRIAL Number: 2023-505640-18

EUDRA CT Number: 2020-003492-18

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM404 is to change the total number of participants planned for enrollment and the minimum number of participants in Subgroups A and B. Additionally, the age for inclusion in Subgroups A or B was changed from ≤ 9 months to < 300 days.

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

Section 5.1, Study Overview

Now reads:

This open-label, single arm, interventional study will evaluate the efficacy and safety of nusinersen in approximately ~~60~~**46** participants who previously received IV onasemnogene abeparvovec in a clinical practice setting. The study will be conducted at approximately ~~30~~**20** sites globally.

This study will be conducted in participants with SMA who have previously received onasemnogene abeparvovec treatment and who are determined by the Investigator to have suboptimal clinical status. Participants must have received onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. All participants will be aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1, and have received IV onasemnogene abeparvovec either before or after symptom onset of SMA. One month is defined as 30 days in this protocol.

Of the approximately ~~60~~**46** participants to be recruited in total, ~~40~~**approximately 28** will be recruited into Subgroup A or Subgroup B. ~~A total of 20~~**Approximately 18** participants will be recruited into the Broader Group~~; approximately 6 participants 12 to 24 months old and approximately 6 participants > 24 months~~.

It is hypothesized that younger participants who receive onasemnogene abeparvovec and then nusinersen may derive the most benefit compared to onasemnogene abeparvovec alone. In order to optimize the evaluation of the benefit of nusinersen after receiving onasemnogene abeparvovec, participants with an SMN2 copy number of 2 and first dose of nusinersen at ~~≤ 9 months~~**< 300 days** of age will be enrolled in Subgroup A or Subgroup B. The maximum age of ~~9 months~~**< 300 days** at first nusinersen dose for participants in these subgroups will ensure adequate time to assess suboptimal clinical status after onasemnogene abeparvovec and ensure sufficient time on nusinersen to evaluate the benefit during the critical window for motor milestone achievement.

Subgroup A

Participants who meet the following additional criteria may enroll in Subgroup A:

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- Received IV onasemnogene abeparvovec at > 6 weeks to ≤ 6 months (43 days to 180 days) of age.
- ~~≤ 9 months~~**< 300 days of age** ~~(270 days)~~ at the time of first nusinersen dose.
- SMN2 copy number of 2.
- SMA symptom onset ≤ 4 months (120 days) of age.
- Must have received IV onasemnogene abeparvovec after SMA symptom onset.

Subgroup B

Participants who meet the following additional criteria may enroll in Subgroup B:

- Received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age.
- ~~≤ 9 months of age (270~~**< 300 days of age**~~)~~ at the time of first nusinersen dose.
- SMN2 copy number of 2.

See Figure 1 for a schematic of the study design.

Rationale: The total number of participants was updated to end enrollment in the study. The cut-off age for inclusion into Subgroups A and B was updated to increase the number of participants in Subgroups A and B.

These changes also affect Figure 1, Study Design; Table 1, Schedule of Activities; Section 6, Study Population; Section 6.1, Inclusion Criteria; [redacted]; and Section 12.11, Sample Size Considerations.

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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 3.1.1, Rationale for Study Population; Section 3.1.2, Rationale for Dosing Regimen; and Section 3.1.3 Rationale for the Use of Authorized and/or Unauthorized Auxiliary Medicinal Products

Change: Section 3.1.1 Rationale for Study Population; Section 3.1.2 Rationale for Dosing Regimen; and Section 3.1.3, Rationale for the Use of Authorized and/or Unauthorized Auxiliary Medicinal Products were added.

Now reads:

3.1.1. Rationale for Study Population

Pediatric participants are included in this study as earlier treatment with nusinersen in symptomatic and presymptomatic infants with SMA has been associated with greater clinical benefit. See the Investigator's Brochure for more details.

It is hypothesized that younger participants who receive onasemnogene abeparvovec and then nusinersen may derive the most benefit compared to onasemnogene abeparvovec alone. See Section 3.2.1 and Section 3.2.2 for additional details.

Participants who have the capacity should provide their assent to participate in the study. See Section 13.4 for additional details.

3.1.2. Rationale for Dosing Regimen

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.

See the Investigator's Brochure for related background data and risk mitigation strategies.

3.1.3. Rationale for the Use of Authorized and/or Unauthorized Auxiliary Medicinal Products

This study does not include the use of auxiliary medicinal products.

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Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

This change also affects Section 13.4, Informed Consent.

Section 4, Study Objectives and Endpoints

Change: Change from baseline in CSF and plasma levels of NF-L was added as a secondary endpoint.

Now reads:

4. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To evaluate the clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Total HINE Section 2 motor milestones score
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Incidence of AEs and SAEs during the treatment period Change from baseline in clinical laboratory parameters, ECGs, vital signs, and other safety assessments
To evaluate clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	WHO motor milestones
	Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, and RULM
	Time to death or permanent ventilation (tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event; Appendix A)
To evaluate the PD of nusinersen in participants who previously received onasemnogene abeparvovec	**Change from baseline in CSF and plasma levels of NF-L**
[redacted]	

[redacted]

Rationale: [redacted]

This change also affects Section 3.1, Study Rationale; Section 9.3, Pharmacodynamic Assessments; Section 12.6, Methods of Analysis for Pharmacodynamic Endpoints; [redacted]; and Appendix B, Laboratory Analytes.

Section 5.5, Start of Study

Change: Section 5.5, Start of Study was added.

Now reads:

5.5. Start of Study

The start of the study is the date the first participant signs the ICF.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

Section 7.4, Auxiliary Medicinal Products

Change: Section 7.4, Auxiliary Medicinal Products was added.

Now reads:

7.4. Auxiliary Medicinal Products

This study does not use auxiliary medicinal products.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

[redacted]

Section 11.4.3, Abuse, Misuse, Medication Error, and Accidental or Occupational Exposure

Change: Section 11.4.3, Abuse, Misuse, Medication Error, and Accidental or Occupational Exposure was added.

Now reads:

11.4.3. Abuse, Misuse, Medication Error, and Accidental or Occupational Exposure

Abuse, misuse, medication error, and accidental or occupational exposure events (defined below) are not considered AEs and should not be recorded as an AE on the CRF; however, all occurrences of abuse, misuse, medication error, and accidental or occupational exposure with study treatment administered must be recorded on a Clinical Trial Special Situation(s) Report form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the event. Abuse, misuse, medication error, and accidental or occupational exposure must be reported to the Sponsor from first dose of study treatment to last study visit or telephone contact, even if the event does not result in an AE. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an AE, the AE must be recorded on the CRF. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an SAE, both the SAE and the Clinical Trial Special Situation(s) Report forms must be completed and faxed or emailed to the Sponsor within 24 hours of awareness. All study treatment-related dosing information must be recorded on the dosing CRF.

These events are defined as follows:

Abuse: persistent or sporadic, intentional excessive use of the study treatment that is accompanied by harmful physical or psychological effects.

Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

Medication error: any preventable incident that may cause or lead to inappropriate study treatment use or participant harm while the study treatment is in the control of the healthcare professionals or participants. Such incident may be due to healthcare professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Accidental or occupational exposure: the unintentional exposure to a study treatment as a result of the participant's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (i.e., study product administered to the wrong participant).

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Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

Section 11.5, Safety Responsibilities

Change: Section 11.5, Safety Responsibilities was updated.

Now reads:

11.5.1. 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 cases of abuse, misuse, medication error, and accidental or occupational exposure with any study treatment administered, and record on a Clinical Trial Special Situation(s) Report form and fax or email to the Sponsor within 24 hours of the site becoming aware of the event.**
- 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.

11.5.2. The Sponsor

Biogen's responsibilities include the following:

- Before a site can enroll any participants, the Site 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.

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- The Sponsor is to notify all appropriate regulatory authorities, **EudraVigilance Database,** central ethics committees, and Investigators of SAEs, as required by local law, within the required time frames.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

Section 13, Ethical Requirements

Change: Text regarding Clinical Trials Regulation (EU) No. 536/2014 or, if applicable, Clinical Trials Directive 2001/20/EC was added.

Now reads:

The Sponsor, any contracted third party, and the Investigator must ~~comply~~ **conduct the clinical trial in compliance** with ~~this~~**the protocol, the principles of** applicable ICH and GCP guidelines**, and the requirements of Clinical Trials Regulation (EU) No. 536/2014 or, if applicable, Clinical Trials Directive 2001/20/EC.**

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 re-lock. 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.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

Section 13.4, Informed Consent

Change: Text regarding periodically obtaining informed consent was added.

Now reads:

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.

The Investigator must reassess the participant's capacity to provide informed consent periodically over the course of the study. In the event the participant is no longer cognitively intact and loses capacity to provide informed consent, the Investigator must obtain participant consent of the participant's legally authorized representative (in accordance with local laws and regulations) or withdraw the participant from the study.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

Section 13.5, Participant Data Protection

Change: Additional details regarding participant data protection were added. The full date of birth was clarified.

Now reads:

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

The sponsor for all EU sites is Biogen Idec Research Limited in the UK. The UK is a third country recognized by the European Commission as having an adequate level of data protection under Art. 45(3) GDPR; therefore, no further arrangements are necessary for a transfer of pseudonymized trial data between the EU trial sites and Biogen Idec Research Limited. Biogen Idec Research Limited transfers pseudonymized trial data it receives for further research to its affiliates in the US on the basis of EU- and UK-approved Standard Contractual Clauses per Article 46(2)© GDPR.

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

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

The Sponsor will conduct this study and process all personal data according to the Sponsor policies related to data privacy, records retention and disposition, and information security. The Sponsor has developed, implemented, and will maintain a comprehensive, documented information security program that requires the implementation of administrative, physical, and technical safeguards to protect personal data against unauthorized or inappropriate use, access, or transmission. Such technical and organizational measures (including organizational processes and procedures) are designed to protect personal data from unauthorized use or access, accidental loss, damage, destruction, theft, or disclosure, and to ensure that such measures are commensurate with the harm that may result from this. The Sponsor's information security controls are compliant with the NIST SP 800-53 (or the ISO equivalent) framework to protect the confidentiality of personal data.

In case of a suspected data security breach, the Sponsor will follow the procedure outlined in its data privacy and information security policies, which require immediate reporting to the Sponsor's Global Privacy Office so that risk and next steps (including reporting to data protection authorities and/or data subjects) can be assessed.

Rationale: This change was made in accordance with EU CTR No. 536/2014 guidance.

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.
- Sponsor Information was updated.
- The Sponsor Signature page was updated.
- The List of Abbreviations was updated.
- In Section 1.1, Synopsis, diagnostic and monitoring procedures were added.
- In Section 3.1, Study Rationale, the Foust 2010 publication was removed and replaced with the Meyer 2015 publication. This change also affected Section 16, References.
- Section 6.1, Inclusion Criteria, was corrected so that the first inclusion criterion was included as a numbered item. Note: This may have been implemented by an administrative update to the protocol and/or protocol clarification letter.
- In Section 12.2, Analysis Sets, "Efficacy Set" was changed to "Evaluable Set." This change also affected Section 12.4, Methods of Analysis for Efficacy Endpoints; Section 12.4.1, Analysis of the Primary Endpoint; Section 12.4.2, Analysis of the Secondary Endpoint; [redacted].

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
[redacted]	[redacted]
CRF	case report form
CSF	cerebrospinal fluid
ECG	electrocardiogram
ET	Early Termination
EU	European Union
EU CTR	European Union Clinical Trials Regulation
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HFSME	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
ICF	informed consent form
ICH	International Council for Harmonisation
ISO	international organization for standardization
IV	intravenous(ly)
NF-L	neurofilament light subunit
NIST SP	National Institute of Standards and Technology Special Publication
[redacted]	[redacted]
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
UK	United Kingdom
US	United States
[redacted]	[redacted]
WHO	World Health Organization

REFERENCES

[redacted]

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AMENDMENT SUMMARY

Biogen Protocol 232SM404

A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec

Version 3.0

Date: 17 June 2022

EUDRA CT Number: 2020-003492-18

Version 3.0 of the protocol has been prepared for this amendment, which supersedes previous Version 2.0 dated 15 July 2021

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PRIMARY REASON FOR AMENDMENT

The main reason for this amendment to Protocol 232SM404 is to add a new subgroup (Subgroup B) to adapt to evolving real-world clinical practice including the increased availability of newborn screening for SMA. The advancement of newborn screening has allowed physicians to diagnose SMA earlier, even before the onset of clinical symptoms and, therefore, patients have the potential to receive treatment like onasemnogene abeparvovec early. The addition of Subgroup B will allow for the evaluation of nusinersen in participants treated early with onasemnogene abeparvovec (≤ 6 weeks of age). The total number of participants enrolled in this study will not increase from previous estimations.

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

Section 5.1, Study Overview

This study will be conducted in participants with SMA who have previously received onasemnogene abeparvovec treatment and who are determined by the Investigator to have suboptimal clinical status ~~and the potential for additional clinical improvement~~. Participants must have received onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. All participants will be aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1, and have received **IV** onasemnogene abeparvovec either ~~when symptomatic~~ **before or** ~~presymptomatic for~~ **after symptom onset** of SMA. **One month is defined as 30 days in this protocol.**

Of the approximately 60 participants to be recruited in total, 40 will be recruited into Subgroup A~~. Of the remaining~~ **or Subgroup B**. **A total of** 20 participants~~,~~ **will be recruited into the Broader Group;** approximately 6 participants ~~will be~~ 12 to 24 months old and approximately 6 participants ~~will be~~ > 24 months old at first nusinersen dose.

It is hypothesized that younger participants who receive ~~nusinersen and~~ onasemnogene abeparvovec ~~in short succession~~ **and then nusinersen** may derive the most benefit compared to onasemnogene abeparvovec alone. **In order to optimize the evaluation of the benefit of nusinersen after** receiving **onasemnogene abeparvovec, participants with an SMN2 copy number of 2 and first dose of nusinersen at ≤ 9 months of age will be enrolled in Subgroup A or Subgroup B**. The maximum age of 9 months **at first nusinersen dose** for participants in ~~this~~ **these** subgroup**s** will ensure **adequate time to assess suboptimal clinical status after onasemnogene abeparvovec and ensure** sufficient **time on** nusinersen to **evaluate the** benefit during the critical window for motor milestone achievement.

~~To optimize exploration of the benefit of nusinersen after onasemnogene abeparvovec, Subgroup A will contain participants who meet all of the following additional criteria:~~

Subgroup A

Participants who meet the following additional criteria **may enroll in Subgroup A**:

- **Received IV onasemnogene abeparvovec at > 6 weeks to ≤ 6 months (43 days to 180 days) of age.**
- **≤** 9 months **of age (270 days)** at the time of first nusinersen dose.
- SMN2 copy number of 2.
- SMA symptom onset ≤ 4 months **(120 days)** of age.
- Must have received IV onasemnogene abeparvovec after SMA symptom onset.

Subgroup B

Participants who meet the following additional criteria may enroll in Subgroup B:

- **Received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age**.
- **≤ 9 months of age (270 days) at the time of first nusinersen dose.**
- **SMN2 copy number of 2.**

Rationale: A diagnosis of SMA at or close to birth is becoming more common, and patients with SMA are receiving IV onasemnogene abeparvovec at ≤ 6 weeks of age more frequently. To be more representative of the patient population who intend to use nusinersen, participants who were diagnosed with SMA and received IV onasemongene abeparvovec at ≤ 6 weeks of age will be included in Subgroup B. The key study criteria for each subgroup are listed in Table 1.

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Table 1: Key Study Criteria

Criterion	Broader Group	Subgroup A	Subgroup B
Dosing between IV OA and first nusinersen dose	≥ 2 months		
Suboptimal Clinical Status as determined by the Investigator	Required		
SMN2 copy	≥ 1	2	
Age at OA dose	≤ 36 months (1080 days) of age before or after SMA symptom onset	> 6 weeks to ≤ 6 months (43 to 180 days) of age **after** SMA symptom onset	≤ 6 weeks (42 days) of age before or after SMA symptom onset
Age of SMA symptom onset	Not applicable	≤ 4 months of age (120 days)	Not applicable
Age at first nusinersen dose	≤ 36 months (1080 days)	≤ 9 months of age (270 days)	

OA = IV onasemnogene abeparvovec

Section 6.1, Inclusion Criteria

Now reads:

The following are additional inclusion criteria that must be met **only** by participants recruited into Subgroup**s** A **and B**:

11. ≤ 9 months **of age (270 days)** at the time of first nusinersen dose.

12. SMN2 copy number of 2.

The following are additional inclusion criteria that must be met only by participants recruited into Subgroup A:

13. SMA symptom onset ≤ 4 months **(120 days)** of age.

14. Must have received IV onasemnogene abeparvovec at **> 6 weeks to** ≤ 6 months **(43 days to 180 days)** of age.

15. Must have received IV onasemnogene abeparvovec after SMA symptom onset.

The following are additional inclusion criteria that must be met only by participants recruited into Subgroup B:

16. Must have received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age.

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Section 12.2, Analysis Sets

The Efficacy Set will be defined as all participants within Subgroup**s** A **and B** who received at least 1 dose of nusinersen and **satisfy one of the following conditions:**

- **Have ≥ 1 postbaseline efficacy assessment on Day 64 or later after removing any data impacted by the use of any disallowed concomitant therapy, OR**
- **Discontinued due to AE or death**

Section 12.4, Methods of Analysis for Efficacy Endpoints

In general, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category. Ninety-five percent CIs will be reported for point estimates as appropriate, such as means or proportions. **The analysis for efficacy will present Subgroups A and B separately.**

Section 12.11, Sample Size Considerations

A **total** sample size of 40 participants in Subgroup**s** A **and B** will allow the 95% CI for the primary endpoint of total HINE Section 2 motor milestones score to be estimated with a halfwidth ± 2.05, assuming a standard deviation of 6.4.

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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, and Section 1.2 Study Design Schematic

The synopsis and study design schematic were revised to reflect changes made throughout the protocol.

Section 4, Study Objective and Endpoints, [redacted]

[redacted].

[redacted]

Section 8.1, Discontinuation of Study Treatment

Change: Treatment with a disallowed concomitant medication would require permanent study termination

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

1. The participant's parent(s)/legal guardian(s) withdraws consent to continue study treatment.
2. The participant experiences an AE that necessitates permanent discontinuation of study treatment.
3. The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment.
4. At the discretion of the Investigator for medical reasons.
5. At the discretion of the Investigator or Sponsor for noncompliance.
6. **The participant receives a disallowed concomitant therapy (Section 7.5.1.2).**

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

Participants who discontinue treatment will continue follow-up (i.e., regular study visits, but with no postdose safety monitoring visits) unless consent is withdrawn (see Section 8.3) **or a participant initiates treatment with a disallowed concomitant therapy**.

Rationale: Participants who receive a disallowed concomitant therapy and continue study treatment could adversely affect the safety of the participant; therefore, discontinuation of study treatment for those participants who are treated with a disallowed concomitant therapy is intended to protect the safety of the study participants. Additionally, the withdrawal of those participants who are treated with a disallowed concomitant therapy will protect the integrity of the study (e.g., evaluation of the primary and secondary objectives).

This change also affects Section 8.3, Withdrawal of Participants From the Study.

Section 8.3, Withdrawal of Participants From the Study

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

- The participant's parent(s)/legal guardian(s) withdraws consent for participation in the study.
- The participant **receives a disallowed concomitant therapy or** enrolls in~~to~~ another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered **(Section 7.5.1.2)**.
- The parent(s)/legal guardian(s) are unwilling or unable to comply with the protocol.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- Clarified 1 month is equivalent to 30 days within the protocol.
- The number of patients treated with nusinersen in a postmarketing setting was updated to 13,000 patients for more than 5-years.
- IV onasemnogene abeparvovec must be given according to the approved local/regional regulations instead of local guidelines.
- Table 1: Schedule of Activities: footnote 9 added that laboratory safety tests can be performed at home by qualified personnel where local regulations allow but not plasma samples. Footnote 10 added that laboratory safety assessments may be repeated at a local laboratory, if necessary, except at Screening when a central laboratory is required. It also added that predose safety assessments (SNAP and growth parameters should be repeated if dosing does not occur within the 7-day window (and [redacted] and immunogenicity assessments). Footnote 11 added optional videotaping to CHOP INTEND, HFMSE, Total HINE Section 2 motor milestones, WHO motor milestones, RULM, [redacted], [redacted], [redacted], and [redacted]. Footnote 16 removed that coagulation testing could be done within 7 days prior to dosing. Footnote 20 clarified that the completion of the daily ventilator use diary is required only for participants who have initiated ventilator use for the duration of the study. Footnote 22 added that the WHO motor milestone assessment will be performed by appropriately trained site personnel, including a physical therapist. [redacted]
- Section 3.1, Study Rationale, was updated to include preclinical animal models, and limited human postmortem studies have demonstrated that onasemnogene abeparvovec transduces only a subpopulation of motor neurons.
- Section 3.2.2, Current Therapies for SMA: the risdiplam USPI 2022 was added as a reference along with its approved indication.
- Section 4, Study Objectives and Endpoints; Section 9.3, Pharmacodynamic Assessments; [redacted] and Appendix B, Laboratory Analytes: references to pNF-H and NF-L were changed to neurofilaments.
- Section 6.2, Exclusion Criteria, number 19 included Subgroup B to the additional exclusion criterion applied to Subgroup A for weight-for-age below the third

percentile based on WHO Child Growth Standards at the time of receiving onasemnogene abeparvovec. Adjustments for the gestational weight of premature babies enrolled in Subgroups A and B are allowed, provided IV onasemnogene abeparvovec was dosed per the approved label or per local/regional regulations.

- Section 7.5.1.2, Disallowed Concomitant Therapy, was updated to add that participants are prohibited from receiving SMN2-directed splicing modifier or entering another interventional study during Study 232SM404.

- Section 8.1, Discontinuation of Study Treatment, and [redacted]

- Section 9.1.1, Motor Milestones: the WHO and HINE Section 2 motor milestones will be assessed for all participants through the end of the study. The Investigator must assess the total HINE Section 2 motor milestones. Appropriately trained site personnel, including a physical therapist can assess the WHO motor milestones (also added in Table 1 and Table 2). Also clarified that caregivers will be asked to record the date a participant achieves a new milestone.

[redacted]

- Section 10.1, Clinical Safety Assessments, added that a neurological examination will be performed for participants who reach > 24 months of age during study participation in addition to those > 24 months at the time of informed consent.

- Section 10.2, Laboratory Safety Assessments, included that AST and ALT samples collected at Screening must be taken at least 72 hours prior to the first dose of nusinersen to allow for laboratory processing timeline.

- Appendix B, Laboratory Analytes, was updated to clarify that urine total protein will be a quantitative assessment.

- The name and credential of the Sponsor signatory have been updated.

- The version number and date were updated throughout the protocol.

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- Abbreviations that were inadvertently spelled out or not in the list of abbreviations in the previous protocol were corrected.

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
CI	confidence interval
HINE	Hammersmith Infant Neurological Examination
IV	intravenous(ly)
NF-L	neurofilament light subunit
[redacted]	[redacted]
pNF-H	phosphorylated neurofilament heavy subunit
SMA	spinal muscular atrophy
SMN2	survival motor neuron 2
SNAP	sensory nerve action potential
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 232SM404

A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec

Date: 15 July 2021

EUDRA CT Number: 2020-003492-18

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.0 dated 01 September 2020.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 232SM404 is to revise the inclusion to reduce the dosing interval between onasemnogene abeparvovec and first nusinersen dose from at least 3 months to at least 2 months. Thus, the study population has been expanded to include participants with SMA who have received IV onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. Additionally, exclusion of steroid use for liver abnormalities was removed. Safety laboratory requirements for ALT and AST levels were revised, and procedures for handling special situations of liver injury were expanded to include platelet and INR specifications and guidance.

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

Section 6.1, Inclusion Criteria

Change: Text was updated to reflect shortened interval in dosing (from ≥ 3 months to ≥ 2 months between onasemnogene abeparvovec and first nusinersen dose. Additionally, ALT and AST inclusion levels were revised, and criteria were reordered.

Now reads:

~~The following inclusion~~ **Inclusion** criteria **1 through 10** must be met by all participants:

1. Signed informed consent of parent or guardian. Ability of the participant's legally authorized representative (e.g., parent 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.

~~2. Maximum age of 36 months at the time of first nusinersen dose.~~

~~3.~~**2.** Genetic documentation of 5q SMA homozygous SMN1 gene deletion or mutation or compound heterozygous mutation.

~~4.~~**3.** SMN2 copy number of ≥ 1.

4. Maximum age of 36 months at the time of first nusinersen dose.

5. Must have received IV onasemnogene abeparvovec per the approved label or per local guidelines including the steroid regimen and monitoring specified therein.

6. Must have received IV onasemnogene abeparvovec ≥ ~~3~~**2** months prior to first nusinersen dose.

7. Suboptimal clinical status, including meeting ≥ 1 of the following conditions at Screening and Day 1 (see Section 9.1.11):

a. Suboptimal motor function as determined by the Investigator
b. Respiratory support as determined by the Investigator
c. Abnormal swallowing or feeding ability for age as determined by the Investigator
d. Any other suboptimal clinical status as determined by the Investigator

8. 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.

9. 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).

10. ALT and AST ≤ ~~1.5 ×~~**2** × ULN ~~during~~ **at** Screening **and within 7 days prior to dosing**. Repeat testing may be performed if needed (see Section 6.3.2).

The following **are** additional inclusion criteria **that** must be met **only** by participants recruited into Subgroup A:

11. Maximum age of 9 months at the time of first nusinersen dose.

12. SMN2 copy number of 2.

13. SMA symptom onset ≤ 4 months of age.

14. Must have received IV onasemnogene abeparvovec at ≤ 6 months of age.

15. Must have received IV onasemnogene abeparvovec after SMA symptom onset.

Section 6.2, Exclusion Criteria

The following exclusion criteria apply to all participants:

Medical History and Current Health Status

1. Severe or serious AEs related to onasemnogene abeparvovec therapy that were ongoing during Screening.

2. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments, including a history of hydrocephalus or implanted shunt for CSF drainage.

~~3. Use of steroids for liver function abnormalities within 1 month prior to first dose of nusinersen.~~

Rationale: Results from the nusinersen clinical development program demonstrated improved clinical outcomes for infantile-onset SMA, with more rapid achievement of motor milestones and diminished disease severity, when therapy is administered at an early age and earlier in the disease course. Amending the RESPOND protocol to shorten the dosing interval between onasemnogene abeparvovec and first nusinersen dose from ≥ 3 months to ≥ 2 months aims to maximize the potential to rescue motor neurons and optimize treatment outcomes in participants who have demonstrated suboptimal response to onasemnogene abeparvovec while also taking into account potential implications on safety and patient burden.

Altered liver function is an expected safety concern associated with onasemnogene abeparvovec treatment. To mitigate against this known effect, prior to receiving onasemnogene abeparvovec, all patients must be placed on prophylactic steroids which continues for at least 3 months after dosing. Where there is no laboratory evidence of liver injury, tapering of steroids begins in the second month and is then discontinued at 3 months.

The shift in LFT thresholds from × 1.5 to × 2 takes onasemnogene abeparvovec labelled steroid requirements into consideration, along with the need for strict adherence to onasemnogene abeparvovec label specified monitoring of liver function as both of these measures will remain ongoing during the dose-shortened interval (i.e., first dose of nusinersen falling ≥ 2 months post onasemnogene abeparvovec administration). Therefore, patients with normal or non-clinically significant LFT abnormalities need not be excluded from the trial, which facilitates means for Investigators to manage their own patients, as appropriate.

In the amended protocol, Investigators are provided with measures for mitigating ongoing (AST and/or ALT levels ≤ 2 × ULN) or new onasemnogene abeparvovec-induced liver effects arising within the dose-shortened interval. These emphasize steroid use and laboratory monitoring of LFTs, as specified within the onasemnogene abeparvovec label, over the duration of the dose-shortened interval. Mitigating measures should permit early detection of any deleterious changes in LFTs with immediate recourse to appropriate medical management in the event of laboratory signs of liver injury. Investigators are also encouraged to consult specialist opinion from gastroenterologist and/or hepatologist at the earliest opportunity in the event of evidence of DILI and/or clinically significant liver injury.

The list of inclusion criteria was reordered for flow of criteria by logical steps in determining participant eligibility.

The change in dosing interval, exclusion of steroid use, and changes to the safety laboratory requirements for ALT and AST levels affect the following:

Section 1.1, Synopsis

Section 1.2, Study Design Schematic (Figure 1)

Section 1.3, Schedule of Activities (Table 1)

Section 3.3, Risk-Benefit Assessment

Section 5.1, Study Overview

Section 6.1, Inclusion Criteria (#6; #10)

Section 6.2, Exclusion Criteria (#3)

Section 6.3.2, Retesting

Section 11.4.1, Liver Injury

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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

Change: The study location section was updated to increase the number of study sites from 20 to 30 globally. The study population section was revised to reflect the shortened dosing interval by including participants who have received onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. Text was updated to clarify that the 17-week follow-up period occurs from Study Day 660 to Study Day 778. The benefit-risk analysis was updated with current nusinersen-treated patient numbers.

Now reads:

…

Study Location:	Approximately ~~20~~ **30** sites globally are planned.
Study Population:	This study will be conducted in participants with SMA who meet the following criteria: • aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1 • have received onasemnogene abeparvovec (at least **2 months** ~~3 months~~ prior to the first nusinersen dose) • who are determined by the Investigator to have suboptimal clinical status Detailed criteria are described in Section 6.

…

Duration of Study Participation:	Study duration for each participant will be approximately 115 weeks: • 3-week screening period (Day -21 to -1) • 95-week treatment period (Day 1 to 659) • 17-week follow-up period (Day ~~659~~ **660** to 778)

Benefit-Risk Analysis:	Nusinersen (Spinraza) has a positive benefit-risk profile, with more than ~~3~~ **4** years of postmarketing experience and more than ~~10,000~~ **11,000** patients treated. It has been effective in all subgroups tested and has been well tolerated without new or unexpected safety issues identified in any of the subpopulations. However, there are no clinical trial data of nusinersen in patients who have previously been treated with onasemnogene abeparvovec.

Rationale: The information on study population was updated to align with the shortened dosing interval between treatment with onasemnogene abeparvovec and first nusinersen dose. The number of approximate study sites globally was increased to accommodate additional study sites. Follow-up period days were revised to correctly align with study duration periods with no overlap in study periods. The number of nusinersen-treated patients was increased to reflect updated numbers as of the amended protocol date.

This change also affects Section 3.1, Study Rationale, Section 3.3, Benefit-Risk Assessment, Section 5.1, Study Overview, and Section 6, Study Population.

Section 1.3, Schedule of Activities

Change: The Schedule of Activities was updated to (1) remove CSF local laboratory assessments; (2) add ventilator or BiPAP use data recording; (3) add and clarify 7-day window for assessments occurring at both Screening and Day 1 if Screening assessments are performed at least 7 days prior to Day 1 (if no abnormal findings at Screening and with the exception of coagulation testing); (4) add guidelines for coagulation testing based on dosing interval between last onasemnogene abeparvovec treatment and first nusinersen administration; (5) add allowable home collection of vital signs, ECG, weight, growth parameters, urine samples, and ventilator use diary by qualified personnel; [redacted]

Now reads:

Table 1: Schedule of Activities

Study Period	Screening	Treatment										Follow -Up	Visits by Participant Age in Months (±14D)[1]		
Study Day/Participant Age	D -21 to D -1	D1[1]			D15, D29 (±1D)			D64 (±7D), D183, D302, D421, D540, D659 (±14D)			1 to 14 Days After Each Dose[2] [3]	D778 (±14D) /ET	15	18	24
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose					
Informed Consent[3~~4~~]	X														
Inclusion/Exclusion Criteria	X	X													
Medical History[4~~5~~]	X														
SMA Genetic Testing[5~~6~~]	X							X[6~~7~~]							
Vital Signs and Pulse Oximetry[7] [8, 9]	X	X		X	X		X	X		X		X			
Weight[9]	X	X			X			X				X		X	
Growth Parameters[9]	X							X[8~~10~~]				X		X	
Physical Examination[9~~11~~]	X	X			X			X				X			
Neurological Examination[~~10~~12]	X	X		X	X		X	X		X		X			
[redacted]															
ECG[~~11~~9, 13]	X	X						X				X			
SNAP[~~12~~14]	X							X[8~~10~~]				X			
Laboratory Safety Tests [~~13~~9, 10, 15]	X	X			X			X[8~~10~~]				X			
Local Coagulation Laboratory Tests[~~14~~16, 17]	X	X			X			~~X~~[8]-**X**				X			
Immunogenicity		X						X[8~~10~~]				X			

Study Period	**Screening**	**Treatment**										**Follow -Up**	**Visits by Participant Age in Months (±14D)[1]**		
Study Day/Participant Age	**D -21 to D -1**	**D1[1]**			**D15, D29 (±1D)**			**D64 (±7D), D183, D302, D421, D540, D659 (±14D)**			**1 to 14 Days After Each Dose[2] [3]**	**D778 (±14D) /ET**	**15**	**18**	**24**
		Pre dose	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**					
[redacted]															
~~CSF Local Laboratory Sample (Cell Count, Protein, and Glucose)~~		~~X~~			~~X~~			~~X~~							
[redacted]															
Study Treatment Injection			X			X			X						
Telephone Contact[23]											X				
Ventilator or BiPAP Use Data Recording		**X**			**X**			**X**			**X**	**X**			
Ventilator Use Diary[9, 20]	**X----------X**														
Concomitant Medication and Ancillary Procedure Recording	X----------X														
AE Collection	X----------X														
~~Ventilator Use Diary[17]~~	~~X----------X~~														
Efficacy Assessments: Motor Assessments[18][21]															
CHOP INTEND	X	~~X[19]~~**X**						X[8][10]				X		X	

Study Period	**Screening**	**Treatment**									**Follow -Up**	**Visits by Participant Age in Months (±14D)[1]**		
Study Day/Participant Age	**D -21 to D -1**	**D1[1]**			**D15, D29 (±1D)**			**D64 (±7D), D183, D302, D421, D540, D659 (±14D)**			**1 to 14 Days After Each Dose[2] [3]**	**D778 (±14D) /ET**	**15**	**18**	**24**
		Pre dose	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**	**Pre dose**	**LP**	**Post dose**					
HFMSE	X	~~X[19]~~X						X[8][10]				X			
Total HINE Section 2 Motor Milestones	X	~~X[19]~~X						X[8][10]				X	X	X	X
~~WHO Motor Milestones[20]~~	~~X~~	~~X[19]~~						~~X[8]~~				~~X~~	~~X~~	~~X~~	~~X~~
~~RULM~~	~~X~~	~~X[19]~~						~~X[8]~~				~~X~~			
[redacted] **WHO** Motor ~~Subset~~ ~~[21]~~**Milestones**[22]	X	~~X[19]~~X						X[8][10]				X	X	X	X
[redacted] **-RULM**	X	~~X[19]~~X						X[10]				X		~~X~~	
[redacted]															
Efficacy Assessments: Other[19]															
[redacted]															

Study Period	Screening	Treatment									Follow -Up	Visits by Participant Age in Months (±14D)[1]		
Study Day/Participant Age	D -21 to D -1	D1[1]			D15, D29 (±1D)			D64 (±7D), D183, D302, D421, D540, D659 (±14D)			1 to 14 Days After Each Dose[2] [3]	D778 (±14D) /ET	15	18	24
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose					
[redacted]															

[redacted]t; [redacted]; [redacted]

~~AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase;~~ [redacted]

~~CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders;~~ [redacted]

~~CSF = cerebrospinal fluid; D = day;~~ [redacted] ~~ECG = electrocardiogram; ET = Early Termination; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Exam; LP = lumbar puncture;~~ [redacted]; [redacted]; [redacted] ~~RULM = Revised Upper Limb Module; SMA = spinal muscular atrophy; SMN = survival motor neuron; SMN2 = survival motor neuron 2; SNAP = sensory nerve action potential; ULN = upper limit of normal;~~ [redacted] ~~; WHO = World Health Organization~~

Note: For RULM, [redacted], [redacted], [redacted], [redacted], and [redacted], if an assessment is not performed at a visit, it may be performed at the next dosing visit but should be recorded as a deviation from the protocol.

[1]Age-based visits are required only for participants ≤ 9 months of age at the time of first nusinersen dose. If the window for an age-based visit overlaps with another scheduled visit, the visits may be combined.

[2]**Assessments (with the exception of coagulation testing) that were performed at Screening within 7 days of the Day 1 dosing visit do not need to be repeated on Day 1 unless results at Screening require reassessment (e.g., abnormal ECG, physical examination findings, out of range laboratory results, etc.). Coagulation testing must be performed at the Day 1 visit regardless of when it was performed prior to Day 1. (Please see footnote 17 for more details.)**

~~2~~[3]Telephone contact for safety monitoring must occur 1 to 14 days after treatment administration on Days 64, 183, 302, 421, 540, and 659 and every other month during the maintenance period when no treatment administration is planned.

~~3~~[4]Including any optional consents.

[redacted]

~~4~~[6]A blood sample will be collected at Screening for SMN2 copy number analysis only from those participants without acceptable genetic documentation of SMN2 copy number.

[6][7]For all other participants, a blood sample will be collected during the study (preferably before or on the first maintenance dosing visit) for the analysis of both SMN1 copy number and deletion/mutation and SMN2 copy number by the central laboratory.

[7][8]Vital signs will include temperature, heart rate, systolic and diastolic blood pressure, pulse oximetry, and respiratory rate. [redacted]

[9]**Vital signs, ECG, weight, growth parameters, plasma samples, urine samples, and ventilator use diaries may be collected/assessed in the home setting by qualified personnel within the prespecified visit window, where local regulations allow.**

[8][10]These assessments may be performed up to 7 days prior to dosing, if necessary. Predose safety assessments (laboratory safety tests, coagulation tests, [redacted], and immunogenicity assessments) should be repeated if dosing does not occur within the 7-day window.

[9][11]Videotaping of motor milestone and function assessments and physical examinations is optional.

~~10~~[12]HINE Sections 1 and 3 will be administered **by the Investigator** to participants ≤ 24 months of age, and a standard neurological examination will be performed in participants > 24 months of age. On dosing visits, neurological examination will be performed at 2 timepoints: predose and at approximately 1 hour postdose (or when sedation has worn off, if it was used). Predose neurological examinations should be repeated if the LP does not occur on the same day.

~~11~~ [13]ECG will be assessed at Screening and on Days 1, 302, and 778/ET only.

~~12~~[14] [redacted] and SNAP will be assessed at Screening and on Days 302 and 778/ET only.

~~13~~~~Includes hematology, blood chemistry, urinalysis, and CSF.~~

[15]**Blood chemistry, hematology, and urinalysis samples will be analyzed by a central laboratory. Urine samples may be collected during lumbar puncture if necessary. Plasma and urine samples (as well as vital signs, ECG, weight, growth parameters, and ventilator use diaries) may be collected in the home setting by qualified personnel within the prespecified visit window, where local regulations allow. Urine total protein will be analyzed by local laboratory only (Appendix B). Predose clinical safety laboratory assessments should be repeated when the assessment falls outside the protocol specified window because of a delay in dosing.**

~~14~~[16]Coagulation testing will be conducted locally at Screening and predose (within 7 days prior to dosing) at each dosing visit. Predose coagulation parameters should be repeated when the assessment falls outside the protocol-specified window because of a delay in dosing. **See also footnote 15.**

[17]**Predose review of coagulation results must be completed on Day 1 prior to administering nusinersen dose for participants who received onasemnogene abeparvovec ≤3 months prior to the first nusinersen dose. Refer to Section 11.4 for guidance on suspension of dosing beyond the specified INR threshold.**

[redacted]

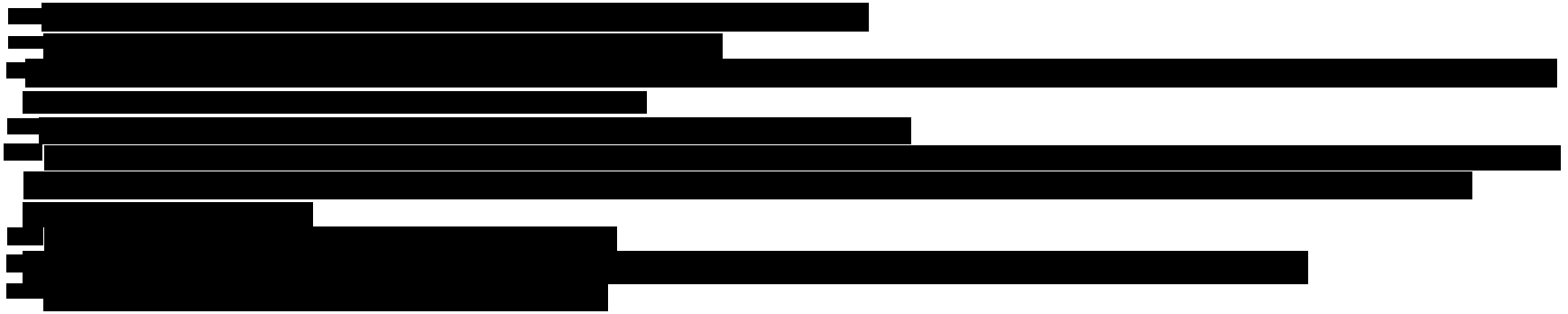
~~17~~[20]Completion of the daily ventilator use diary is required only for participants who have initiated ventilator use.

~~18~~ [21]Efficacy assessments will be selected by the Investigator according to the criteria in Table 2.

~~19~~~~Assessments that were performed at Screening within 7 days prior to the Day 1 dosing visit do not need to be repeated on Day 1.~~

~~20~~ [22]WHO motor milestone assessments will be performed by the Investigator ~~or physical therapist~~ at study visits independently of the assessments made by the participant's caregiver. During the study period, caregivers will be asked to record the date a participant achieves new milestones.

[redacted]



Rationale: Updates to the Schedule of Activities were made to align with changes throughout the protocol and to provide additional guidance for assessments and dosing throughout the study.

Section 3.1, Study Rationale

Change: The number of patients who have been treated with nusinersen has been updated.

Now reads:

Nusinersen has demonstrated efficacy and safety across a broad range of SMA phenotypes and patient populations. It is delivered IT and acts by binding the SMN2 pre-mRNA transcript. This leads to inclusion of exon 7 in the SMN2 mRNA transcripts with resulting increased production of full-length SMN protein. Since receiving FDA approval in December 2016, more than ~~10,000~~ **11,000** patients have been treated with nusinersen.

Rationale: The text was updated to reflect current patient numbers as of the amended protocol date.

This change also affects Section 3.2.3, Profile of Previous Experience With Nusinersen, and Section 3.3, Benefit-Risk Assessment.

Section 3.2.2, Current Therapies for SMA

Change: Updates for approval information and indications were added.

Now reads:

There are several therapies available for the treatment of SMA. Nusinersen, also referred to as ISIS 396443, BIIB058, or ~~Spinraza~~ **Spinraza™**, **developed by Biogen** is approved for the treatment of SMA in the ~~US, EU~~ **US (December 2016), EU (5q SMA) [May 2017],** and other major markets (5q SMA, infantile SMA, and all other SMAs). **The** gene transfer agent ~~and an adeno-associated virus vector~~ **onasemnogene abeparvovec-xioi (Zolgensma), developed by AveXis and Novartis, is an AAV9 vector** expressing ~~a~~ **an** SMN1 gene delivered ~~IV~~ **IV.** Zolgensma ~~was~~ **is** approved in the ~~US~~ **US** ~~in 2019~~ **(May 2019**~~), in the EU in May 2020,~~ **and** ~~in~~ **Japan** ~~in 2020~~ **(March 2020)** for the treatment of ~~pediatric patients younger than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene.~~ **SMA Type I in patients < 2 years old and in the EU (May 2020) for the treatment of 5q SMA in patients who weigh up to 21 kg.** Risdiplam (Evrysdi™, formerly RG7916), **developed by Genentech, is** an oral **SMN2-directed** splicing modifier indicated for the treatment of SMA~~, was approved by the FDA in August 2020~~ **in patients ≥ 2 months of age. It was first** approved **in the US (August 2020) and has since received approval in at least 5 other markets.**

Rationale: The text was updated to be consistent with current available therapies for SMA as of the amended protocol date and to align with the IB.

Section 3.3, Benefit-Risk Assessment

Risk of Liver Injury

Change: Information concerning the potential for ongoing or new liver effects was added, including the allowance of steroid therapy (as per label and the Investigator's discretion), ongoing monitoring of ALT and AST levels, and predose coagulation testing and review with specified parameters warranting outside consultation with hepatologists/gastroenterologists.

Now reads:

~~There are several key differences between these 2 known cases of liver failure and the 232SM404 trial design. The 2 liver failure cases involved patients who resumed nusinersen within 2 months of onasemnogene abeparvovec treatment, while still receiving steroid treatment~~. ~~In contrast, a minimum of 3 months is required between onasemnogene abeparvovec and initial nusinersen dosing for study participants to minimize the risk of hepatotoxicity~~. **Amelioration of potential for ongoing or new** onasemnogene abeparvovec**-induced liver effects (AST and/or ALT levels ≤ 2 × ULN) arising within the dose-shortened interval will be mitigated by patients continuing to receive steroids as specified in the** onasemnogene abeparvovec **label throughout this period.** Furthermore, ~~prior to initial nusinersen dosing, participants must be off steroids ≥ 1 month, have AST and ALT levels that are ≤ 1.5 × ULN, and be naïve to nusinersen.~~ **onasemnogene abeparvovec label-specific monitoring will also be ongoing over the duration of the dose-shortened interval, allowing early detection of any deleterious changes in LFTs. This should permit immediate application of appropriate medical management steps in the event of laboratory signs of liver injury.**

~~Furthermore,~~ **Prior to initial nusinersen dosing, participants must ~~be off steroids ≥ 1 month,~~ have AST and ALT levels that are ≤ 2 × ULN and be naïve to nusinersen. Past history of DILI or hepatic failure are exclusion criteria as well for receiving study treatment with nusinersen. Coagulation assessments will be undertaken predose at each study visit, and test results will be reviewed prior to dosing with nusinersen. Within the dose-shortened interval, where patients may still be at risk for onasemnogene abeparvovec-induced liver injury, the requirement for review of coagulation assessments precludes dosing of patients with nusinersen in situations where coagulation assessments show an INR ratio of > 1.5. Investigators are also advised to maintain a low threshold for consulting hepatologists/gastroenterologists when dosing nusinersen during the dose-shortened interval.**

Rationale: The text was revised to provide further guidance in dosing for participants that have AST and ALT levels and INR ratios outside the allowable ranges in order to ensure ongoing participant safety.

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Section 4, Study Objectives and Endpoints

[redacted]

Section 5.1, Study Overview

Change: The study design section was updated to reflect changes in the dosing interval. The criteria for participants in Subgroup A was revised to add 2 additional criteria concerning onasemnogene abeparvovec treatment and to clarify criteria.

Now reads:

This open-label, single-arm, interventional study will evaluate the efficacy and safety of nusinersen in approximately 60 participants who previously received IV onasemnogene abeparvovec in a clinical practice setting. The study will be conducted at approximately ~~20~~**30** sites globally.

This study will be conducted in participants with SMA who have previously received onasemnogene abeparvovec treatment and who are determined by the Investigator to have suboptimal clinical status and the potential for additional clinical improvement. Participants must have received onasemnogene abeparvovec at least ~~3~~ **2** months prior to the first nusinersen dose. All participants will be aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1, and have received onasemnogene abeparvovec either when symptomatic or presymptomatic for SMA.

…

Subgroup A

It is hypothesized that younger participants who receive nusinersen and onasemnogene abeparvovec in short succession may derive the most benefit compared to onasemnogene abeparvovec alone. To optimize exploration of the benefit of nusinersen after onasemnogene

abeparvovec, Subgroup A will contain participants who meet all of the following additional criteria:

- Maximum age of 9 months at **the time of** first nusinersen dose.
- SMN2 copy number **of** 2.
- SMA symptom onset ≤ 4 months of age ~~and prior to receiving onasemnogene abeparvovec.~~
- **Must have received IV onasemnogene abeparvovec at ≤ 6 months of age.**
- **Must have received IV onasemnogene abeparvovec after SMA symptom onset.**

The maximum age of 9 months for participants in this subgroup will ensure sufficient nusinersen exposure to assess benefit during the critical window for motor milestone achievement.

See Figure 1 for a schematic of the study design.

Rationale: The criteria for participants in Subgroup A were updated in this section to fully align with the presentation of inclusion criteria in Section 6.1, Inclusion Criteria.

Section 5.4, Unscheduled Visits

Change: The text was updated to clarify the definition of unscheduled visits and the need to document the reason for any unscheduled visits.

Now reads:

Data collected during unscheduled visits should be recorded on CRFs only if the data support protocol objectives and/or are required for safety monitoring. **Visits, when occurring on non-visit days, are considered unscheduled visits. The reason for an unscheduled visit should be documented on the CRF.**

Rationale: The text was updated to provide further clarification concerning repeat visits on non-visit days, which are considered unscheduled visits.

Section 6.2, Exclusion Criteria

Change: Exclusion criterion #3 concerning the use of steroids for liver function abnormalities was removed. The exclusion criterion for Subgroup A concerning growth parameters was revised for clarification to specify weight-for-age based on WHO Child Growth Standards.

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Now reads:

The following exclusion criteria apply to all participants:

Medical History and Current Health Status

1. Severe or serious AEs related to onasemnogene abeparvovec therapy that were ongoing during Screening.

2. History of brain or spinal cord disease that would interfere with the LP procedure, CSF circulation, or safety assessments, including a history of hydrocephalus or implanted shunt for CSF drainage.

~~3. Use of steroids for liver function abnormalities within 1 month prior to first dose of nusinersen.~~

~~4.~~**3.** Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA).

~~5.~~**4.** History of or current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

~~6.~~**5.** Serious infection (e.g., pneumonia, septicemia) that has not completely resolved, as indicated by the absence of signs, symptoms, or ongoing investigations, or remained resolved within 1 month prior to nusinersen dosing.

~~7.~~**6.** Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection), which have not resolved within 14 days prior to nusinersen dosing. Participants are eligible to be rescreened after successful treatment or resolution of the infection.

~~8.~~**7.** History of any clinically significant abnormalities that would render the participant unsuitable for inclusion, as determined by the Investigator.

~~9.~~**8.** Clinically significant abnormal laboratory test (such as thrombocytopenia) at Screening (as determined by the Investigator) that would render the participant unsuitable for inclusion.

~~10.~~**9.** History of DILI or liver failure.

~~11.~~**10.** Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities.

~~12.~~**11.** Permanent ventilation, defined as tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event.

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~~13.~~**12.** Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia, and respiratory parameters) that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.

~~14.~~**13.** Participant's parent or legal guardian is not willing to meet standard-of-care guidelines for care (including vaccinations and RSV prophylaxis if available) nor provide nutritional and respiratory support throughout the study. 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.

Medications

~~15.~~**14.** Prior exposure to nusinersen

~~16.~~**15.** Treatment with an investigational drug, 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-**directed** splicing modifier; prior antisense oligonucleotide treatment or cell transplantation; gene therapy for the treatment of SMA other than onasemnogene abeparvovec. Note: treatment with onasemnogene abeparvovec as part of an investigational study is allowed (per inclusion criterion 0).

Others

~~17.~~**16.** Plans to undergo elective procedures or surgeries at any time after signing the ICF through the end of the study.

~~18.~~**17.** Inability to comply with study requirements.

~~19.~~**18.** Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

The following additional exclusion criterion applies **only** to participants recruited into Subgroup A:

~~20.~~**19.** ~~Growth parameters at~~**Weight-for-age is below the** third percentile ~~or less~~ **based on WHO Child Growth Standards** at the time of receiving onasemnogene abeparvovec.

Rationale: The exclusion criteria were revised to allow the use of steroids for liver function abnormalities and to clarify acceptable weight parameters.

Section 6.3.2, Retesting

Change: ALT and AST parameters were revised to increase the allowable laboratory levels prior to nusinersen dosing.

Now reads:

Participants who fail the screening criteria can be retested once. 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.

If ALT and/or AST are > ~~1.5~~**2** and ≤ ~~2~~**2.5** × ULN during the Screening period, repeat testing may be performed once and ALT and AST must be ~~≤ 1.5~~ **≤ 2 × ULN at Screening and within 7 days** prior to dosing. Repeat testing may be performed at a local laboratory if necessary.

Rationale: Retesting parameters were revised to align with the primary reason for the protocol amendment.

Section 7.1, Regimen

Change: Nusinersen IT administration specifications were revised to remove administration via catheter.

Now reads:

Each participant will receive 4 loading doses of 12 mg of nusinersen administered IT by LP ~~or catheter~~ on Days 1, 15, 29, and 64. Maintenance dosing of 12 mg of nusinersen will be administered IT on Days 183, 302, 421, 540, and 659.

Rationale: This revision was made to the protocol because administration via catheters is not an option in this study.

Section 7.2, Study Treatment Management

Change: Text was revised to provide clarification of treatment management.

Now reads:

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

Site staff should ~~refer to~~ **follow** the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA ~~supersedes~~ **aligns with** all other references ~~(e.g., protocol)~~**, including the protocol.**

Study treatment ~~is to~~ **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 vials are for one-time use only; **do not use** any study treatment remaining in the vial ~~should not be used~~ for another participant.

Rationale: This revision was made to reflect current study protocol template language requirements.

[redacted]

Table 2: Efficacy Assessment Criteria

Assessment	**Criteria**
Total HINE Section 2 motor milestones	All participants through end of study.
WHO motor milestones [redacted]	All participants.
[redacted]	[redacted]
CHOP INTEND	Participants < 2 years of age at the time of informed consent Participants 2 to ≤ 3 years of age at the time of informed consent if they did not achieve independent sitting prior to Screening[1]. Participants may discontinue these assessments after Day 421 once they have demonstrated a maximum score at one visit.

Assessment	Criteria
HFMSE RULM [redacted]	Participants ≥ 2 years of age (Note: The HFMSE and RULM will be performed in addition to the CHOP INTEND and HINE Section 2 motor milestones if those assessments are continued beyond 2 years of age [see above]).
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]; ~~CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders;~~ [redacted]; ~~HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination;~~ [redacted]; ~~RULM = Revised Upper Limb Module ;~~ [redacted]; ~~WHO = World Health Organization~~

[1]Sitting independently is defined as able to sit without support per WHO motor milestones (Test Item No. 1 – Sitting Without Support).

[2]Ambulatory is defined as any participant who has achieved independent walking as defined by the WHO motor milestones criteria (Test Item No. 6 – Walking Alone).

Rationale: This revision was made to accommodate sites with local regulations on the use of radiation.

Section 9.1.1, Motor Milestones

Change: Text was updated to provide clarification that WHO motor milestones will be assessed by the Investigator.

Now reads:

The WHO motor milestones will be assessed in all participants **by the Investigator**; the total HINE Section 2 motor milestones will be assessed in all participants up to the end of the study. Videotaping of the WHO and/or HINE Section 2 motor milestone assessments will be optional.

Rationale: The text was updated to align with standardized WHO assessment criteria.

[redacted]

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[redacted]

This change also affects Section 9.1, Clinical Efficacy Assessments.

[redacted]

[redacted]

Section 10.1, Clinical Safety Assessments

Change: HINE (Sections 1 and 3) assessment information was updated to indicate the assessment should be completed by the Investigator.

Now reads:

Neurological examinations: HINE Sections 1 and 3 will be administered **by the Investigator** to participants ≤ 24 months of age at the time of informed consent. A standard neurological examination will be performed in participants > 24 months of age at the time of informed consent.

Rationale: This revision was made to clarify that only the Investigator may administer the neurological examination (HINE Sections 1 and 3) to study participants.

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Section 10.2, Laboratory Safety Assessments

Change: The CSF local laboratory sample was removed. Additionally, creatine phosphokinase and creatine kinase were combined to reflect the acceptance of either blood chemistry laboratory value as they represent the same laboratory assessment, but may be reported differently across study sites.

Now reads:

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

The following laboratory tests will be performed to assess the safety profile of nusinersen:

- Hematology: complete blood count with differential and platelet count
- Coagulation parameters (by local laboratory): activated partial thromboplastin time, prothrombin time, and international normalized ratio
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, bilirubin (direct and indirect), alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, **and** creatine phosphokinase and/**or** creatine kinase
- Urinalysis: urine total protein (by local laboratory); specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, WBCs, epithelial cells, bacteria, casts, and crystals
- ~~CSF local laboratory sample: RBC and WBC counts, protein, and glucose~~

A complete list of laboratory analytes is provided in Appendix B.

Rationale: The CSF local laboratory assessment was removed to align with other nusinersen study protocols conducted at labelled dose.

Section 10.3, Telephone Assessments

Change: The text was updated to include dose administration days.

Now reads:

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 1 to 14 days after each nusinersen dose **administration on Days 64, 183, 302, 421, 540, and 659**. Participants will also

be contacted via telephone every other month during the maintenance period when no treatment administration is planned.

Rationale: Dose administration days were added for clarification of the timing of telephone assessments.

Section 11.3.2, Serious Adverse Events

Change: Reporting requirements for serious adverse events were updated.

Now reads:

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 must also be reported ~~with~~ **within** 24 hours **or according to national law**.

Rationale: This revision was made to reflect current study protocol template language requirements.

Section 11.3.3, Immediate Reporting of Serious Adverse Events

Change: Reporting requirements for serious adverse events were updated.

Now reads:

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.

Rationale: This revision was made to reflect current study protocol template language requirements.

Section 11.3.3.1, Deaths

Change: Reporting requirements for deaths were updated.

Now reads:

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.

Rationale: This revision was made to reflect current study protocol template language requirements.

Section 11.4.1, Liver Injury

Change: Safety laboratory requirements for ALT and AST levels were revised, and procedures for handling special situations of liver injury were expanded to include platelet and INR specifications and guidance.

Now reads:

The risk of liver injury following onasemnogene abeparvovec treatment is discussed in Section 3.3. Investigators should therefore bear in mind the possibility of liver injury **with** all AEs, and consider further investigation at their discretion as needed within the clinical context.

~~In the event that a participant meets the criteria for DILI (as per Hy's law, ALT and/or AST > 3 × ULN and bilirubin > 2 × ULN) or other indications of DILI [FDA 2009], the Investigator may consult a hepatologist or other appropriate specialist to ensure comprehensive investigation, management, and monitoring of the participant. However, consultation of a hepatologist or other appropriate specialist should not be limited to this scenario, and the Investigator should consider further consultation with specialists if this is warranted based on AE or laboratory abnormalities.~~

~~In the following situations, the Investigator should withhold dosing as per below:~~

- ~~SUSARs: withhold dosing until the event has been assessed~~
- ~~SAE of DILI or liver failure, either related or unrelated to study drug: withhold dosing until the event has resolved and coagulation parameters are acceptable for LP~~

Nusinersen dosing for individual participants should be suspended until discussion with the Sponsor if any of the following circumstances are met:

- **platelets are < 50 × 10^9/L.**
  - **The American Association of Blood Banks guidelines recommend a minimum platelet count for 50 × 10^9/L for lumbar puncture. However, Investigators may use their discretion in considering dose suspension for participants with platelet counts < 75 × 10^9/L to < 100 × 10^9/L, if desired.**

- **INR is > 1.5 (see Table 1 and footnotes for coagulation testing requirements).**
- **participant experiences a liver-related SAE.**

Investigators should have a low threshold for consulting hepatologists/gastroenterologists, particularly when dosing nusinersen < 3 months after receiving onasemnogene abeparvovec.

Rationale: The language was updated to provide detailed guidance for identifying and assessing potential liver injury and determining dosing of participants to ensure ongoing safety throughout the study.

Section 11.5.1, The Investigator

Change: The Investigator responsibilities were updated.

Now reads:

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.
- 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.

Rationale: This revision was made to reflect current study protocol template language requirements.

[redacted]

[redacted]

Section 12.8.3, SNAP Amplitudes

Change: Summary of SNAP analysis was added under Section 12.8, Methods of Analysis for Safety Endpoints.

Now reads:

SNAP Amplitudes

Changes from Baseline to each visit in SNAP amplitudes in the sural and radial nerves will be presented over time using descriptive statistics.

Rationale: Description of SNAP amplitudes was added to align with summaries provided for other safety endpoints.

Section 14.1.4, Central Laboratories for Laboratory Assessments

Change: CSF protein was removed to reflect accurate laboratory assessments.

Now reads:

Central laboratories have been 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. [redacted]

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

Rationale: Reference to CSF protein local analysis was removed from this section to align with the removal of CSF local laboratory analyses throughout the study.

Appendix B, Laboratory Analytes

Change: [redacted] Creatine phosphokinase and creatine kinase were combined to reflect acceptance of either blood chemistry laboratory value. CSF local laboratory sample was removed from the local laboratory collection list.

Now reads:

Clinical Safety Assessments (Minimum Requirements)		**Other Assessments**
Blood Chemistry	Urinalysis	[redacted]
Sodium	Specific gravity	
Potassium	pH	
Chloride	Protein	
Total protein	Glucose	
Albumin	Ketones	
Calcium	Bilirubin	
Phosphorus	Blood	
Bicarbonate	RBC	
Glucose	WBC	
Blood urea nitrogen	Epithelial cells	
Creatinine	Bacteria	
~~Creatine phosphokinase~~	Casts	
~~Creatine kinase~~	Crystals	Immunogenicity Evaluation

Creatine phosphokinase and/or Creatine kinase Cystatin C Total serum bilirubin (direct and indirect) Alkaline phosphatase AST ALT GGT	<u>Hematology</u> Red blood cells Hemoglobin Hematocrit Platelets WBCs WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Plasma anti-nusinersen antibodies The following are to be assessed by local laboratory only: Urine total protein Coagulation (activated partial thromboplastin time, prothrombin time, and international normalized ratio) ~~CSF Local Lab Sample~~ ~~Cell count (RBC and WBC)~~ ~~Protein~~ ~~Glucose~~

ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted]; [redacted]; GGT = gamma glutamyl transferase; [redacted](s); RBC = red blood cell; [redacted]; WBC = white blood cell.

Rationale: [redacted] Creatine phosphokinase and creatine kinase were combined to reflect the acceptance of either blood chemistry laboratory value as they represent the same laboratory assessment but may be reported differently across study sites. The CSF local laboratory sample was removed from the list of assessments for compliance with similar changes in this version of the protocol.

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.
- The Sponsor Signature Page was updated to change the signatory.
- Section 2, List of Abbreviations, was updated.

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BiPAP	bilevel positive airway pressure
[redacted]	[redacted]
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
[redacted]	[redacted]
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
DHA	Directions for Handling and Administration
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GGT	gamma glutamyl transferase
HCV	hepatitis C virus
HFMSE	Hammersmith Functional Motor Scale - Expanded
HINE	Hammersmith Infant Neurological Examination
IB	Investigator's Brochure
ICF	informed consent form
INR	international normalized ration
IT	intrathecal(ly)
IV	intravenous(ly)
LFT	liver function test(s)
LP	lumbar puncture
NF-L	neurofilament light subunit
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
pNF-H	phosphorylated neurofilament heavy subunit
[redacted]	[redacted]
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SMA	spinal muscular atrophy
SNAP	sensory nerve action potential
US	United States

[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization