13 November 2025
EMA/CHMP/379593/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spinraza

International non-proprietary name: Nusinersen

Procedure No. EMEA/H/C/004312/X/0038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
aCSF	Artificial cerebrospinal fluid
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
APS	Aseptic Process Simulation
AR	Assessment Report
ASMD	Absolute standardized mean difference
ASO	Antisense oligonucleotide
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the last measured concentration
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human use
CHMP	Committee for Medicinal Products for Human Use
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CSF	Cerebrospinal fluid
CSF	Cerebrospinal fluid
C_{trough}	The lowest concentration reached by a drug before the next dose is administered
EC	European Commission
EMA	European Medicines Agency
EOP2	End of Phase 2
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOF	Goodness-of-fit
HA	Health authority
HED	Human equivalent dose
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
hnRNP	Heterogeneous nuclear ribonucleoproteins
HVLD	High voltage leak detection
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IES	Interim Efficacy Set

INFARMED	National Authority of Medicines and Health Products, Portugal
IPAQ-SF	International Physical Activity Questionnaire – Short Form
IPC	In-process control
IP-HPLC-UV-MS	Ion pair-high performance liquid chromatography with ultraviolet and mass spectrometry detection
IT	intrathecal(ly)
ITT	intent-to-treat
IU	International Units
JP	Japanese Pharmacopoeia
JPC	Japanese Pharmaceutical Codex
JPE	Japanese Pharmaceutical Excipients
JRT	Joint rank test
LoD	Limit of Detection
LOESS	Locally estimated scatterplot smoothing
LOQ	Limit of Quantitation
LoQ	List of Questions
LS	Least squares
LT	Less than
LTE	Long-term extension
MA	Marketing Authorisation
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MO	Major objection
MOE	Methoxyethyl
mRNA	Messenger ribonucleic acid
N/A	Not applicable
ND	Not detected
NLT	Not less than
NMT	Not more than
NOAEL	No observed adverse effect level
NT	Not tested
PAM	Post-authorization measure
PD	Pharmacodynamic(s)
PDE	Permitted Daily Exposure
PedsQL	Pediatric Quality of Life Inventory™
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
pNF-H	Phosphorylated neurofilament heavy chain
popPK	Population pharmacokinetics
PPQ	Process Performance Qualification
PT	Preferred term
PVC	Polyvinyl chloride

PVDC	Polyvinylidene chloride
Q.S.	Quantity sufficient
QbD	Quality by design
QC	Quality Control
QOS	Quality Overall Summary
QP	Qualified person
QTPP	Quality target product profile
RH	Relative Humidity
RMSEP	Root Mean Square Error Prediction
RSD	Relative standard deviation
RTRT	Real-time release testing
RULM	Revised Upper Limb Module
SAE	Serious adverse event
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
SE	Standard error
SMA	Spinal muscular atrophy
SMAIS-ULM	SMA Independence Scale – Upper Limb Module
SMN	Survival motor neuron
SMN1	Survival motor neuron gene 1
SMN2	Survival motor neuron gene 2
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UDU	Uniformity of dosage Unit
UHPLC	Ultra-high performance liquid chromatography
US	United States
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VHI	Voice Handicap Index
VPC	Visual Predictive Check
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Biogen Netherlands B.V. submitted on 22 November 2024 an extension of the marketing authorisation.

Extension application to add a new strength of 28 mg and 50 mg.
The RMP (version 12.x) is updated in accordance (version 12.2 is under assessment in procedure EMEA/H/C/004312/II/0034/G)

The MAH applied for an addition of a new strength.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (1) point(s) (a) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0123/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0123/2018 was completed.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: N/A

The application was received by the EMA on	22 November 2024
The procedure started on	27 December 2024

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	27 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	18 September 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 October 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Spinraza on	13 November 2025
The CHMP adopted a report on similarity of Spinraza with Zolgensma on (see Appendix on similarity)	13 November 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk and neuromuscular weakness [Swoboda 2009]. In almost every case, SMA is caused by a deletion or mutation in the *SMN1* gene located on chromosome 5q, which is responsible for the majority of SMN protein production. This deletion or mutation results in a deficiency of SMN protein and degeneration of the motor neurons in the anterior horn of the spinal cord. In less

than 5% of cases, a clinical diagnosis of SMA may be caused by non 5q forms of the disease [Farrar and Kiernan 2015].

A second gene (SMN2) located near SMN1 is responsible for a small amount of SMN protein production. The best-known predictor of clinical phenotype is the SMN2 copy number. Infants with the most severe phenotype of SMA (Type 0) are symptomatic at birth and die within the first few weeks of life. Patients with all other SMA phenotypes are asymptomatic at birth. The duration of the asymptomatic phase is variable but is usually correlated with disease severity, with more severe disease associated with earlier symptom onset and less SMN protein production.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Prior to the development of advanced molecular medicine techniques that allow genotyping of both *SMN1* and *SMN2* copy number, SMA was diagnosed based on clinical presentation and categorized retrospectively (Type I, II, III, or IV) based on the maximal motor milestone achieved and the age at symptom onset. Generally, symptom onset and severity of SMA correlate with *SMN2* gene copy number [Arnold 2015].

2.1.3. Biologic features, Aetiology and pathogenesis

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, which results in atrophy of the voluntary muscles of the limbs and trunk.

There are multiple underlying genetic etiologies for SMA. The disease can have variable severity and age of symptom onset as well as different inheritance patterns based on the disease-causing mutation. More than 90% of SMA cases can be attributed to mutations in chromosomal region 5q11-q13, all of which lead to loss of function of the survival motor neuron 1 (*SMN1*) gene [Lefebvre 1995] [Ogino 2002].

5q SMA (hereafter referred to as SMA) is a direct result of reduced levels of the survival motor neuron (SMN) protein, caused by homozygous deletions and, infrequently, by mutations within the *SMN1* gene. The lack of SMN protein causes dysfunction and eventually death of motor neurons. The *SMN1* gene lies in a duplicated, inverted region of chromosome 5 that includes a nearly identical copy of the *SMN1* gene, *SMN2*. Although both genes encode proteins with identical amino acid sequences, *SMN2* differs from *SMN1* by 11 nucleotides. One of the 11 base differences, a cytosine to thymine substitution, occurs in exon 7 of the *SMN2* gene, resulting in an alternative splicing pattern that favors skipping of exon 7. Eighty to 90% of the transcripts produced from the *SMN2* gene lack exon 7 [Cho and Dreyfuss 2010] [Wirth 2013], resulting in a truncated protein product that is defective and unstable [Cho and Dreyfuss 2010]. Increasing the amount of full-length transcript from the SMN2 gene could result in an increase in SMN protein in patients with SMA [Hua 2010]. Humans have a variable number of copies of the SMN2 gene (0 to 8 copies). *SMN2* copy number is an important predictor of SMA disease severity, and patients with more copies generally have a less severe form of the disease.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Type I SMA is the most common form of SMA and represents approximately 58% of the birth prevalence [Ogino 2004]. More than 90% of patients with 2 copies of *SMN2* will develop Type I SMA [Feldkötter 2002], and these infants usually present with hypotonia, loss of motor function, and failure to achieve new milestones within the first 6 months of life. These infants are never able to sit without support [De Sanctis 2016; Russman 2007; Wang 2007]. The major cause of morbidity and mortality in patients with

Type I SMA is pulmonary disease due to neuromuscular weakness [Wang 2007]. In the absence of respiratory support, only 1.3% of infants with Type I SMA survive beyond 24 months of age [Gregoretti 2013].

Type II SMA represents approximately 29% of the birth prevalence [Ogino 2004]. More than 80% of patients with 3 copies of SMN2 will develop Type II SMA but the SMN2 gene number can vary between 2 and 4 copies [Feldkötter 2002]. Children fail to achieve motor milestones because of proximal weakness and hypotonia that typically develop within the first 18 months of life [Rudnik-Schöneborn 2001]. This group is generally defined by an ability to sit independently but inability to walk unaided [Rudnik-Schöneborn 2001]. However, the progressive nature of the disease means some of these patients will lose their ability to sit unaided over time [Faravelli 2015; Russman 2007; Wang 2007]. Orthopedic and respiratory complications are a major cause of morbidity and mortality, and only 70% of patients with Type II SMA are alive at 25 years [Faravelli 2015].

Type III SMA represents approximately 13% of the birth prevalence [Ogino 2004]. More than 80% of patients with 4 copies of *SMN2* will develop Type III SMA but the *SMN2* gene number can vary between 3 or 4 copies [Feldkötter 2002]. These patients are able to stand and walk without support, but may lose these abilities as the disease progresses [Zerres and Rudnik-Schöneborn 1995]. While these patients may have normal life expectancy, neuromuscular and orthopedic complications are similar to those of Type II SMA and are a major cause of morbidity [Arnold 2015; Haaker and Fujak 2013; Wang 2007].

Type IV SMA (adult-onset) is the mildest form of SMA, and its occurrence is rare (<1%). Patients with Type IV SMA usually have 4 or more copies of the SMN2 gene. After symptom onset, which has been reported after 10 years of age but more commonly after 20 to 30 years of age [Wang 2007], patients experience mild to moderate muscle weakness and increasing disabilities. Patients are ambulatory and their life expectancy is normal [Faravelli 2015].

2.1.5. Management

The following other therapies have been authorized for the treatment of SMA besides nusinersen:

The gene transfer agent onasemnogene abeparvovec-xioi (Zolgensma®) is an AAV9 vector expressing an *SMN1* gene delivered intravenously. Zolgensma is approved in the United States (May 2019), Japan (March 2020), the European Union (May 2020), and in several other markets.

Risdiplam (Evrysdi™, formerly RG7916) is an oral SMN2 directed splicing modifier. It was first approved in the United States (August 2020) and has since received approval in several other markets, including in the European Unit (March 2021).

In regions where nusinersen or other SMA therapies have not yet been approved, medical care is supportive once patients become symptomatic. Due to neuromuscular weakness, patients with SMA lose motor milestones or never achieve them, and the most affected patients die or require permanent ventilation by 2 years of age [Gregoretti 2013]. For patients with infantile onset SMA, supportive care is targeted to respiratory and nutritional support [Finkel 2018; Mercuri 2018; Wang 2007]. Respiratory support consists of noninvasive ventilation, such as bilevel positive airway pressure, cough assist, and oral suctioning, that can require multiple hours of treatment per day. Tracheostomy for chronic ventilation may be performed if additional respiratory support is required. Patients with SMA may develop difficulty swallowing and require assistance with food intake or supplemental feedings through a gastrostomy tube. Medical care of patients with later-onset SMA depends on the level of disease progression but can include nutritional support, physical and occupational therapy, pain management, orthotics, spinal surgery, and environmental controls and home modifications to facilitate safe mobility.

However, despite even the most robust support, disease progression, including respiratory deficits and weakness in the more severe forms of the disease, is relentless, leading to premature death.

Patients with SMA and the families who care for them describe a significant need for therapies that improve motor function and increase survival [Qian 2015] and have expressed that stabilization of the current clinical state would represent therapeutic progress [Rouault 2017]. Furthermore, improvements in motor function would ease the significant burden of supportive care, offer greater independence, and improve the patient's quality of life as well as that of their caregivers.

2.2. About the product

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.

Spinraza has been marketed with the 12 mg formulation administered every 4 months, and is now being recommended to be administered with a loading dose of 50 mg twice with a 14 day interval, followed by 28 mg every 4 months. The 12 mg previously approved regimen will also be kept in the market, with 3 x 12 mg loading doses every 14 days, and a 4^{th} loading dose 35 days afterwards, followed by 12 mg every 4 months. The decision to select one or the other regimen is at the physician discretion.

The finished product is presented as a solution for injection containing 28 mg (5.6 mg/mL) or 50 mg (10 mg/mL) of Nusinersen per vial (5 mL).

2.3. Type of Application and aspects on development

Rationale for Higher Dose Nusinersen Regimen

The clinical PK, safety, and efficacy of nusinersen have been evaluated across a broad range of patients (infants, pediatrics, teenagers, and adults) and SMA types (infantile onset [SMA symptom onset ≤ 6 months (≤ 180 days) of age], later onset [SMA symptom onset > 6 months (> 180 days) of age], and presymptomatic). The initially approved dosing regimen of nusinersen is 12 mg administered in 3 loading doses at 14-day intervals, a fourth loading dose 30 days after the third dose, and maintenance doses every 4 months thereafter. In the original development program, 2 different dosing regimens (4 loading doses followed by maintenance doses every 4 months and 3 loading doses followed by maintenance doses every 6 months) were evaluated in sham controlled-studies.

While nusinersen has provided a known benefit to patients with SMA, unmet need remains, such as a way to reach the sickened cells and work its protective effect as soon as possible. This might be theoretically achieved through a dedicated delivery system into the brain or a higher dosing regimen of nusinersen that more rapidly slows neurodegeneration in patients with SMA while also being safe and well-tolerated.

Results from initial nusinersen studies, as well as population PK and exposure-response modeling and nonhuman primate safety studies (described below) were used as the basis for selecting the regimens used in the clinical studies exploring higher doses of nusinersen.

An exploratory exposure-response analysis performed in participants with infantile-onset SMA (Studies CS3A, CS3B, 232SM201 [henceforth referred to as SM201], and CS11) showed a statistically significant positive correlation between nusinersen CSF exposure and motor function (e.g., CHOP INTEND scores).

Based on the exposure-response analysis that assumed a direct relationship between CHOP INTEND and C_{trough} at steady state, it was predicted that a 5-point increase in CHOP INTEND score could be achieved by increasing the anticipated steady-state CSF exposures from 5 ng/mL to 12 ng/mL. Therefore, it was

hypothesized that administration of a 2.4-fold higher dose (i.e., approximately 28 mg) compared to the standard dose of 12 mg may lead to meaningful clinical benefit.

Simulations were conducted using a popPK model to help define an appropriate dosing regimen for Study 232SM203 (DEVOTE; henceforth referred to as Study SM203). Previous popPK modeling assumed proportionality of CSF C_{trough} with dose. This assumption was supported by nusinersen toxicokinetic results in nonhuman primates, which showed nearly dose-proportional PK in the plasma and CNS tissues (target of action) up to 15 mg (human equivalent dose of 150 mg). Based on PK modeling performed, relative to the approved 12 mg dosing regimen, 28 mg administered as 3 loading doses (biweekly) or 50 mg administered as 2 loading doses (biweekly), each followed by maintenance doses of 28 mg every 4 months, were identified to achieve the desired CSF C_{trough} levels more rapidly at the end of the loading dose period. In particular, it was predicted that the median C_{trough} level within the maintenance phase at steady state would be approximately 5 ng/mL with the label-approved maintenance dosing regimen (12 mg administered every 4 months) and approximately 12 ng/mL with the proposed maintenance dosing regimen for Study SM203 (28 mg administered every 4 months).

The PK/PD relationship has thus far been demonstrated primarily in the infantile-onset SMA population. However, the same positive PK/PD relationship is expected across SMA types and patient age groups because they share the same disease mechanism. This is supported by the preliminary correlation analysis from Study 232SM202 (henceforth referred to as Study SM202), which showed a positive relationship between CSF C_{trough} and total motor milestones scores in participants with infantile- and later-onset SMA who received 12 mg of nusinersen as 4 loading doses followed by maintenance doses every 4 months.

At this time, no dose-limiting toxicity has been identified with nusinersen. Toxicology studies in juvenile monkeys evaluating the nonhuman primate equivalent of the 28 and 50 mg doses have been conducted and support the safety of these doses in a clinical study (see 2.4 Nonclinical Overview, 2.6.6 Toxicology Written Summary, and 2.6.7 Toxicology Tabular Summary). Given the safety profile in toxicology studies up to a 50 mg human equivalent dose, the observed clinical safety profile in the 12 mg dosing regimen, and modeling data suggest the increased likelihood of clinical benefit, the 28 mg dose (administered as 3 loading doses at biweekly intervals), 50 mg dose (administered as 2 loading doses at biweekly intervals), and 28 mg maintenance dose were recommended for additional clinical evaluation.

There have been 2 clinical studies, completed Study SM203 and its long-term extension, ongoing Study 232SM302 (ONWARD; henceforth referred to as SM302; interim data cut of 30 May 2024).

2.3.1. Scientific advice

The MAH sought advice from FDA, PMDA, and INFARMED (Portugal) in 2019 on clinical aspects and overall design elements of Study SM203 to support safety and efficacy of the 50/28 mg dosing regimen. These included the initial proposal of primary analysis comparing 50/28 mg with the 12 mg dosing regimen with higher than the traditional type 1 error rate (2-sided alpha of 0.05), subsequent change to the current comparison between 50/28 mg cohort and matched sham (from Study CS3B) with the traditional type 1 error rate of 2-sided alpha of 0.05. Additional topics where agency advice was sought included use of CHOP-INTEND as the primary efficacy endpoint, clinically relevant secondary endpoints, general statistical framework, utility of neurofilament as a prognostic and predictive biomarker in SMA, as well as potential of inclusion of multiple doses in the label. While agencies recognized the challenge of a statistically powered comparison between the 50/28 mg dosing regimen versus the approved 12 mg dosing regimen in a rare SMA population, they independently noted the clinical importance of the comparison between 50/28 mg and 12 mg dosing regimens and recommended assessment within Study SM203, with varied levels of statistical flexibility.

The MAH engaged with the FDA and PMDA between 2021 and 2022 to further solicit advice on details of planned analyses and the SAP for Part B of Study SM203 in the pivotal infantile-onset and supportive later-onset cohorts. Agency advice from FDA and PMDA on key SAP elements such as comparability of baseline characteristics between Study CS3B sham and 50/28 mg regimen as well as overall matching approaches in infantile- and later-onset participants in Study SM203 with respective matched controls in Study CS3B and Study CS4, were incorporated into development of the current SAP.

The MAH also sought scientific advice from the FDA, EMA, and PMDA (informal) between 2023 and 2024 for finalization of the SAP for Part B of Study SM203 in the pivotal infantile-onset cohort and proposed protocol amendment for Study SM203 (Version 7). Alignment was solicited on the proposal for assessing baseline comparability between Study CS3B-matched sham with the 50/28 mg Study SM203 cohort, as well as proposed changes to the secondary endpoints as a result of implementing the matching algorithm. While alignment was gained from FDA and PMDA on proposed changes to Study SM203 (Version 7, dated 05 May 2024) and the SAP for Part B of Study SM203, EMA recommended that the primary and key secondary analyses be those conducted versus the internal controls. Analyses versus historical controls would generally be considered exploratory but considering the rarity of infantile SMA, failure to reach statistical significance in the internal comparison would not necessarily preclude a positive benefit-risk assessment. Consistent clinically meaningful effects sizes for the 50/28 mg dosing regimen and clinically relevant secondary endpoints, disease subtypes, ages of participants/disease durations, will have more weight in the benefit-risk assessment than statistical significance reached using a non-robust methodological strategy.

2.4. Quality aspects

2.4.1. Introduction

The finished products introduced with this line extension are presented as solution for injection containing 28 mg (5.6 mg/mL) or 50 mg (10 mg/mL) of nusinersen per vial (5 mL) as active substance.

Other ingredients are: sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

The product is available in single-use Type I glass vial with bromobutyl red (28 mg) or blue (50 mg) rubber stopper and an aluminium over-seal and plastic cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance used to manufacture these new strengths is the same as that used for the already authorised solution for injection 12 mg (2.4 mg/mL). No information on the active was submitted as part of this line extension application.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as clear and colourless solution with pH of approximately 7.2. The qualitative and quantitative composition of the new product strengths is well defined.
The finished product is ready to use at both 5.6 mg/mL and 10 mg/mL concentrations, and requires no additional dilution with artificial cerebrospinal fluid diluent prior to intrathecal injection.

Spinraza 28 mg and 50 mg solution for injection are packaged in a single-use vial with a labelled volume of 5 mL. The target fill volume is 5.5 mL which includes a 0.5 mL overfill to ensure a 5 mL volume for dosing can be extracted.

All excipients are widely used materials in pharmaceutical formulations with a long story of safe utilisation by injectable administration. No novel excipients or excipients of human or animal origin are used in the finished product. The list of excipients is included in section 6.1 of the SmPC. Compendial excipients comply with the respective Ph.Eur. monograph specifications, including microbial contamination and bacterial endotoxins tests, being analysed accordingly.

The manufacturer of the water for injection in bulk and details of the manufacturing process are stated.

A comparison of the newly proposed strengths (5.6 mg/mL & 10 mg/mL formulations) with the 2.4 mg/mL commercial formulation and the 12 mg/mL development formulation has been provided. The new product strengths have the same excipient concentrations as the approved commercial finished product with the exception of slightly lower concentrations of sodium chloride in order to maintain tonicity at higher concentrations.

An overview of the finished product manufacturing processes, the manufacturing history (including a comparison between the manufacturing processes of the 5.6 mg/mL & 10 mg/mL *vs* 2.4 mg/mL & 12 mg/mL formulations, and a summary of the development studies establishing the suitability of the Nusinersen 5.6 mg/mL & 10 mg/mL solution for injection manufacturing process were provided.

The possible variables during various stages involved in manufacturing process were identified and the effect of the critical variables on the performance of the formulation was evaluated. The manufacturing processes for the Nusinersen 2.4 mg/mL, 5.6 mg/mL, 10 mg/mL & 12 mg/mL Solution for injection presentations utilize the same unit operations.

The manufacturing process development for the finished product has duly covered the main critical parameters and aspects of the process. The manufacturing process includes sterile filtration and vial filling under aseptic conditions like the authorised strength. The choice of the sterilisation method (sterile filtration) is justified.

The characterisation of primary packaging in relation to protection, qualification of international transportation and extractable/leachable testing was evaluated.

During manufacturing, Nusinersen 5.6 mg/mL & 10 mg/mL solution for injection comes in direct contact with polyethylene and glass compounding containers, stainless steel filling equipment, common pharmaceutical grade plastics (such as polycarbonate, polyvinylidene fluoride, polypropylene), and silicone transfer tubing.

In-use stability data and compatibility with administration materials for intrathecal administration of the newly proposed strengths were provided. All stability and compatibility results met the acceptance criteria, and it can be concluded that under the tested conditions (24 hours at room temperature and 30°C/75%RH), the solution is stable and compatible with the intrathecal delivery. This is in line with the

approved strength and confirm that Nusinersen is stable and compatible with intrathecal injection components in a range from 2.4 -12 mg/mL.

The primary packaging is single-use Type I glass vial with bromobutyl red (28 mg) or blue (50 mg) rubber stopper and an aluminium over-seal and plastic cap as stated in the SmPC. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The container and closure system is well described and characterised. The specifications and quality control information for the proposed container closure systems are provided. Compliance has been stated with European legislation and Ph. Eur. monographs. Certificates of analysis are enclosed.

2.4.3.2. Manufacture of the product and process controls

Satisfactory GMP documentation on the proposed finished product manufacturing site has been provided.

The manufacturing process consists of 10 main steps:

- Step 0: Receipt and storage of the drug substance at manufacturing site
- Step 1: Temperature equilibration of the drug substance to room temperature
- Step 2: Excipient dispensing for artificial cerebrospinal fluid (aCSF) preparation
- Step 3: aCSF preparation
- Step 4: Drug substance concentrate preparation
- Step 5: Compounding
- Step 6: Bioburden reduction filtration
- Step 7: Sterilizing filtration
- Step 8: Vial Filling, Stoppering and Crimping
- Step 9: 100% visual inspection of filled vials.

Details regarding the description, duration and holding times of different steps of manufacturing process of Nusinersen 5.6 mg/mL & 10 mg/mL Solution for injection were provided.

The process is considered to be a non-standard manufacturing process.

The commercial batch size proposed for Nusinersen 5.6 mg/mL & 10 mg/mL solution for injection has been defined Process validation data from three commercial scale batches manufactured at the proposed finished product manufacturing site were provided. The process validation studies (process validation, process hold times validation, media fill validation, filter validation and shipping qualification) demonstrate consistent and robust process performance and assurance of product quality.

It was demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur), identification (IP-HPLC-UV-MS), assay, purity and impurities (IP-HPLC-UV-MS),

extractable volume (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (high voltage leak detection).

The validation data of the analytical methods provided are in accordance with the requirements of the relevant ICH guidelines and can therefore be accepted.

A risk-based approach to assess the potential presence of elemental impurities in the nusinersen 5.6 mg/mL & 10 mg/mL solution for injection in line with the ICH Q3D guideline for elemental impurities was provided. The conclusion based on Option 2b demonstrates that all elemental impurities fall below the control threshold (30% of the Permissible Daily Exposure). As a result, it is concluded that there is negligible risk to the patient and no additional controls are required.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used were adequately described and appropriately validated in accordance with the ICH guidelines. The reference standards used for the analysis of the finish product are the same used for nusinersen active substance. This is acceptable.

Batch analysis results were provided for three commercial batches of each product strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from six pilot and commercial scale batches of the authorized 12 mg strength (2.4 mg/mL) stored for up to 60 months under long term conditions (5°C ± 3°C) and up to 9 months under accelerated conditions (25 ºC / 60% RH), three pilot scale batches of the proposed new strengths stored for up to 48 months at 5°C ± 3°C and up to 9 months at 25 ºC / 60% RH, and 3 pilot scale 12 mg/mL development batches stored for up to 60 months at 5°C ± 3°C and up to 9 months at 25 ºC / 60% RH according to the ICH guidelines were provided. The batches of Spinraza are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

A bracketing approach based on ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, has been applied across the range of product strengths.

Samples were tested for appearance, assay, purity, specified degradation products, pH, particulate matter, bacterial endotoxins, and container closure integrity testing. The analytical procedures used are stability indicating.

All stability data for nusinersen batches, 2.4 mg/mL, 5.6 mg/mL, 10 mg/mL and 12 mg/mL, met specifications for all attributes at the long term storage condition up to 60 months. No significant changes were observed at the accelerated condition.

The resulting stability data demonstrated no significant impact on product quality due to strength differences. As the data across all strengths are comparable, it is accepted to use this dataset collectively to support the shelf-life for the proposed product strengths (5.6 mg/mL and 10 mg/mL).

A shelf life of 60 months at refrigerated temperature (5°C ± 3°C/Ambient RH) is proposed for nusinersen 5.6 mg/mL and 10 mg/mL finished product based on 60 months of long-term stability data from the bracketing extremes, 2.4 mg/mL and 12 mg/mL finished products and the comparable stability profiles demonstrated between the intermediate dosage strengths up to 48 months.

Satisfactory post-approval stability was provided including the commitment to continue the long-term stability studies of Nusinersen 5.6 mg/mL & 10 mg/mL Solution for injection and the commitment to inform the authorities in case of any deviation related to specification at the end of shelf life of drug product.

Confirmation on compliance with CPMP/QWP/072/96 regarding start of shelf-life of the finished dosage form was presented.

Based on available stability data, the proposed shelf-life of 60 months when stored in refrigeration at 5°C±3°C as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension is aimed at introducing two new product strengths: Spinraza 28 mg (5.6 mg/mL) and 50 mg (10 mg/mL). The development of the new product strengths was based on the work conducted for the approved strength (Spinraza 12 mg; 2.4 mg/mL). No new information on the active substance was presented.

The ingredients, the manufacturing process and the in-process controls of the new strengths are similar to the ones from the approved strength, correspond to the current standard of pharmaceutical technology and are suitable to guarantee an appropriate product quality.

Information on development, manufacture and control of the finished product was presented in a satisfactory manner. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

The present application is for the approval of two additional strengths of Spinraza, 28 mg/5 mL and 50 mg/5ml.

A nonclinical program supported the approval of the 12 mg dose of nusinersen in the original marketing application. The nonclinical program consisted of *in vitro* and *in vivo* studies to characterize the pharmacology, pharmacokinetics (PK), safety pharmacology, and toxicology of nusinersen.

There were no new nonclinical pharmacology or pharmacokinetic studies conducted to support the higher dosing regimen of nusinersen.

2.5.2. Toxicology

2.5.2.1. Single dose toxicity

No information was provided.

2.5.2.2. Repeat dose toxicity

To support the clinical development of higher dose regimens, namely, the proposed 50/28 mg regimen of nusinersen, a combined 6-/13-week repeat-dose toxicology study (P058-17-03) was conducted in cynomolgus monkeys (initial age of 10 to 11 months). This study was GLP-compliant. Additionally, further detailed information on a previously submitted 53-week repeated dose toxicity study in cynomolgus monkeys was also included in the provided module 2.

In Study P058-17-03, 4 groups of animals received 0 (vehicle), 5, 10 or 15 mg/dose of nusinersen on Days 1, 15 and 29 and were sacrificed on Day 43 (2 weeks after the last dose). Two other groups of animals received 0 (vehicle) or 10 mg/dose of nusinersen on Days 1, 29, 57 and 85 and were sacrificed on Day 99 (2 weeks after the last dose). Each group of nusinersen dosed animals comprised 4 males and 4 females; each group of negative control animals, 2 males and 2 females. The vehicle consisted on artificial cerebrospinal fluid.

Assessments included clinical observation, body weight, food consumption, physical examinations, neurologic examinations (including general sensomotory aspects, cerebral reflexes [pupillary, orbicularis oculi], spinal reflexes [patellar, anal], and foot grip reflex), neurobehavioral observations (modified Irwin test), cardiovascular safety (electrocardiogram [ECG] and blood pressure), respiratory safety (respiration rate), ophthalmic examinations, blood clinical pathology (hematology, serum chemistry, coagulation), CSF chemistry and cell count, urinalysis, complement factors, organ weight, gross pathology, histopathology, plasma toxicokinetics (sampling from prior to dosing up to 168 hours post-dose), CSF nusinersen concentration (sampling prior to each dosing day), and nusinersen concentration in selected CNS and peripheral tissues (brain, spinal cord and kidney).

The study revealed no adverse effects and the NOAEL were set at the highest tested doses (15 and 10 mg/dose for the Q2W and Q4W dose regimens, respectively).

In the previously submitted 53-week repeated dose toxicity conducted in cynomolgus monkeys (Study 396443-AS06), nusinersen was administered IT to juvenile monkeys at 3 dose levels, 0.3 mg, 1 mg, and

4 mg, with 5 weekly doses on Days 1, 8, 15, 22 and 29, followed by additional 8 doses administered every 6 weeks on Days 71, 113, 155, 197, 239, 281, 323, and 365. All main study animals (5 animals/sex/group) were sacrificed on Day 372 after 53 weeks of dosing. Another 2 animals/sex/group for Groups 1 and 4 were sacrificed on Day 554, after a 26-week recovery period.

The study gave no indications of systemic toxicity, based on in-life, laboratory, and pathology assessments.

2.5.2.3. Genotoxicity

No additional information provided in this submission.

2.5.2.4. Carcinogenicity

As summarised in the provided Toxicology Written Summary (Module 2), a previously submitted 2-year carcinogenicity study (Study P058-17-02) in mice was conducted for nusinersen as part of postmarketing requirement for approval of the 12 mg dose. In this study, nusinersen was administered to male and female mice by subcutaneous injection at 0, 5, 15, or 50 mg/kg, once every 2 weeks for 2 years. An increase in the incidence of vascular tumours (combined haemangioma and hemangiosarcoma) was observed at the 50 mg/kg dose, which was associated with an AUC_{0-24} that is 156-fold and 284-fold the clinical serum exposure[a] at 28 mg and 12 mg nusinersen maintenance dose (on annual dose basis), respectively. No evidence of an oncogenic effect due to nusinersen was observed at dose levels up to 15 mg/kg. This dose was associated with a serum AUC_{0-24} that is 30-fold and 55-fold the clinical serum exposure [a] at 28 mg and 12 mg nusinersen maintenance dose (on annual dose basis), respectively.

2.5.2.5. Reproductive and developmental toxicity

No additional information provided in this submission.

2.5.2.6. Toxicokinetic data

Toxicokinetic data for the new 6-/13-week repeated dose toxicity study (Study P058-17-03) showed no marked differences between males and females in terms of nusinersen plasma concentrations. Systemic exposure to nusinersen (assessed by mean C_{max} and AUC_{0-t}) increased either proportionally with increasing dose or in a greater than dose proportional manner over the tested dose range (5 to 15 mg/dose). No accumulation was observed. Analysis of CSF prior to each dosing revealed the presence of nusinersen at all dosing days, except for Day 1, with concentrations ranging from 9.40 up to 181 ng/mL. Nusinersen tissue concentrations were higher in the kidney, compared to those found in the brain or spinal cord.

2.5.2.7. Tolerance

No additional information provided in this submission.

2.5.2.8. Other toxicity studies

No additional information provided in this submission.

2.5.3. Ecotoxicity/environmental risk assessment

The MAH submitted an environmental risk assessment (ERA) Phase 1 for the present application following the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, Rev1, 2024).

Table 1. Summary of main study results

Substance (INN/Invented Name): Nusinersen			
CAS-number (if available): 1258984-36-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log DOW -1.65 at pH 5, -1.89 at pH 7 -1.74 at pH 9	Potential PBT: **N**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log DOW -1.65 at pH 5, -1.89 at pH 7 -1.74 at pH 9	**not B**
PBT-statement:	The compound is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw,refined}$	1.1×10^{-5} Based on prevalence and treatment regime	µg/L	≥ 0.01 threshold: **N**
Other concerns (e.g., chemical class)			**N**

A Phase 1 Environmental Risk Assessment (ERA) for Nusinersen Spinraza 28 mg and 50 mg, solution for injection was submitted, complying with *Guideline on medicinal product environmental risk assessment* EMEA/CHMP/SWP/4447/00, Rev 1, 2024.

Log Pow values experimentally determined at pH 5, 7 and 9, according to the OECD 107 method, were < -1.9, far below the threshold value of 4.5 for further screening of persistence, bioaccumulation and toxicity (PBT). Given the available data, it is appropriate to conclude that Nusinersen does not meet the criteria for classification as a PBT substance, and no further assessment is necessary. The prevalence of 5q SMA affects less than 0.4 in 10,000 persons in the European Union (EU) (EMA 2017). As the ERA is based on the worst-case EU estimate for the prevalence of 5q SMA, the Fpen was refined based on a prevalence of 0.4 in 10,000 persons.

The MAH's Fpen adjustment meets Phase 1 requirements, per the Guideline EMEA/CHMP/SWP/4447/00, Rev 1, 2024. Based on this data, the PECsw was calculated to be 0.0000243 µg/L, which is significantly lower than the action limit of 0.01µg/L.

Based on the provided data, the risk assessment stops in Phase I. Therefore, a Phase II environmental fate and effects analysis is deemed unnecessary, following Guideline EMEA/CHMP/SWP/4447/00, Rev 1, 2024.

The data's relevance supports that no environmental risk is associated with the approval of the present application.

Following the guidelines specified in EMEA/CHMP/SWP/4447/00, 2024, the MAH has applied suitable precautionary and safety measures within the SmPC and PL. These measures are designed to inform patients and healthcare professionals, mitigate environmental risks, and promote environmental protection, in general conformity with standard regulatory practices.

2.5.4. Discussion on non-clinical aspects

To support the clinical development of higher dose regimens, namely, the proposed 50/28 mg regimen of nusinersen, a combined 6-/ 13-week repeat-dose toxicology study (P058-17-03) was conducted in cynomolgus monkeys. The results from this study were intended to support the higher loading doses. The higher maintenance dose was considered to be supported by the results of the previously submitted chronic toxicity study in cynomolgus monkeys.

Additionally, further detailed information on two previously submitted toxicological studies has also been included in the provided module 2. These studies are a 53-week repeated dose toxicity study in cynomolgus monkeys and a long-term carcinogenicity study in mice.

There were no new nonclinical pharmacology or pharmacokinetic studies conducted to support the higher dosing regimen of nusinersen, which is acceptable.

In study P058-17-03, 4 groups of animals received 0 (vehicle), 5, 10 or 15 mg/dose of nusinersen on Days 1, 15 and 29 and were sacrificed on Day 43 (2 weeks after the last dose). Two other groups of animals received 0 (vehicle) or 10 mg/dose of nusinersen on Days 1, 29, 57 and 85 and were sacrificed on Day 99 (2 weeks after the last dose). Each group of nusinersen dosed animals comprised 4 males and 4 females; each group of negative control animals, 2 males and 2 females. The vehicle consisted on artificial cerebrospinal fluid.

Assessment of toxicity was based on clinical observation, body weight, food consumption, physical examinations, neurologic examinations (including general sensomotory aspects, cerebral reflexes [pupillary, orbicularis oculi], spinal reflexes [patellar, anal], and foot grip reflex), neurobehavioral observations (modified Irwin test), cardiovascular safety (electrocardiogram [ECG] and blood pressure), respiratory safety (respiration rate), ophthalmic examinations, blood clinical pathology (hematology, serum chemistry, coagulation), CSF chemistry and cell count, urinalysis, complement factors, organ weight, gross pathology, and histopathology. Furthermore, data was obtained on plasma toxicokinetics (sampling from prior to dosing to up to 168 hours post-dose), CSF nusinersen concentration (sampling prior to each dosing day), and nusinersen concentration in selected CNS and peripheral tissues (brain, spinal cord and kidney).

The study revealed no adverse effects of nusinersen, with the NOAEL for the administrations Q2W and Q4W set at the respective highest tested doses, i.e., 15 and 10 mg/dose, respectively.

Effects observed, which were not considered to be adverse, included transient clinical observations and neurological findings – uncoordinated movement, limited use of the extremities and/or hypoactivity, and reduction or absence of the patellar, foot grip and/or anal reflexes – and microscopic findings in the brain and lymph nodes consistent with previously described class effects of ASOs and considered potentially related to lysosomal uptake and accumulation of ASO.

In terms of toxicokinetics, data from concentrations of nusinersen in plasma showed no notable sex difference in exposure. Systemic exposure to nusinersen (assessed by mean C_{max} and $AUC_{0\text{-}t}$) increased either proportionally with increasing dose or in a greater than dose proportional manner over the tested dose range (5 to 15 mg/dose). No accumulation was observed. Analysis of CSF prior to each dosing revealed the presence of nusinersen at all dosing days, except for Day 1, with concentrations ranging from 9.40 up to 181 ng/mL. Nusinersen tissue concentrations were higher in the kidney, compared to those found in the brain or spinal cord.

For the determination of safety margins regarding the new intended clinical dosing regimen, the MAH has addressed, separately, safety margins for the loading and maintenance doses (2 doses of 50 mg/dose with a 2 weeks interval, and 28 mg/dose every 4 months, respectively).

Safety margins for the loading doses were based on the results of the new repeated dose toxicity study (Study P058-17-03), human equivalent dose and cumulative doses. In the new study, the NOAEL for a Q2W regimen was 15 mg/dose, which corresponds to an HED of 150 mg/dose. This indicates a safety margin of 3, on a single dose basis. Regarding a determination of safety margins based on cumulative doses, it may not be justified to consider this approach as the same dosing frequency intended for humans was employed in the animal study and, moreover, animals received only one additional dose compared to the number of loading doses in the proposed clinical dose regimen (3 dose administrations in the animal study versus 2 in humans).

Safety margins for the maintenance dose in the intended dosing regimen (28 mg/dose every 4 months) were determined based on the results of the previously submitted 53-week repeated dose toxicity study in cynomolgus monkeys. In this study in monkeys, animals received, by IT injection, 5 weekly doses followed by additional 8 doses administered every 6 weeks. The maximum tested dose, 4 mg/dose, was the NOAEL.

A 4 mg/dose administered IT to cynomolgus monkeys is equivalent to a human dose of 40 mg/dose. Therefore, on a single dose basis, this gives a safety margin of 1.4. However, a safety margin based on cumulative dose is also to be considered as the frequency of dosing in the animal study was significantly higher compared to that intended in humans. On the basis of a cumulative dose over a 1-year period, a safety margin of 6.2 was calculated.

Based on the results of the new 6-/13-week repeated dose toxicity study and the new calculated safety margins, information on repeated dose toxicity in section 5.3 of the SmPC has been adequately revised.

In addition to further detailed information on a previously submitted 53-week repeated dose toxicity study, more detailed information on a previously submitted carcinogenicity study was also included in module 2.

As summarised in the provided Toxicology Written Summary, a 2-year carcinogenicity study (Study P058-17-02) in mice was conducted for nusinersen as part of postmarketing requirement for approval of the 12 mg dose. In this study, nusinersen was administered to male and female mice by subcutaneous injection at 0, 5, 15, or 50 mg/kg, once every 2 weeks for 2 years. An increase in the incidence of vascular tumours (combined haemangioma and hemangiosarcoma) was observed at the 50 mg/kg dose, which was associated with an AUC_{0-24} that is 156-fold and 284-fold the clinical serum exposure[a] at 28 mg and 12 mg nusinersen maintenance dose (on annual dose basis), respectively. No evidence of an oncogenic effect due to nusinersen was observed at dose levels up to 15 mg/kg. This dose was associated with a serum AUC_{0-24} that is 30-fold and 55-fold the clinical serum exposure [a] at 28 mg and 12 mg nusinersen maintenance dose (on annual dose basis), respectively.

([a] Clinical exposure data from Study CS4 for 12 mg and Study 232SM203Part C for 28 mg)

The MAH clarified that the new information regarding the mouse carcinogenicity study results from a re-evaluation of the tumour data for study. While, previously, the mouse study had been considered to show no carcinogenicity, the conclusion of the data re-evaluation is that an increase in the incidence of vascular tumours was observed at the high tested dose (50 mg/kg).

Information on carcinogenicity in section 5.3 of the SmPC has been revised accordingly.

Finally, the MAH clarified that an identified discrepancy, between study report versus tabulated toxicology summary, on the information on purity and impurity concentration of the batch tested in the new repeated dose toxicity study (Study P058-17-03) was the result of an incorrection. Information mistakenly included in the tabulated toxicology summary was based on the results generated at an earlier timepoint for stability analysis.

2.5.5. Conclusion on non-clinical aspects

To support the new clinical dosing regimen (regimen 50/28 mg), a new toxicity study has been performed. This is a combined 6-/13-week repeat dose toxicity study (P058-17-03) conducted in cynomolgus monkeys. Additionally, further detailed information was also provided regarding two previously submitted studies. These are a 53-week repeated dose toxicity study in cynomolgus monkeys and a carcinogenicity study in mice.

As for the previous studies, no adverse effects were observed in the new study.

Concerning the content of section 5.3 of the SmPC, the MAH proposed a revision of the information on repeated dose toxicity and carcinogenicity. The revision is agreed with.

Nusinersen is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- **Tabular overview of clinical studies**

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Study Phase	Phase 2/3			Phase 3
Study Design	Open-label, multiple-dose	Randomized, double-blind, multiple-dose, active-controlled	Open-label, multiple-dose	Open-label, multiple-dose, long-term extension
Study Population	Participants with symptomatic later-onset SMA	Participants with symptomatic infantile (pivotal) or later-onset SMA	Participants with any SMA status (Cohort 1) Adult participants with SMA (Cohort 2)	See study populations for Study SM203, Parts A, B, and C
Study Start **Enrollment Status** **Total Enrolled (Planned)**	26 March 2020 Completed 6 participants (6 participants)	12 November 2020 Completed 99 participants (99 participants)	04 August 2021 Completed 40 participants (40 participants)	19 April 2021 Ongoing 113 participants (145 participants) as of the 30 May 2024 data cutoff
Study Status	Completed	Completed	Completed	Ongoing
Study Objectives	Safety, tolerability, efficacy, and PK	Efficacy, safety, tolerability, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK
Primary Efficacy Endpoint	NA	CHOP INTEND (infantile-onset): Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the JRT (comparison of higher dose to Matched Sham Control) (infantile-onset)	NA	NA
Secondary Efficacy Endpoints	HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA	CHOP INTEND, HINE motor milestones, CSF and plasma levels of NF-L, time to death or permanent ventilation, overall survival, hospitalizations, CGIC, serious respiratory events, time on ventilation, ventilator use, PASA (infantile-onset) HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, CSF and plasma levels of NF-L, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA (later-onset)	HFMSE, RULM, WHO motor milestones, ACEND. hospitalizations, CGIC, serious respiratory events, ventilator use (Cohorts 1 and 2) PedsQL, CHOP INTEND, HINE motor milestones (Cohort 1 only)	WHO motor milestones, ventilator use, time to death (all participants) CHOP INTEND, HINE motor milestones, HINE responders, time on ventilation, time to death or permanent ventilation (participants who were evaluated for these endpoints in SM203) HFSME, RULM (participants ≥ 2 years of age)

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Study Phase	Phase 2/3			Phase 3
Study Design	Open-label, multiple-dose	Randomized, double-blind, multiple-dose, active-controlled	Open-label, multiple-dose	Open-label, multiple-dose, long-term extension
Study Population	Participants with symptomatic later-onset SMA	Participants with symptomatic infantile (pivotal) or later-onset SMA	Participants with any SMA status (Cohort 1) Adult participants with SMA (Cohort 2)	See study populations for Study SM203, Parts A, B, and C
Study Start **Enrollment Status** **Total Enrolled (Planned)**	26 March 2020 Completed 6 participants (6 participants)	12 November 2020 Completed 99 participants (99 participants)	04 August 2021 Completed 40 participants (40 participants)	19 April 2021 Ongoing 113 participants (145 participants) as of the 30 May 2024 data cutoff
Study Status	Completed	Completed	Completed	Ongoing
Study Objectives	Safety, tolerability, efficacy, and PK	Efficacy, safety, tolerability, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK
Primary Efficacy Endpoint	NA	CHOP INTEND (infantile-onset): Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the JRT (comparison of higher dose to Matched Sham Control) (infantile-onset)	NA	NA
Secondary Efficacy Endpoints	HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA	CHOP INTEND, HINE motor milestones, CSF and plasma levels of NF-L, time to death or permanent ventilation, overall survival, hospitalizations, CGIC, serious respiratory events, time on ventilation, ventilator use, PASA (infantile-onset) HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, CSF and plasma levels of NF-L, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA (later-onset)	HFMSE, RULM, WHO motor milestones, ACEND. hospitalizations, CGIC, serious respiratory events, ventilator use (Cohorts 1 and 2) PedsQL, CHOP INTEND, HINE motor milestones (Cohort 1 only)	WHO motor milestones, ventilator use, time to death (all participants) CHOP INTEND, HINE motor milestones, HINE responders, time on ventilation, time to death or permanent ventilation (participants who were evaluated for these endpoints in SM203) HFSME, RULM (participants ≥ 2 years of age)

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Test Product, Route of Administration Dosage Regimen Duration of Treatment	Nusinersen, IT injection by LP: 28 mg loading doses on Days 1, 15, and 29 and 28 mg maintenance doses on Days 149 and 269 Treatment duration: approximately 269 days	Nusinersen, IT injection by LP: 12-mg Group: 12 mg loading doses on Days 1, 15, 29, and 64 and 12 mg maintenance doses of Days 183 and 279 (and a sham procedure on Day 135) 50/28-mg Group: 50 mg loading doses on Days 1 and 15 and maintenance doses of 28 mg on Days 135 and 279 (and sham procedures on Days 29, 64, and 183) Treatment duration: approximately 279 days	Nusinersen, IT injection by LP: 50 mg single bolus on Day 1 and 28 mg maintenance doses on Days 121 and 241 Treatment duration: approximately 241 days	Nusinersen, IT injection by LP: 28 mg loading doses ~every 4 months or 50 mg loading dose on Day 1, followed by 28 mg maintenance doses ~every 4 months Treatment duration: up to 1921 days
Number of Participants Dosed by Arm	28 mg: 6	Infantile-onset: 12-mg Group: 25 50/28-mg Group: 50 Matched Sham: 20 Later-onset: 12-mg Group: 8 50/28-mg Group: 16 Matched CS4 Sham: 16 Matched CS4 12 mg: 32	50/28 mg: 40	50/28 mg Part A: 6 Part B: Infantile-onset: 12-mg to 50/28-mg Group: 9 50/28-mg Group: 26 Later-onset: 12-mg to 50/28-mg Group: 7 50/28-mg Group: 16 Part C: Infantile-onset: 2 Later-onset: 37
Sex	83.3% male 16.7% female	Infantile-onset: 53.3% male 46.7% female Later-onset: 16.7% male 83.3% female	Infantile-onset: 50.0% male 50.0% female Later-onset: < 18 years: 57.1% male 42.9% female ≥ 18 years 66.7% male 33.3% female	Part A: 83.3% male 16.7% female Part B: Infantile-onset: 45.7% male 54.3% female Later-onset: 17.4% male 82.6% female Part C: 61.5% male 38.5% female

[a] For study SM302, mean (median) age at first dose is presented.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

No new information was provided. The drug is administered by IT route and no absorption process is involved.

Distribution

No new information was provided. The PK of Nusinersen in the CSF and plasma were best described, simultaneously, by a four compartment model with two compartments representing the CSF and CNS tissue compartments and two compartments representing the plasma, as in the previous popPK models.

Elimination

The updated model predicted much longer terminal elimination half-life in the CSF (t½) than the previous Nuventra PPK2 model. Assuming a 5-years old, 15-kg, later-onset SMA patient on 12 mg of nusinersen, the Nuventra PPK2 model estimated CSF t½ to be ~6 months while the updated model estimated CSF t½ to be ~20 months.

The terminal elimination half-life in plasma was initially estimated to be 63 to 87 days based on the clinical data and a non-compartmental approach. The current PopPK model is predicting a terminal elimination half-life of 58 days for a 15 kg children.

Dose proportionality and time dependencies

Overall, plasma concentrations of nusinersen increased approximately proportionally with dose across all measured timepoints. A less-than-dose-proportional increase in CSF C_{trough} levels was observed over the range of 12 mg to 50 mg doses with an approximately 2-fold higher CSF C_{trough} following the 50 mg dose compared to the 12 mg dose on Day 15. However, higher variability was observed in the 50/28 mg Group.

The popPK analysis of CSF trough concentrations data across all nusinersen studies including the long-term treatment data confirmed slow accumulation of CSF trough concentrations over time, suggesting that the apparent t½ in CSF could be significantly longer than was originally predicted. No accumulation was observed in the plasma data.

2.6.2.2. Pharmacodynamics

Mechanism of action

Nusinersen is a uniformly modified 2’-O-(2-methoxyethyl) antisense oligonucleotide that is administered to the CNS as an intrathecal (IT) infusion. It is supplied as an isotonic solution.

Given that the current report concerns the assessment of a change in the existing market authorization (Spinraza) namely to the addition of a new strength (higher) according to the Annex I of Regulation 1234/2008, the analysis of the chapter in question does not apply. However, and according to cross

references (allowed in the Article 8(3) for extensions of full applications), nusinersen is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using *in vitro* assays and studies in transgenic animal models of SMA, nusinersen was shown to increase exon 7 inclusion in *SMN2* messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein. Nusinersen acts to replace the SMN protein deficit which causes SMA, by increasing the splicing efficiency of the *SMN2* pre- mRNA. More specifically, nusinersen is a 18-mer 2'-MOE phosphorothioate antisense oligonucleotide that acts as a splice-altering oligonucleotide. Nusinersen was designed to pair with a specific target sequence on the *SMN2* pre-mRNA to displace heterogeneous ribonucleoproteins (hnRNPs) at the intronic splice silencing site-1 (ISS-1) between exons 7 and 8 to allow for more complete translation of SMN protein from the paralogous gene *SMN2*. Further reinforcing this concept, SMA phenotype is closely tied to *SMN2* copy number. *SMN2* serves to produce SMN protein, however at a greatly reduced rate because of differential splicing caused by the binding of the hnRNPs at the ISS-1.

Primary and Secondary pharmacology

Neurofilament levels (e.g., NF-L) are a marker of axonal injury and neurodegeneration, with higher levels of neurofilament associated with faster disease progression in SMA and other neurodegenerative diseases [Darras 2019; Xu 2016]. Neurofilament levels concentrations were measured in Studies SM203 and SM302 as a sensitive and objective marker of treatment response.

The Clinical Pharmacology Studies submitted by the MAH included results for the higher dose of nusinersen from the final analysis of completed Study 232SM203 (DEVOTE; henceforth referred to as SM203) and an interim analysis of ongoing Study 232SM302 (ONWARD [data cutoff 30 May 2024]; referred to as SM302).

Study SM203

Study SM203 is a 3-part (Parts A, B, and C) study in which participants were followed for approximately 10 to 13 months after the first dose of study treatment.

Part A was an open-label safety evaluation. Six participants with later-onset SMA who were 2 to ≤ 15 years of age, inclusive, at the signing of informed consent received 3 loading doses of 28 mg of nusinersen on Days 1, 15, and 29, followed by 2 maintenance doses of 28 mg on Days 149 and 269 (referred to as the 28/28 mg dosing regimen). A sentinel dosing approach was used, in which the first participant was enrolled and dosed with 28 mg of nusinersen. Following the availability of 72 hours of safety data after the first loading dose in the first participant, data for this participant were reviewed by the Investigator and the Sponsor before the next 5 participants were enrolled. Only 1 participant could receive their first dose of study treatment on a given day. After 6 participants completed the loading period (i.e., when the last participant had available safety data through the Day 64 visit), an IDMC reviewed the available safety data to recommend whether Part B could be initiated. Meanwhile, participants in Part A proceeded to maintenance dosing without interruption.

Part B of Study SM203 was the pivotal, double-blind, active-controlled part of the study in which the primary endpoint (the change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the JRT [comparison of higher dose to matched sham control]) was evaluated in participants with infantile-onset SMA. Participants received either 2 or 4 loading doses of nusinersen (for the 50/28-mg Group and 12-mg Group, respectively) administered IT followed by maintenance doses approximately every 4 months thereafter.

Approximately 99 participants with infantile- or later-onset SMA were to be randomized in a 1:2 ratio to receive either the currently approved dosing regimen of 4 loading doses of 12 mg of nusinersen

administered IT (Days 1, 15, 29, and 64) followed by 2 maintenance doses of 12 mg on Days 183 and 279 (referred to henceforth as the 12-mg Group) or 2 loading doses of 50 mg of nusinersen administered IT (Days 1 and 15) followed by 2 maintenance doses of 28 mg on Days 135 and 279 (referred henceforth as the 50/28-mg Group). In order to maintain blinding, 1 sham procedure was administered in the 12-mg Group on Day 135, and 3 sham procedures were administered in the 50/28-mg Group on Days 29, 64, and 183 to ensure the same dosing visit schedule as the 12-mg Group. The blinded dosing schedule for Part B is summarized in Table 2.

Table 2. Study SM203 part B blinded dosing schedule

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

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

Part C of Study SM203 provides supportive safety, efficacy, PK, and PD data for the nusinersen 50/28 mg dosing regimen. In Part C, approximately 40 participants who had already received the approved dose of nusinersen 12 mg for at least 1 year prior to entry were enrolled and switched to the 50/28 mg dosing regimen. The initial cohort in Part C (i.e., Cohort 1) consisted of approximately 20 participants of any age or SMA status. For Cohort 1, an attempt was made to enroll at least 8 but no more than 12 participants ≥ 18 years of age (participants in Cohort 1 ≥ 18 years of age were required to be ambulatory). Up to 5 participants with severe scoliosis and/or severe contractures could have been enrolled in Cohort 1 of Part C after consultation with the Medical Monitor. An additional cohort (i.e., Cohort 2) consisting of up to approximately 20 adult participants (≥ 18 years of age) was subsequently added to Part C in Protocol Version 5 in order to enable collection of data in adults transitioning from the currently approved nusinersen dosing regimen to the 50/28 mg dosing regimen. Participants in Cohort 2 could be either ambulatory or nonambulatory.

All participants in Part C received a single bolus dose of 50 mg (to be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241 (Table 3).

Table 3. Study SM203 part C dosing schedule

Prior Treatment	Dose 1	Dose 2	Dose 3
≥ 1 year receiving nusinersen 12 mg	Day 1 1 x 50 mg transition dose	Day 121 28 mg maintenance dose	Day 241 28 mg maintenance dose

Study SM302

Study SM302 is a Phase 3 long-term extension study of Study SM203 evaluating the long-term safety, tolerability, and efficacy of nusinersen administered by IT injection at higher doses (50 or 28 mg loading/28 mg maintenance) for up to 1921 days to participants with SMA. This submission includes an interim analysis for the ongoing SM302 study with a data cutoff date of 30 May 2024; as of the cutoff date, 108 participants were enrolled, and 103 participants had been dosed: 6 participants from Part A,

35 participants with infantile-onset SMA from Part B, 23 participants with later-onset SMA from Part B, and 39 participants from Part C of Study SM203.

Overall, the participants with infantile-onset SMA in Part B of Study SM203, the 50/28 mg dosing regimen robustly slowed neurodegeneration, as measured by reductions in NF-L, including a statistically significantly greater reduction from baseline to Day 183 in plasma concentration of NF-L for the 50/28-mg Group compared to the Matched Sham. Consistent with the more rapid loading period, the 50/28 mg regimen reduced NF-L more quickly than the 12 mg regimen. Similarly, in participants with later-onset SMA in Part B, the 50/28 mg dosing regimen achieved a faster lowering of NF-L in plasma than the 12 mg regimen. An exploratory analysis of the potential relationship between plasma NF-L levels and CSF concentration showed that a more rapid reduction in NF-L levels can be linked to greater early nusinersen exposures.

The results from Studies SM203 and SM302 demonstrate that CSF trough concentrations of nusinersen were higher with the 50/28 mg dosing regimen than with the 12 mg dosing regimen. In Part B of Study SM203, a less-than-dose-proportional increase in CSF trough concentration was observed over the range of 12 to 50 mg doses, with greater variability observed in the 50/28 mg Group. Although the increase in CSF exposures was less than proportional with dose, the higher dosing regimen achieved comparable levels of CSF trough in fewer days (15 days versus 64 days) and with fewer doses (1 dose of 50 mg versus 3 doses of 12 mg). As demonstrated by participants who switched from receiving commercial treatment of nusinersen 12 mg to the 50/28 mg dosing regimen in Part C of Study SM203, the majority of individual CSF trough concentrations from Part C participants who transitioned to Study SM302 generally tended to be higher than those from the comparable population in Study CS11.

Plasma concentrations of nusinersen in Part B of Study SM203 increased linearly with dose across all measured timepoints. Plasma concentrations at Day 15 were approximately 4- to 5-fold higher in the 50/28-mg Group than in the 12-mg Group.

For the integrated immunogenicity analyses that used final results from Study SM203, interim results from Study SM302 (data cut 30 May 2024), final results from Study CS11 and its index studies, and interim results from Study SM201 (data cut 19 February 2020), 38 of 367 participants (10.4%) dosed with nusinersen 12 mg or lower and 11 of 117 participants (9.4%) dosed with nusinersen 28 mg or higher were positive for treatment-emergent anti nusinersen antibodies at any timepoint during evaluation. PopPK analysis of the immunogenicity data revealed a decrease in nusinersen plasma clearance and elevated plasma C_{trough} in a subset of ADA-positive participants. Additionally, no impact of immunogenicity on safety and efficacy outcomes was observed. The overall data from clinical studies continue to support the assessment of nusinersen as a low risk molecule with regards to immunogenicity.

An exposure-response (ER) analysis using combined data from SM203 and SM302 studies evaluated the relationship between plasma/CSF concentration of nusinersen and effect (evaluated with measure of plasma and CSF levels of NF-L and measure the CHOP-INTEND score) and safety (evaluated thought immunogenicity studies).

2.6.3. Discussion on clinical pharmacology

2.6.3.1. Pharmacokinetics

The clinical efficacy of nusinersen has been evaluated across a broad range of patients in all age groups (infants, paediatrics, teenagers, and adults) and SMA types (infantile-onset [SMA symptom onset ≤ 6 months (≤ 180 days) of age], later-onset [SMA symptom onset > 6 months (> 180 days) of age], and presymptomatic). The approved dosing regimen of nusinersen in the majority of countries 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. PK and PD analyses indicated that nusinersen drug exposures higher than those achieved with 12 mg in patients with SMA may produce an even greater benefit in motor function. Additionally, PK modelling and simulations identified dosing regimens that achieved higher drug exposure more rapidly. Based on these PK/PD analyses, two new clinical studies (Study SM203 and Study SM302) were conducted to evaluate a higher dose nusinersen regimen, including a 28 mg loading dose (administered as 3 doses at biweekly intervals), a 50 mg loading dose (administered as 2 doses at biweekly intervals), and a 28 mg maintenance dose. The PK obtained in these two new studies is evaluated in this application.

The PK and Immunogenicity analytical methods used in the current application are the same as the ones discussed in previous submissions. Their performance was considered acceptable. Regarding the PD analytical method, aiming at quantifying the plasma and CSF NF-L, its performance based on the validation values seems acceptable and following the M10 ICH guideline. Dilution and lack of Hook effect up to 16,7000 pg/ml was defined. Overall, the methods seem acceptable.

In the individual studies, a non-compartmental approach was undertaken in order to describe the observed data. in addition, a new popPK including all available data was also presented. Given the sparse sampling performed in most of the studies, this is acceptable.

The MAH presented a new popPK analysis including all the previously available data as well as the new data including the higher 28 mg and 50 mg doses. The final model presented the same base model as the previous ones, just differing in the inclusion of some different co-variables. The description of the number of subjects, data and excluded information in all the popPK models developed up to now can be seen in the following table. It can be seen that the last model includes a significantly higher number of data, especially when comparing to the previous iteration (PPK2):

Model[a]	**Ionis PPK0**			**Nuventra PPK1**			**Nuventra PPK2**			**Biogen PPK6**		**Biogen PPK7**		
Report	396443-IS11			CPP-17-001-BIIB058			CPP-17-005-BIIB058			CPP-24-001-BIIB058 (Plasma Only)		CPP-24-003-BIIB058 (Current Report)		
Cutoff	27 Jan 2016			27 Jan 2016			Jun 2017			21 Mar 2024		Aug 2024		
Data Included[b]	N Subject	N CSF	N Plasma	N Subject	N CSF	N Plasma	N Subject	N CSF	N Plasma	N Subject	N Plasma	N Subject	N CSF	N Plasma
CS1	24	15	105	26	24	156	27	25	163	27	163	27	25	154
CS2	32	53	458	33	56	473	34	59	487	34	488	34	57	466
CS3A	20	89	183	20	95	194	20	96	194	20	255	20	138	250
CS3B	–	–	–	–	–	–	80	305	616	80	620	80	295	592
CS4	–	–	–	–	–	–	84	243	823	84	830	84	240	818
CS10	16	16	118	18	16	118	18	16	118	18	118	18	9	111
CS11	–	–	–	–	–	–	45	54	51	290	4071	292	4400	4009
CS12	43	100	293	46	106	314	47	123	405	47	425	47	153	406
201	–	–	–	–	–	–	19	77	61	25	312	25	327	308
202	–	–	–	–	–	–	14	60	52	20	131	20	174	130
203	–	–	–	–	–	–	–	–	–	6	60	145	394	1251
302	–	–	–	–	–	–	–	–	–	–	–	103	441	633
402	–	–	–	–	–	–	–	–	–	50	419	50	262	401
Total Data	72	279[c]	1181[c]	75	297	1255	274	1058	2970	406	7892	547	6915	9529
Data Excluded[d]	N Subject	N CSF	N Plasma	N Subject	N CSF	N Plasma	N Subject	N CSF	N Plasma	N Subject	N Plasma	N Subject	N CSF	N Plasma
BLQ	0	Not Available		0	13	88	0	69	69	0	115	0	13	118
Outlier	4	Total 174		1	17	33	0	26	21	0	9	0	259	298
Outlier Criteria	ID=20, 22, 25, 50; |CWRES| > 6			ID=20; |CWRES| > 6			|CWRES|>5			1 at 0.13 h postdose (expect predose); 8 from graphical analysis		Based on graphical analysis (See Section 4.1.1)		

The final model parameters and co-variables included in each individual popPK model developed over time can be seen in the following table. In general, similar values are obtained showing that the added data is just allowing to determine the PK with more confidence.

Model[a]	Ionis PPK0	Nuventra PPK1	Nuventra PPK2	Biogen PPK6	Biogen PPK7
NONMEM Version	7.2	7.3	7.3	7.5	7.5
Model Structure	2-cmt CSF + 2-cmt in plasma Drug clears unilaterally from CSF to plasma and eliminates from plasma			2-compartment in plasma; first order absorption	2-cmt CSF + 2-cmt in plasma
CSF					
CLc (L/h)	0.136	0.105	0.158 * (1 + 0.159 * POP2 – 0.577 * POP3)	N/A	0.0476
Qc (L/h)	0.0712	0.068	0.0783	N/A	$0.0106 * (Dose/12)^{-0.307}$
V1 (L)	$0.433 * (WT/14.55)^{0.596}$	0.245 * (WT up to 10/10)	0.391 * [1 + 0.0303*(WT - 20)]	N/A	$0.188 * (Age\ up\ to\ 18/18)^{0.481}$
V4 (L)	263	295	324	N/A	$190 * [Age / (Age + 0.302)] * 0.475^{POP3}$
Plasma					
CLp (L/h)	$2.36 * (WT/14.55)^{0.689}$	$3.19 * (WT\ up\ to\ 20/20)^{1.17}$	2.78 * [1 – 0.0483 * (WT under 20) + 0.0206 * (WT over 20)] * [1 + 0.694 * POP3]	$2.50 * (WT/20)^{0.681} * (0.127)^{ADACUM,Mix1}$ (Mix1: 36.8%)	$6.40 * (WT/70)^{0.812} * (1 – 0.882 * ADAHFLG)$
Qp (L/h)	0.568	0.451	0.240	1.76 * (WT/20)	3.27 * (WT/70)
V2 (L)	29.0 * [1 + 0.047 * (WT - 14.55)]	$49.1 * (WT\ up\ to\ 20/20)^{1.14}$	39.3 * [1 – 0.0546*(WT under 20) + 0.0281*(WT over 20)] * [1 – 0.494 * POP3]	52.2 * (WT/20)	139 * (WT/70)
V3 (L)	418	382	166	3350 * (WT/20)	4730 * (WT/70)
Ka (h^{-1})	N/A	N/A	N/A	1.28 * exp(-0.135 * Age up to 18)	N/A
IIV	CLc, CLp, V1, V2; IOV on CLc	CLc, CLp, V1, V2	CLc, CLp, V1, V2	CLp, V2, Ka	CLc, CLp, V1, V2, V4
Residual Error	Proportional	Proportional	Proportional	Proportional	Proportional

In this regard, it should be mentioned that the GOF are acceptable except for the presymptomatic subjects. In this particular case, it may be due to the small number of subjects and the high variability of the data. The VPC confirm the ability of the model to describe the central tendency and the variability of the data in most of the cases. In general, the model seems acceptable for the intended use. When compared to the previous presented PopPK model, no major differences were observed.

Regarding the absorption process, the drug is administered by IT route. As such, no absorption process is involved. Since the drug is administered by IT route, an absolute bioavailability in the CNS is assumed. Drug is distributed in the CNS tissues and eliminated by movement to plasma. This is a very slow process that spans for a long period of time, that is now estimated to be with a t1/2 of around 20 months.

The MAH used different strengths/formulations in the clinical trials. These included the same excipients at equal concentrations except in nusinersen and sodium chloride. In the ready to use formulations (2.4 mg/mL, 5.6 mg/mL and 10 mg/mL), the final volume to be administered is always 5 mL. Since these are simple aqueous solutions to be administered by IT route, no biopharmaceutical differences are expected.

Regarding the distribution, the PopPK model assuming a two-compartment system for both CSF and plasma predicted an extensive distribution in the CNS tissues. Plasma data also shows a large distribution of the drug in the tissues. This goes in line with the previous knowledge of the drug.

Nusinersen presents a long elimination half-life from both CSF and plasma. From CSF, elimination half-life was estimated around 20 months, significantly higher than initially determined at the time of the initial application, being this information updated in the SmPC. This estimated value has been increasing as more data covering more time has been made available. Adequate estimation of CSF t½ requires PK assessment over at least 3-4 half-lives, so estimation of nusinersen t½ was likely constrained by the duration of PK assessment in most subjects. In the updated dataset, CSF C_{trough} in patients did not plateau after the loading phase and continued to rise throughout much of the decade that PK data was collected for. In non-presymptomatic subjects over 1 year of age on 12 mg of nusinersen, median CSF C_{trough} by year approximately doubled in 3 years and tripled in 5 years; the number of CSF samples tapered after 7 years. For plasma, elimination half-life was determined to be around 60 days, as previously determined. No new information was made available on metabolism and the PK of metabolites.

Regarding the dose proportionality, the initial application with doses from 1 mg to 12 mg, the CSF fluid concentrations appear to increase in a less than dose proportionality from 1 mg to 12. However, due to large variability and low number of subjects, dose proportionality could generally be concluded. The new data seems to result in similar conclusions. In CSF, a less-than-dose-proportional increase in CSF C_{trough} levels was also observed over the range of 12 mg to 50 mg doses, with only a ≈2x increase, however with a high variability observed in the 50/28 mg Group. In spite of this, CSF C_{trough} of nusinersen on Day 15 in the 50/28 mg Group were similar to those observed in the 12 mg Group before the last loading dose of the standard dosing regimen (Day 64 after 3x 12 mg administrations) for both SMA onset types. At day 279, C_{trough} concentrations were basically the same in the 12 mg group and in the 50/28 mg, although due to the different administration regime it is difficult to directly compare the two concentrations and proportionality cannot be concluded by side-by-side comparison of time-dependent profiles from the 2 dosing regimens due to different dosing schedules. In this regard, the popPK included a dose dependent effect as a covariate in the Q_{CSF}, that results in an increase in the terminal elimination half-life for higher doses, but not in a significant way for the 12 mg *vs* 28 mg (≈20 months to ≈23 months). In plasma, the 50 mg dose usually resulted in PK metrics that are generally 5x the ones observed with the 12 mg dose, and the C_{trough} at day 279 after administration of 28 mg doses resulted in values approximately 2x the ones observed with the 12 mg dose.

The popPK model did not identify any time dependent covariate (besides age and weight) that could influence the drug's PK. In CSF, long-term treatment data confirmed slow accumulation of CSF trough concentrations over time, suggesting that the apparent t½ in CSF is around 20 months. In plasma, no accumulation was observed. Similar trend was observed in both the 12 mg protocol and the 50/28 mg protocol. This information was included in the SmPC.

The CSF and plasma concentrations variability are moderate to high in all the population studied. In the popPK model, intra-subject variabilities are also moderate to high in the CLp, CLcsf, V1, V2 and V4 parameters.

No further data was provided related to the drug's PK and, thus, no further changes in the SmPC are proposed.

2.6.3.2. Pharmacodynamics

Overall, the MAH, according to the bibliographic sources, identified the plasma neurofilaments (namely the plasma neurofilament light chain (Nf-L)) as disease progression markers, taking in account that a translatable primary pharmacology biomarker was not available. The results obtained in the clinical trial SM203 (part B) with this biomarker are included in an acceptable manner in point 5.1 of the SmPC. Indeed, in participants with infantile-onset SMA in Part B of Study SM203, the 50/28 mg dosing regimen robustly slowed neurodegeneration, as measured by reductions in NF-L, including a statistically significantly greater reduction from baseline to Day 183 in plasma concentration of NF-L for the 50/28-mg Group compared to the Matched Sham. Consistent with the more rapid loading period, the 50/28 mg regimen reduced NF-L more quickly than the 12 mg regimen. Similarly, in participants with later-onset SMA in Part B, the 50/28 mg dosing regimen achieved a faster lowering of NF-L in plasma than the 12 mg regimen.

Taken together, the totality of data from Study SM203, along with longer-term integrated analyses with Study SM302, provide evidence of the benefit of the higher-dose regimen for the treatment of SMA without safety concerns.

The MAH proposed 50/28 mg dosing regimen based on the following data:

Exploratory Exposure-Response Analysis for NF-L:

The greater reduction in plasma NF-L concentrations for the 50/28 mg Group compared with the 12 mg Group is associated with higher trough CSF concentrations of nusinersen following the first loading dose of 50 mg.

Exploratory Exposure-Response Model of CHOP-INTEND:

Direct comparison of data from Studies SM203 Part B and SM302 data with data from Studies CS3B and CS11 demonstrated a trend towards higher CHOP-INTEND score for the 50/28 mg dose regimen as compared to the 12 mg dose regimen.

The clinical data in conjunction with ER modelling support the use of 50/28 mg as the recommended dosing regimen for nusinersen.

2.6.4. Conclusions on clinical pharmacology

No major differences in nusinersen PK were observed with the higher doses, and the previously known behaviour is still basically the same. The only major change is in the updated terminal elimination half-life that is now estimated to be around 20 months.

Given that the current report concerns the assessment of a change in the existing market authorization (Spinraza - nusinersen) namely to an addition of a new strength (higher) according to the Annex I of Regulation 1234/2008, the clinical pharmacodynamic characterization of nusinersen can be considered adequate to support the proposed new dosing regimen.

2.6.5. Clinical efficacy

2.6.5.1. Dose-response studies

Not applicable.

2.6.5.2. Main study(ies)

Study 232SM203: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy

Methods

This is a 3-part study Part A, Part B (infantile-onset and later-onset), and Part C.

Part A was an open label safety evaluation in which later-onset SMA subjects received 3 loading doses of 28 mg of nusinersen and 2 maintenance doses of 28 mg. All 6 participants enrolled in Part A completed the study.

Part B was double-blind, active-controlled study designed to evaluate the proposed higher dosing regimen and included infantile and later-onset SMA participants.

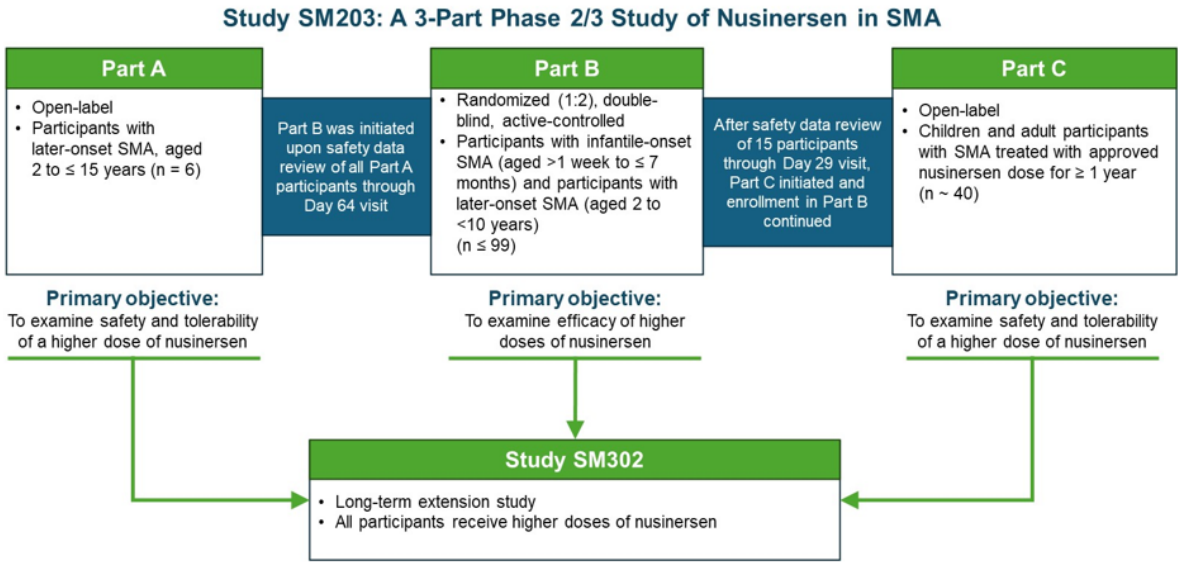
Part C was an open label safety evaluation in which infantile and later-onset SMA of the participants, who were on the currently approved dose of nusinersen (12-mg maintenance for at least 1 year after the initiation of treatment) received higher dosing regimen via the administration of a single bolus dose of 50 mg of nusinersen (which should be administered 4 months ± 14 days after their most recent maintenance dose of 12 mg), with maintenance dosing at 28 mg thereafter.

All 40 participants enrolled in Part C completed.

Study Participants

A total of 66 sites in 28 countries were activated for participant screening, of which 32 screened participants, 29 randomized participants, and 29 dosed participants.

Participants Enrolled in Studies SM203 and SM302



A total of 75 participants with infantile-onset SMA received nusinersen, 25 of whom were randomized to the 12-mg Group and 50 participants were randomized to the 50/28-mg Group.

Participants with onset of clinical signs and symptoms consistent with SMA ≤ 6 months of age were considered to have infantile-onset SMA, and those with onset > 6 months were considered to have later-onset SMA.

Eligibility Criteria

In Study SM203, the eligibility criteria were designed to be similar to those in Study CS3B for infantile-onset SMA and similar to those in Study CS4 for later-onset SMA. However, differences in the populations were expected between Study SM203 and the earlier studies since the current landscape for SMA patients has changed, with patients often identified and treated earlier, thus enabling more optimal outcomes. Specifically, Study SM203 had to be conducted in new countries, where treatment-naïve infantile-onset patients could be identified and willing to participate in clinical studies.

All participants in Study SM203 were required to have genetic documentation of 5q SMA (homozygous gene deletion, homozygous mutation, or compound heterozygote).

Part A of Study SM203 was conducted in participants with later-onset SMA, 2 to ≤ 15 years of age and with a life expectancy > 2 years at Screening.

Part B included participants with both infantile-onset and later-onset SMA. Similar to the criteria in earlier studies of SMA, participants with infantile-onset SMA had 2 copies of *SMN2*, were in at least the third percentile for body weight, and had onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age. Participants with later-onset SMA were able to sit independently, but not able to

walk, and had onset of clinical signs and symptoms consistent with SMA at > 6 months of age, with a life expectancy of > 2 years and an HFMSE score ≥ 10 and ≤ 54 at Screening.

Part C was conducted in participants with SMA who had been receiving nusinersen 12 mg treatment for at least 1 year prior to entry in this study, across participants of all ages (Cohort 1) and participants ≥ 18 years of age (Cohort 2). Participants should have been receiving nusinersen as per local label and have had no missed doses in the last year prior to Screening. Part C was designed to evaluate the safety of transitioning participants from the 12 mg dosing regimen to the 50/28 mg dosing regimen in a representative patient population.

Treatments

For Part B, a Matched Sham Set compared data from matched historical sham control participants from Study CS3B matched to all higher-dose participants with infantile-onset SMA in the ITT Set and was the main population for comparisons of 50/28 mg and sham. Data from historical sham control participants and participants receiving 12 mg from Study CS4 were matched to all higher-dose participants with later-onset SMA in the ITT Set and were used for comparisons to the 50/28-mg Group for select secondary endpoints. The main population for comparisons of the 50/28-mg Group and 12-mg Group was the ITT Set considering only SM203 participants. The study was not powered to detect significant differences between the 50/28-mg Group and the 12-mg Group.

Of the 100 participants randomized, 99 participants were enrolled and treated (75 participants with infantile-onset SMA and 24 participants with later-onset SMA).

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

Demographic characteristics were generally well balanced across treatment groups. In general, in infantile-onset SMA, the 50/28-mg and 12-mg Groups in Part B of Study SM203 had shorter disease duration (time from symptom onset to screening) and lower baseline CHOP INTEND scores, suggesting they were progressing more quickly and further into their disease course than the population evaluated in Study CS3B. While the protocol stipulated a requirement for participants to be offered standard of care in line with SMA consensus guidelines [Finkel 2018; Mercuri 2018] or provided nutritional and respiratory support per the Investigator's judgment, standard of care can vary geographically. Prespecified matching to a subgroup of the Study CS3B sham control group helped minimize some of this imbalance; however, baseline mean (SD) disease duration remained shorter and baseline CHOP INTEND remained lower in the 50/28-mg and 12-mg Groups relative to the Matched Sham Control Group. Other key baseline demographic characteristics (age at first dose age at Screening, age at symptom onset, SMN2 copy number, and baseline motor function) were balanced between the 50/28-mg, 12-mg, and Matched Sham Groups. Still, there was a shift towards earlier treatment in the 50/28 than in the matched sham: Mean age at diagnosis was 7.5 weeks for the 50/28 arm, and 8.8 weeks for the matched sham. Mean age at baseline was 119 days for the 50/28 as compared to the matched sham 139 days.

In later-onset SMA, baseline disease characteristics were similar in the 50/28-mg and 12-mg Groups in Part B of Study SM203, except for baseline HFMSE score, RULM score, and WHO motor milestones, which were lower in the 12-mg Group than the 50-28-mg Group. A Matched Sham Control Group and matched 12-mg Group from Study CS4 were comprised of a larger number of participants and, thus, were better

balanced with the 50/28-mg Group. The mean (SD) age at first dose was similar for participants with infantile-onset SMA in the ITT Set (124.3 [61.50] days) and in the Matched Sham (154.2 [55.70] days). The majority of participants in the ITT Set were male (53.3%); the majority of participants in the Matched Sham were female (55.0%). Most participants in the Matched Sham (16 participants [80.0%]) and the ITT Set (46 participants [61.3%]) were White. Most participants in the Matched Sham (18 participants [90.0%]) and ITT Set (43 participants [57.3%]) were not Hispanic or Latino. The mean (SD) age at first dose was similar for the 12-mg Group (115.5 [56.23] days) and the 50/28-mg Group (128.7 [64.06] days). Sex, race, ethnicity, and geographic region were well balanced between the 12-mg Group and the 50/28-mg Group.

Table 4. Clinical studies in participants with SMA contributing to higher dose (50/28 mg) efficacy

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Study Phase	Phase 2/3			Phase 3
Study Design	Open-label, multiple-dose	Randomized, double-blind, multiple-dose, active-controlled	Open-label, multiple-dose	Open-label, multiple-dose, long-term extension
Study Population	Participants with symptomatic later-onset SMA	Participants with symptomatic infantile (pivotal) or later-onset SMA	Participants with any SMA status (Cohort 1) Adult participants with SMA (Cohort 2)	See study populations for Study SM203, Parts A, B, and C
Study Start **Enrollment Status** **Total Enrolled (Planned)**	26 March 2020 Completed 6 participants (6 participants)	12 November 2020 Completed 99 participants (99 participants)	04 August 2021 Completed 40 participants (40 participants)	19 April 2021 Ongoing 113 participants (145 participants) as of the 30 May 2024 data cutoff
Study Status	Completed	Completed	Completed	Ongoing
Study Objectives	Safety, tolerability, efficacy, and PK	Efficacy, safety, tolerability, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK
Primary Efficacy Endpoint	NA	CHOP INTEND (infantile-onset): Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the JRT (comparison of higher dose to Matched Sham Control) (infantile-onset)	NA	NA
Secondary Efficacy Endpoints	HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA	CHOP INTEND, HINE motor milestones, CSF and plasma levels of NF-L, time to death or permanent ventilation, overall survival, hospitalizations, CGIC, serious respiratory events, time on ventilation, ventilator use, PASA (infantile-onset) HFMSE, RULM, WHO motor milestones, ACEND, PedsQL, CSF and plasma levels of NF-L, hospitalizations, CGIC, serious respiratory events, ventilator use, PASA (later-onset)	HFMSE, RULM, WHO motor milestones, ACEND. hospitalizations, CGIC, serious respiratory events, ventilator use (Cohorts 1 and 2) PedsQL, CHOP INTEND, HINE motor milestones (Cohort 1 only)	WHO motor milestones, ventilator use, time to death (all participants) CHOP INTEND, HINE motor milestones, HINE responders, time on ventilation, time to death or permanent ventilation (participants who were evaluated for these endpoints in SM203) HFSME, RULM (participants ≥ 2 years of age)

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Test Product, Route of Administration Dosage Regimen Duration of Treatment	Nusinersen, IT injection by LP: 28 mg loading doses on Days 1, 15, and 29 and 28 mg maintenance doses on Days 149 and 269 Treatment duration: approximately 269 days	Nusinersen, IT injection by LP: 12-mg Group: 12 mg loading doses on Days 1, 15, 29, and 64 and 12 mg maintenance doses of Days 183 and 279 (and a sham procedure on Day 135) 50/28-mg Group: 50 mg loading doses on Days 1 and 15 and maintenance doses of 28 mg on Days 135 and 279 (and sham procedures on Days 29, 64, and 183) Treatment duration: approximately 279 days	Nusinersen, IT injection by LP: 50 mg single bolus on Day 1 and 28 mg maintenance doses on Days 121 and 241 Treatment duration: approximately 241 days	Nusinersen, IT injection by LP: 28 mg loading doses ~every 4 months or 50 mg loading dose on Day 1, followed by 28 mg maintenance doses ~every 4 months Treatment duration: up to 1921 days
Number of Participants Dosed by Arm	28 mg: 6	Infantile-onset: 12-mg Group: 25 50/28-mg Group: 50 Matched Sham: 20 Later-onset: 12-mg Group: 8 50/28-mg Group: 16 Matched CS4 Sham: 16 Matched CS4 12 mg: 32	50/28 mg: 40	50/28 mg Part A: 6 Part B: Infantile-onset: 12-mg to 50/28-mg Group: 9 50/28-mg Group: 26 Later-onset: 12-mg to 50/28-mg Group: 7 50/28-mg Group: 16 Part C: Infantile-onset: 2 Later-onset: 37
Sex	83.3% male 16.7% female	Infantile-onset: 53.3% male 46.7% female Later-onset: 16.7% male 83.3% female	Infantile-onset: 50.0% male 50.0% female Later-onset: < 18 years: 57.1% male 42.9% female ≥ 18 years 66.7% male 33.3% female	Part A: 83.3% male 16.7% female Part B: Infantile-onset: 45.7% male 54.3% female Later-onset: 17.4% male 82.6% female Part C: 61.5% male 38.5% female

Study ID	Study SM203			Study SM302
	Part A	Part B	Part C	
Mean (Median) Age at Baseline[a]	9.28 (9.40) years	Infantile-onset: 12-mg Group: 104.2 (99.0) days 50/28-mg Group: 119.2 (119.0) days Matched Sham: 139.1 (140.0) days Later-onset: 12-mg Group: 5.6 (5.6) years 50/28-mg Group: 6.1 (6.1) years	Infantile-onset: 4.8 (4.8) years Later-onset: < 18 years: 10.7 (10.3) years ≥ 18 years: 37.4 (32.5) years	Part A: Not calculated Part B: Infantile-onset: 1.49 (1.50) years Later-onset: 7.25 (7.51) years Part C: Infantile-onset: 5.82 (5.82) years Later-onset: < 18 years: 11.68 (11.29) years ≥ 18 years: 38.99 (36.08) years
Mean (Median) Age at Symptom Onset	22.17 (19.50) months	Infantile-onset: 12-mg Group: 5.8 (4.0) weeks 50/28-mg Group: 7.5 (6.0) weeks Matched Sham: 8.8 (8.0) weeks Later-onset: 12-mg Group: 9.9 (9.0) months 50/28-mg Group: 11.1 (11.5) months Matched CS4 Sham: 11.88 (10.50) months Matched CS4 12 mg: 10.66 (10.00) months	Infantile-onset: 5.0 (5.0) months Later-onset: < 18 years: 16.3 (11.5) months ≥ 18 years: 76.2 (36.0) months	NA
Number *SMN2* Copies	3 (n = 3) 4 (n = 3)	Infantile-onset: 12-mg Group: 2 (n = 25) 50/28-mg Group: 2 (n = 50) Matched Sham: 2 (n = 20) Later-onset: 12-mg Group: 2 (n = 1) 3 (n = 7) 50/28-mg Group: 3 (n = 15) 4 (n = 1)	Infantile-onset: 3 (n = 2) Later-onset: < 18 years: 2 (n = 1) 3 (n = 12) 4 (n = 1) ≥ 18 years: 1 (n = 1) 2 (n = 2) 2-3 (n = 1) 3 (n = 6) 3-4 (n = 1) 4 (n = 13)	NA
Report Type Location	CSR SM203 Part A 5.3.5.2, Study Reports and Related Information of Uncontrolled Clinical Studies	CSR SM203 Part B 5.3.5.1, Study Reports and Related Information of Controlled Clinical Studies	CSR SM203 Part C 5.3.5.2, Study Reports and Related Information of Uncontrolled Clinical Studies	Interim CSR SM302 5.3.5.2, Study Reports and Related Information of Uncontrolled Clinical Studies

[a] For study SM302, mean (median) age at first dose is presented.

Objectives

Primary Objective:

To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA in the 232SM203 50/28 mg Group compared to the CS3B Matched Sham Control Group, as measured by change in CHOP INTEND total score.

Secondary Objectives

To examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with SMA in the 232SM203 50/28 mg group compared to:

- CS3B Matched Sham Control Group
- AND 232SM203 nusinersen 12 mg Group

Hypothesis

- Superiority of 50/28 mg *versus* Matched Sham from study CS3B (powered)
- Superiority of 50/28 mg *versus* 12/12mg (not formally powered)

Outcomes/endpoints

Within the infantile-onset population in Part B of Study SM203, to control the overall type 1 error at a 2-sided alpha level of 0.05, a sequential testing procedure ranked in the order of the primary and secondary endpoints was utilized. Inferential conclusions about each successive analysis require statistical significance of the prior one.

Table 5. Sequential testing procedure for primary and secondary endpoints

Rank	Endpoint	Comparison of Higher Dose to:	Population	Description
1	Change from Baseline to Day 183 in CHOP INTEND total score	CS3B sham control	Matched Sham Set	Primary
2	Proportion of HINE Section 2 motor milestone responders at Day 183	CS3B sham control	Matched Sham Set	Secondary
3	Change from Baseline to Day 183 in HINE Section 2 total score	CS3B sham control	Matched Sham Set	Secondary
4	Change from Baseline to Day 183 in plasma NF-L	CS3B sham control	Matched Sham Set	Secondary
5	Change from Baseline to Day 302 in CHOP INTEND total score	SM203 Part B 12 mg	ITT set	Secondary
6	Change from Baseline to Day 302 in HINE Section 2 total score	SM203 Part B 12 mg	ITT set	Secondary
7	Change from Baseline to Day 64[a] in plasma NF-L	SM203 Part B 12 mg	ITT set	Secondary
8	Time to death or permanent ventilation	CS3B sham control	Matched Sham Set	Secondary
9	Time to death	CS3B sham control	Matched Sham Set	Secondary
10	Time to death or permanent ventilation	SM203 Part B 12 mg	ITT set	Secondary
11	Time to death	SM203 Part B 12 mg	ITT set	Secondary

Secondary Safety Objectives

To examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA.

Secondary Safety Endpoints

- Incidence of AEs, including SAEs
- Shifts from baseline in clinical laboratory parameters, ECGs, and vital signs
- Change in growth parameters
- Shifts from baseline in coagulation parameters (aPTT, PT, and INR)
- Change in urine total protein
- Change from baseline in neurological examination outcomes
- The proportion of participants with a post baseline platelet count below the lower limit of

- normal on at least 2 consecutive measurements
- The proportion of participants with a post baseline QTcF of > 500 msec and an increase
- from baseline to any post baseline timepoint in QTcF of > 60 msec

Sample size

For the purposes of sample size determination, it is assumed that the higher dose will achieve an additional 4.5 improvement in CHOP INTEND and additional 3% in survival over the 12 mg dose. For the infantile-onset SMA population in Part B, a sample size of approximately 50 participants in the 50/28 mg Group and 20 sham subjects from study CS3B will provide at least approximately 99% power for the primary endpoint to detect an improvement of 24 points on CHOP INTEND and 23% survival rate benefit (compared to that observed in Study CS3B participants receiving sham control) at Day 183 based on the joint-rank test at a 2-sided significance level of 0.05. This power calculation is based on simulations using data generated from a joint model of survival and functional change. The model used a difference of 24 points for the Day 183 change from baseline in CHOP INTEND total score (50/28 mg Group Study CS3B Sham Control Group) and a population standard deviation of 8.8 for change from baseline.

Statistical methods

Part B of Study SM203 was powered to assess efficacy in infantile-onset participants for the 50/28-mg Group *versus* a prespecified matched sham group from Study CS3B. A hierarchical testing procedure was used for the primary and key secondary endpoints for the infantile-onset cohort. While inclusion of the 12 mg dosing regimen in Part B of Study SM203 was intended to provide clinically relevant supportive evidence, Part B was not sufficiently powered to detect statistically significant differences between those randomized to the 50/28-mg Group and the 12-mg Group. Powering the study to demonstrate superiority of the 50/28 mg dosing regimen compared to the approved 12 mg regimen would have required a prohibitively large number of treatment-naïve infantile-onset patients (at least 2.5 times more), which are increasingly rare given the evolving treatment landscape in SMA.

The models utilized for the primary and secondary endpoints included ANCOVA for change in motor function, Fisher's exact test for the responder analysis, and log-rank test for survival data.

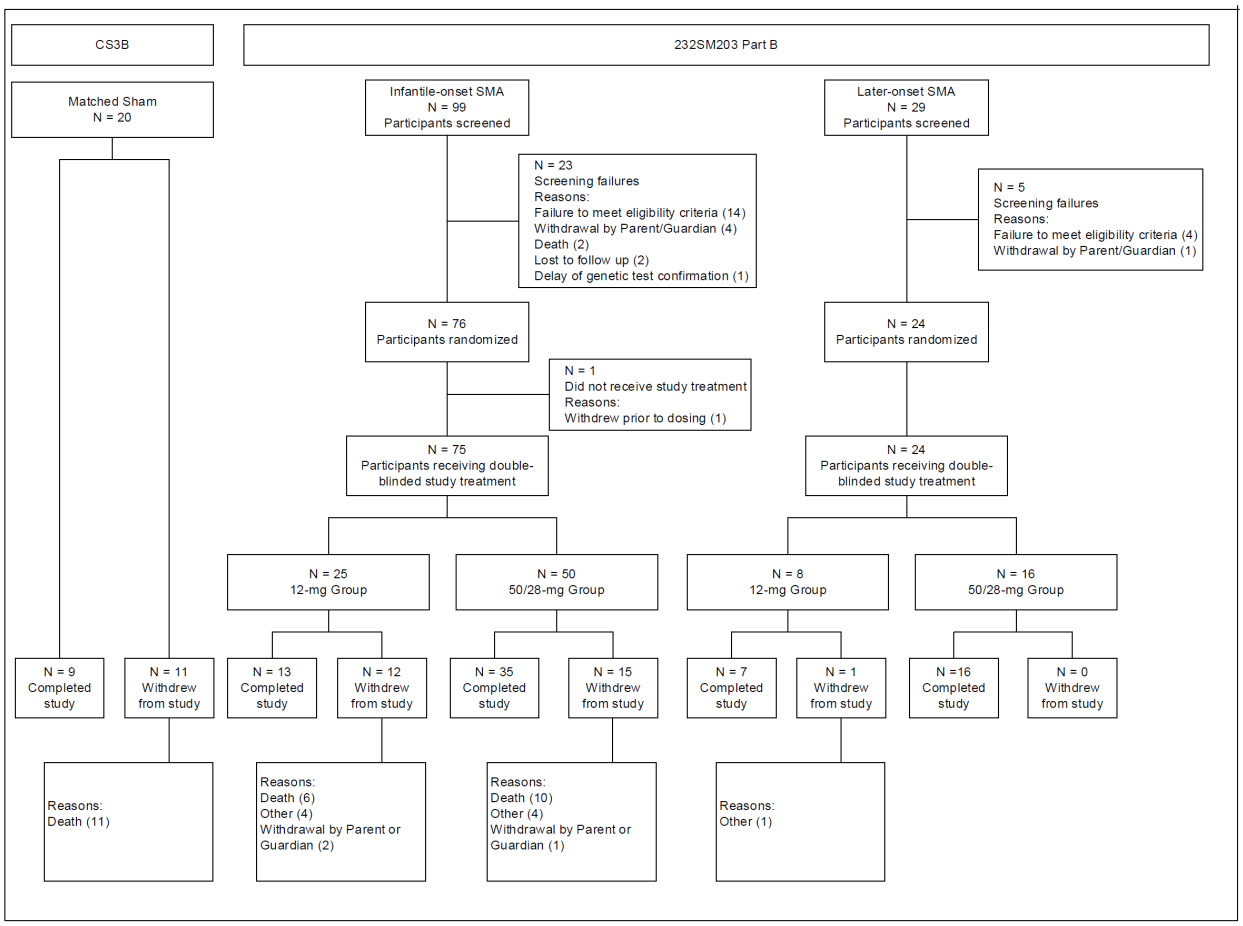
The primary endpoint was based on an analysis of ranks, and due to the potential for differences in the variance for change to Day 302 within each group, a sensitivity analysis was included using an ANCOVA model with variance estimated separately for each treatment group. For the primary endpoint, the results were consistent with the main analysis.

Post hoc analyses were performed on the following endpoints

- Change from baseline to Day 302 in CHOP INTEND total score, accounting for mortality/dropout using the JRT (comparison of higher dose to 12 mg dose).
- Change from baseline to Day 302 in HINE Section 2 motor milestones total score (comparison of higher dose to 12 mg dose).

Results

Participant flow



Source: Section 14.1.1, Output 1; Section 14.1.2, Output 1; Appendix 16.2.1, Table 1, Table 2, Table 3, and Table 4.
N = number of participants

Recruitment

Date of first treatment: 12 November 2020. End of Study Date: 30 May 2024.

Conduct of the study

The following protocols and protocol amendment summaries are described below.

Protocol Version	Date	Primary Reason(s) for Change
Original (Version 1)	06 September 2019	Not applicable
Version 2	04 December 2019	To clarify the objectives and endpoints for the different parts of the study (Parts A, B, and C) and to clarify that the IDMC review of the first 15 participants in Part B with Day 29 safety and PK data would determine whether enrollment in Part B of the study would continue.
Version 2.1	09 January 2020	Canada CSA: To exclude females who are pregnant, breastfeeding, or intending to become pregnant from the study.
Version 2.2	13 January 2020	VHP countries (Estonia, Hungary, Ireland, Italy, Latvia, Poland, and Spain) CSA: To clarify that dosing initiation in Part B would be limited to 15 participants until the IDMC review of the available safety and PK data from those participants. After the Part B IDMC review, the remaining participants in Part B could be dosed if there were no safety concerns. This amendment also clarified that, at a minimum, the Day 15 PK data from those first 15 participants who completed the Day 29 visit would be reviewed as part of the Part B IDMC review.
Version 3	05 June 2020	To clarify that the study stopping rules only applied to the primary safety portions of the study, i.e., the participants enrolled in Part A and the first 15 participants enrolled in Part B.
Version 3.3	16 July 2020	Japan CSA: To specify that participants from Japan would not be enrolled in Part A, and that only participants with later-onset SMA (i.e., no participants with infantile-onset SMA) would be enrolled prior to the IDMC review of the first 15 participants in Part B. Japanese participants with infantile-onset SMA could only be enrolled after the prespecified review of Part B data by the IDMC. This amendment also clarified that participants who received at

Protocol Version	Date	Primary Reason(s) for Change
		least 1 year of treatment with nusinersen per the approved label (i.e., not necessarily 12 mg in Japan) prior to study entry would be eligible to enroll in Part C.
Version 4/4.3	05 August 2020/ 27 August 2020	To revise the study stopping rules so that they apply to all participants in Parts A and B of the study. Japan CSA: To incorporate Version 4 changes.
Version 4.4	07 October 2020	United Kingdom CSA: To add exclusion criteria related to history of systemic hypersensitivity reaction to the study treatment (nusinersen), its excipients, or to any diagnostic agents administered during the study. To require a serum pregnancy test for eligibility during Screening, rather than using the serum test only as confirmation of a positive or equivocal urine pregnancy test result. To clarify that authorization from a competent authority would be sought prior to resuming dosing of participants in the event that study stopping rules were met.
Version 5/5.3/5.4	01 October 2021/ 08 December 2021/ 08 December 2021	To increase the sample size for Part C by adding a second cohort consisting of up to approximately 20 adult participants. Japan CSA: To incorporate Version 5 changes. United Kingdom CSA: To incorporate Version 5 changes.
Version 5.5	24 November 2021	VHP countries (Germany, Greece, Hungary, Ireland, Latvia, Poland, Spain) CSA: To include additional details regarding the revision of the target CSF C_{trough} and the clinical relevance of this change for the benefit-risk assessment of the study.
Version 6/6.3	05 May 2022/ 25 July 2022	To reduce the sample size for Part B infantile-onset participants to 75. As a result, the total sample size for the study was adjusted to 145 participants. Japan CSA: To incorporate Version 6 changes.
Version 6.6	07 November 2022	Germany CSA: To remove Section 16, Public Health or Humanitarian Emergencies, because the mitigating options do not align with the European “Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic.”
Version 7	11 June 2024	To update the comparisons of nusinersen higher dose (50/28 mg) versus sham in participants with infantile-onset SMA to utilize a matched sham control group consisting of participants from the Study CS3B sham arm selected through a matching algorithm. To update the previous hypothesis testing framework to clearly indicate the primary and secondary comparisons as nusinersen 50/28 mg versus sham or nusinersen 50/28 mg versus 12 mg. To elevate the endpoints of change from baseline in CSF NF concentration and change from baseline in plasma NF concentration from exploratory to secondary endpoints, and to change and the neurofilament biomarker from pNF-H to NF-L. To change the timepoint of evaluation of proportion of HINE-2 responders (higher

Protocol Version	Date	Primary Reason(s) for Change
		dose versus sham) from Day 302 to Day 183. To change the timepoint of evaluation of change from baseline in CHOP INTEND (higher dose versus 12 mg) from Day 183 to Day 302.

Baseline data

Demographics and Baseline disease characteristics

Infantile-Onset SMA

Demographic characteristics (e.g., age at first dose, sex, ethnicity, and race) of the Matched Sham, the 12-mg Group, and the 50/28-mg Group were similar. Geographically, more participants in the Matched Sham were from North America and more participants in the ITT Set were from Asia-Pacific and South/Central America.

The mean (SD) age at first dose for participants with infantile-onset SMA in the ITT Set (124.3 [61.50] days) and in the Matched Sham (154.2 [55.70] days) was similar. The mean (SD) age at first dose for the 12-mg Group (115.5 [56.23] days) and the 50/28-mg Group (128.7 [64.06] days) was similar.

Forty participants (53.3%) with infantile-onset SMA in the ITT Set were male and 35 participants (46.7%) were female. Sex was well balanced between the 12-mg Group and the 50/28-mg Group. Nine participants (45.0%) in the Matched Sham were male and 11 participants (55.0%) were female.

Most participants in the Matched Sham (16 participants [80.0%]) and the ITT Set (46 participants [61.3%]) were White. Race was well balanced between the 12-mg Group and the 50/28-mg Group.

Most participants in the Matched Sham (18 participants [90.0%]) and ITT Set (43 participants [57.3%]) were not Hispanic or Latino. Ethnicity was well balanced between the 12-mg Group and the 50/28-mg Group.

Geographically, a higher proportion of participants in the Matched Sham (13 participants [65.0%] were from North America than the ITT Set (1 participant [1.3%]). A higher proportion of participants in the ITT Set were from Asia-Pacific (28 participants [37.3%]) than the Matched Sham (2 participants [10.0%]). A higher proportion of participants in the ITT Set were from South/Central America (27 participants [36.0%]) than the Matched Sham (no participants). A similar proportion of participants in the Matched Sham (5 participants [25.0%]) and the ITT Set (19 participants [25.3%]) were from Europe. The geographic regions of the 12-mg Group were similar.

In general, demographic characteristics were similar across subgroup analyses (disease duration, CHOP INTEND score at Baseline, and geographic region) and across the Per Protocol Set.

Baseline disease characteristics of the ITT and Matched Sham Sets and the Study CS3B Sham Pool Baseline disease characteristics (age at SMA diagnosis, time from SMA diagnosis to first study dose, SMN2 copy, and HINE Section 2 score at Baseline) of the Matched Sham Set, the 12-mg Group, and the 50/28-mg Group were similar. Although disease duration and CHOP INTEND scores at Baseline were higher in the CS3B Sham Pool and Matched Sham than the 12-mg Group and 50/28-mg Group, the Matched Sham more closely resembled the 50/28-mg Group.

The mean (SD) age at symptom onset was 9.5 (4.49) weeks in the CS3B Sham Pool, 8.8 (5.11) weeks in the Matched Sham, 5.8 (4.44) weeks in the 12-mg Group, and 7.5 (5.26) weeks in the 50/28-mg Group.

The mean (SD) age at SMA diagnosis was 16.8 (7.50) weeks in the CS3B Sham Pool, 13.7 (7.98) weeks in the Matched Sham, 11.6 (7.12) weeks in the 12-mg Group, and 13.8 (8.20) weeks in the 50/28-mg Group.

The mean (SD) time from SMA diagnosis to first study dose was higher in the Study CS3B Sham Pool (8.7 [3.60] weeks) and in the Matched Sham (8.4 [3.33] weeks) than in the 12-mg Group (4.9 [3.06] weeks) and in the 50/28-mg Group (4.5 [3.78] weeks).

The mean (SD) disease duration at informed consent was higher in the CS3B Sham Pool (13.7 [5.50] weeks) and in the Matched Sham (11.1 [4.92] weeks) than in the 12-mg Group (9.1 [6.11] weeks) and in the 50/28-mg Group (9.6 [5.29] weeks).

All participants in the Matched Sham, 12-mg Group, and 50/28-mg Group had 2 copies of SMN2. Thirty-six participants (97.3%) in the Study CS3B Sham Pool had 2 copies of SMN2, and 1 participant (2.7%) had 3 copies.

The mean (SD) CHOP INTEND score at Baseline was higher in the CS3B Sham Pool (28.0 [7.62]) and in the Matched Sham (23.6 [5.84]) than in the 12-mg Group (19.9 [9.63]) and in the 50/28-mg Group (20.9 [10.23]).

The mean (SD) HINE Section 2 score at Baseline was 1.4 (1.26) in the CS3B Sham Pool, 1.3 (1.02) in the Matched Sham, 1.4 (1.29) in the 12-mg Group, and 1.4 (1.36) in the 50/28-mg Group.

Seven participants (35.0%) in the Matched Sham, 2 participants (8.0%) in the 12-mg Group, and 3 participants (6.0%) in the 50/28-mg Group required a gastrointestinal tube at Baseline (Section 14.1.1, Output 15).

In general, baseline disease characteristics were similar across subgroup analyses (disease duration, CHOP INTEND score at Baseline, and geographic region).

Later-Onset SMA

Demographic characteristics (e.g., age at first dose, sex, ethnicity, race, and geographic region) of the 12-mg Group, and the 50/28-mg Group were similar.

The mean (SD) age at first dose for participants with later-onset SMA was 6.0 (2.67) years. The mean (SD) age at first dose for the 12-mg Group (5.7 [3.00] years) and the 50/28-mg Group (6.1 [2.59] years) was similar.

More participants in the ITT Set were female (20 participants [83.3%]) than male (4 participants [16.7%]). Sex was well balanced between the 12-mg Group and the 50/28-mg Group.

Most participants were White (11 participants [45.8%]) or Asian (7 participants [29.2%]). Most participants were not Hispanic or Latino (16 participants [66.7%]). Race and ethnicity were well balanced between the 12-mg Group and the 50/28-mg Group.

Geographically, 10 participants (41.7%) were from North America, Taiwan, and Europe, and 14 participants (58.3%) were from other regions. Geographic regions were well balanced in the 12-mg Group (4 participants [50.0%] from each region), while a lower proportion of participants were from North America, Taiwan, and Europe (6 participants [37.5%]) than other regions (10 participants [62.5%]) in the 50/28-mg Group.

In general, demographic characteristics were similar across the Per Protocol and Safety Sets.

Baseline disease characteristics (age at symptom onset, time from disease onset to enrollment, and SMN2 copy) of the 12-mg Group and the 50/28-mg Group were similar, except for baseline HFMSE score,

RULM score, and WHO motor milestones, which were lower in the 12-mg Group than the 50/28-mg Group.

The mean (SD) age at symptom onset was 9.9 (2.36) months in the 12-mg Group and 11.1 (4.11) months in the 50/28-mg Group.

The mean (SD) age at SMA diagnosis was 2.3 (0.76) years in the 12-mg Group and 2.9 (1.39) years in the 50/28-mg Group.

The mean (SD) time from SMA diagnosis to enrollment was 3.3 (3.26) years in the 12-mg Group and 3.2 (2.95) years in the 50/28-mg Group.

Seven participants (87.5%) in the 12-mg Group and 15 participants (93.8%) in the 50/28-mg Group had 3 copies of SMN2. One participant (12.5%) in the 12-mg Group had 2 copies of SMN2, and 1 participant (6.3%) in the 50/28-mg Group had 4 copies of SMN2.

Mean (SD) Cobb angles at Baseline were 25.53° (20.383°) in the 12-mg Group and 24.10° (16.991°) in the 50/28-mg Group. Mean (SD) HFMSE total scores at Baseline were lower in the 12-mg Group (13.75 [4.590]) than in the 50/28-mg Group (20.31 [10.051]). Mean (SD) RULM total scores at Baseline were lower in the 12-mg Group (14.88 [5.963]) than in the 50/28-mg Group (20.19 [5.307]).

The following WHO motor milestones were achieved at Baseline: sitting without support (8 participants [100%] in the 12-mg Group; 16 participants [100%] in the 50/28-mg Group), hands and knees crawling (no participants in the 12-mg Group; 5 participants [31.3%] in the 50/28-mg Group), standing with assistance (no participants in the 12-mg Group; 3 participants [18.8%] in the 50/28-mg Group) walking with assistance (no participants in the 12-mg Group; 1 participant [6.3%] in the 50/28-mg Group), standing alone (no participants in the 12-mg Group; 1 participant [6.3%] in the 50/28-mg Group), and walking alone (no participants in the 12-mg Group or 50/28-mg Group).

Growth parameters at Baseline in the 12-mg Group and the 50/28-mg Group were similar. Five participants (62.5%) in the 12-mg Group and 9 participants (56.3%) in the 50/28-mg Group used a wheelchair. In general, baseline disease characteristics were similar across the Per Protocol and Safety Sets.

Notable outcomes for propensity score matching analyses on baseline disease characteristics are presented in the following subsections.

Propensity Score Matching: 50/28 mg Nusinersen Versus CS4 Sham Control Although the HFMSE, RULM, and WHO motor milestones at Baseline in the 12-mg Group and the 50/28-mg Group were different in the study, the HFMSE, RULM, and WHO motor milestones at Baseline in the 50/28-mg Group were similar to the CS4 Sham and Matched CS4 Sham. Of relevance, the mean (SD) age at first dose in the 50/28-mg Group (6.11 [2.589]) was higher than the Matched CS4 Sham (5.13 [1.817]) and the CS4 Sham (3.89 [1.589]).

Baseline medical history

Infantile-Onset SMA

The most common SOCs in participants with infantile-onset SMA were Nervous system disorders (20 participants [100.0%] in the Matched Sham, 19 participants [76.0%] in the 12-mg Group, and 35 participants [70.0%] in the 50/28-mg Group), Musculoskeletal and connective tissue disorders (18 participants [90.0%] in the Matched Sham, 8 participants [32.0%] in the 12-mg Group, and 27 participants [54.0%] in the 50/28-mg Group), and Respiratory, thoracic and mediastinal disorders (18 participants [90.0%] in the Matched Sham, 12 participants [48.0%] in the 12-mg Group, and 14 participants [28.0%] in the 50/28-mg Group). Baseline medical history was similar across treatment groups.

Later-Onset SMA

The most common SOCs in participants with later-onset SMA were Nervous system disorders (8 participants [100.0%] in the 12-mg Group and 14 participants [87.5%] in the 50/28-mg Group), Musculoskeletal and connective tissue disorders (6 participants [75%] in the 12-mg Group and 14 participants [87.5%] in the 50/28-mg Group), and General disorders and administration site conditions (3 participants [37.5%] in the 12-mg Group and 12 participants [75.0%] in the 50/28-mg Group). Baseline medical history was similar across treatment groups.

Numbers analysed

Part B of Study SM203 consisted of a pivotal randomized, double-blind, active-controlled treatment period with either 2 or 4 loading doses of nusinersen (for the 50/28-mg Group and the 12-mg Group, respectively) administered IT followed by maintenance doses approximately every 4 months thereafter. Participants with infantile-onset (76 participants) or later-onset SMA (24 participants) were randomized in a 1:2 ratio to receive either the currently approved dosing regimen of 4 loading doses of 12 mg of nusinersen administered IT (Days 1, 15, 29, and 64) followed by 2 maintenance doses of 12 mg on Days 183 and 279 (12-mg Group) or 2 loading doses of 50 mg of nusinersen administered IT (Days 1 and 15) followed by 2 maintenance doses of 28 mg on Days 135 and 279 (50/28-mg Group). In order to maintain blinding, 1 sham procedure was administered in the 12-mg Group on Day 135, and 3 sham procedures were administered in the 50/28-mg Group on Days 29, 64, and 183 to ensure the same dosing visit schedule as the 12-mg Group.

For Part B, a Matched Sham Set compared data from matched historical sham control participants from Study CS3B matched to all higher-dose participants with infantile-onset SMA in the ITT Set and was the main population for comparisons of 50/28 mg and sham. Data from historical sham control participants and participants receiving 12 mg from Study CS4 were matched to all higher-dose participants with later-onset SMA in the ITT Set and were used for comparisons to the 50/28-mg Group for select secondary endpoints. The main population for comparisons of the 50/28-mg Group and 12-mg Group was the ITT Set considering only SM203 participants. The study was not powered to detect significant differences between the 50/28-mg Group and the 12-mg Group.

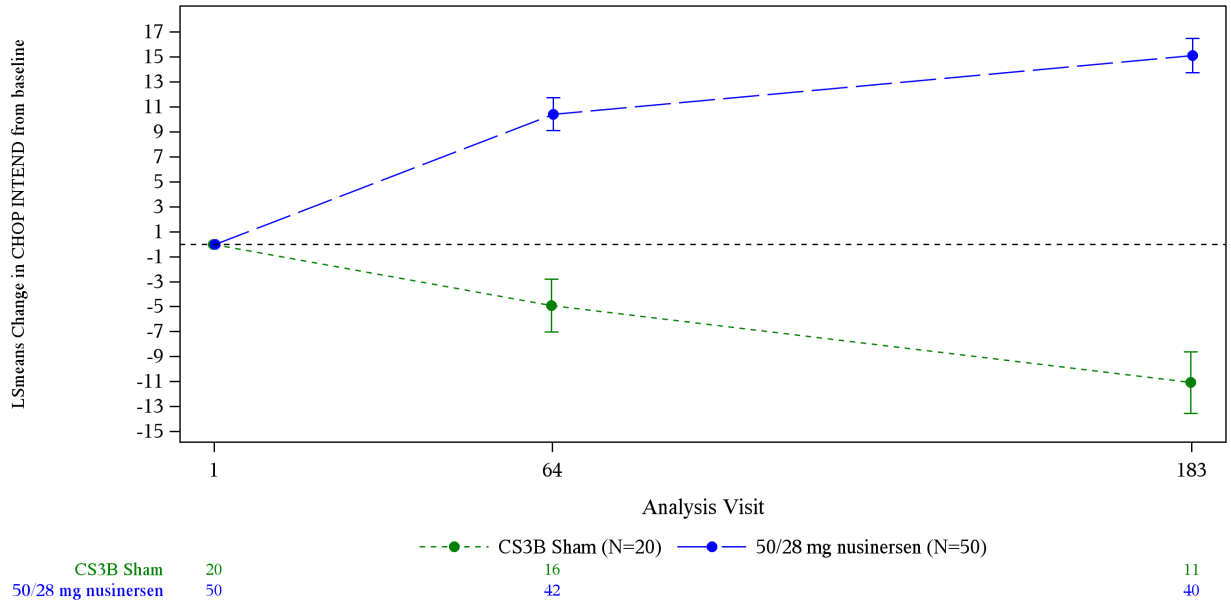
Of the 100 participants randomized, 99 participants were enrolled and treated (75 participants with infantile-onset SMA and 24 participants with later-onset SMA).

Outcomes and estimation

The Primary Endpoint is Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the joint-rank test (comparison of higher dose to matched sham control).

The primary efficacy endpoint of this study was met. The change from baseline to Day 183 in CHOP INTEND total score was significantly higher (indicating improved motor function) in the 50/28-mg Group than in the Matched Sham Control Group, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 26.06 [17.941, 34.172]; joint-rank $p < 0.0001$). Change from baseline to Day 183 in CHOP INTEND total score (LS mean [95% CI]) was higher in the 50/28-mg Group (15.1 [12.4, 17.8]) than in the Matched Sham (-11.1 [-15.9, -6.2]), based on ANCOVA with MI (LS mean difference [95% CI] = 26.19 [20.7, 31.7]; $p < 0.0001$).

Figure 1. Part B: Infantile-onset SMA: CHOP INTEND: figure of mean change (± SE) from baseline by visit ANCOVA analysis using MI: 50/28-mg and matched sham groups



NOTE: Baseline presented at analysis visit 1.

MI is used for missing data.

Results of the secondary efficacy endpoints for participants with infantile-onset SMA are as follows:

A statistically significant, higher proportion of participants in the 50/28-mg Group were HINE Section 2 motor milestone responders (indicating improved motor function) at Day 183 than the Matched Sham, based on the Fisher exact test (difference in proportion = 58.00%; $p < 0.0001$). No participants in the Matched Sham and 29 participants (58%) in the 50/28-mg Group were HINE Section 2 motor milestone responders at Day 183. In a supplementary analysis, 60% of participants in the 50/28-mg Group and 44% of participants in the 12-mg Group met the HINE Section 2 responder definition at Day 302.

The change from baseline to Day 183 in HINE Section 2 motor milestone total score was significantly higher (indicating improved motor function) in the 50/28-mg Group than the Matched Sham, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 26.67 [18.812, 34.526]; joint-rank $p < 0.0001$). Change from baseline to Day 183 in HINE Section 2 motor milestone total score (LS mean [95% CI]) was higher in the 50/28-mg Group (3.7 [3.0, 4.4]) than the Matched Sham (-0.2 [-1.5, 1.0]), based on ANCOVA with MI (LS mean difference [95% CI] = 3.94 [2.458, 5.424]; $p < 0.0001$).

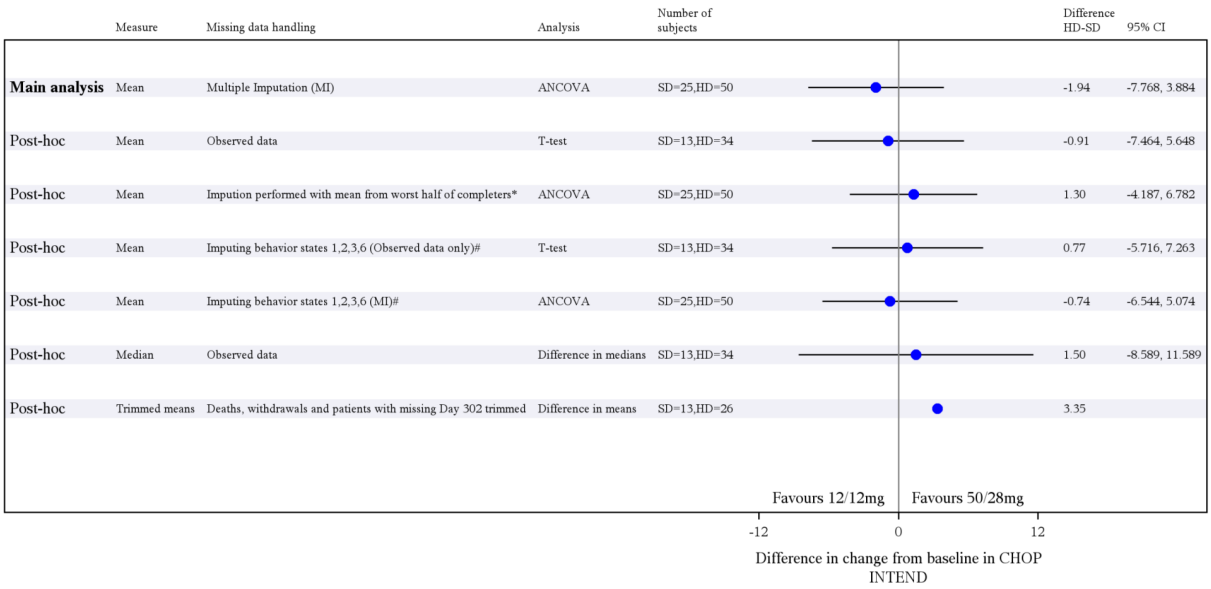
The reduction from baseline to Day 183 in plasma concentration of NF-L was significantly greater (e.g., lower ratio to baseline; indicating reduced levels of a marker of axonal injury and neurodegeneration) in the 50/28-mg Group than the Matched Sham, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 29.58 [22.118, 37.042]; joint-rank $p < 0.0001$). The reduction from baseline to Day 183 in plasma concentrations of NF-L (LS geometric mean ratio to baseline [95% CI]) was greater (e.g., lower ratio from baseline) in the 50/28-mg Group (0.06 [0.05, 0.07]) than Matched Sham (0.70 [0.43, 1.12]), based on ANCOVA with MI (50/28-mg / Matched Sham LS geometric mean ratio [95% CI] = 0.08 [0.05, 0.14]; $p < 0.0001$).

The change from baseline to Day 302 in CHOP INTEND total score was numerically higher in the 50/28-mg Group than the12-mg Group, based on the difference in ranks, but not statistically significant

based on the JRT (LS mean difference [95% CI] = 1.00 [-9.290, 11.299]; joint-rank p = 0.8484). Therefore, inferential conclusions of subsequent endpoints for the infantile-onset SMA population were stopped and only nominally significant differences are presented for subsequent endpoints. Change from baseline to Day 302 in CHOP INTEND total score (LS mean [95% CI]) was numerically higher in the 12-mg Group (21.6 [16.6, 26.6]) than the 50/28-mg Group (19.6 [16.5, 22.8]), based on ANCOVA with MI (LS mean difference [95% CI] = -1.94 [-7.768, 3.884]; p = 0.5132). The inconsistency of the CHOP INTEND results relative to the results for other endpoints (NF-L, survival, HINE Section 2, etc.) is likely confounded by sources of variability. To further understand potential confounders, additional post hoc sensitivity analyses were performed for CHOP INTEND, including alternative statistical methodologies for accounting for deaths and withdrawals and analyses imputing for behavioural scores of 1, 2, 3, and 6. These post hoc analyses showed that whether a favourable result was observed for the 50/28-mg Group or the 12-mg Group in CHOP INTEND was dependent on the approach taken for handling missing data, and accounting for variability. These findings suggest that the results are inconclusive regarding a true effect in favor of 12 mg.

Figure 2. Part B: Infantile-onset SMA: Forest plot for main and sensitivity analyses of change from baseline in CHOP INTEND to day 302: ITT set or observed data at day 302

Part B: Infantile-Onset SMA: Forest plot for main and sensitivity analyses of change from baseline in CHOP INTEND to Day 302: ITT Set or observed data at Day 302
Page: 1 of 1



* Impute missing Day 302 total scores including due to death/discontinuation with mean from worst half of completers (both arms)
# Imputing any behavior items of states 1,2,3,6 with most recent behavior item 4 or 5
Source: isis396443/232sm203-part-b-infant/csr/f-chop-fplot-d302.sas **Run Date:** 19SEP2024

Proportion of HINE Section 2 Motor Milestone Responders at Day 183 (Comparison of Higher Dose to Matched Sham Control)

A statistically significant larger proportion of the HINE Section 2 motor milestone responders at Day 183 was observed in the 50/28-mg Group compared to the Matched Sham, indicating that nusinersen 50/28 mg improved motor function in participants with infantile-onset SMA. As a result, this key secondary endpoint was considered to be met.

Part B: Infantile-Onset SMA: HINE 2: Proportion of Motor Milestones responders at Day 183: Matched Sham Set (main)

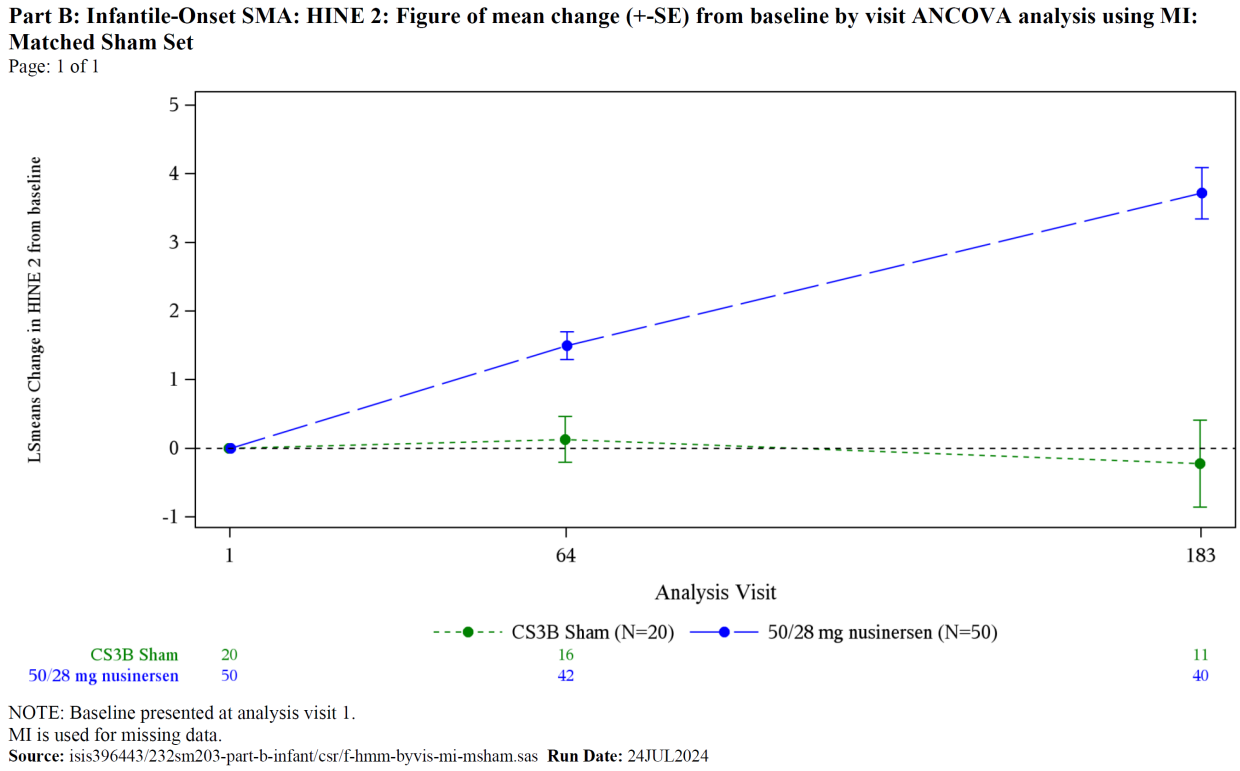
	Matched CS3B	232SM203
	Sham control (N=20)	50/28 mg nusinersen (N=50)
Number of subjects who died (a)	9 (45)	7 (14)
Number of subjects withdrawn for reasons other than death (a)	0	2 (4)
Number of subjects with an improvement from baseline in motor milestones (b) :		
Ability to kick:		
At least a 2-point increase	0	9 (18)
Achievement of touching toes	0	4 (8)
Head control: at least a 1-point increase	0	23 (46)
Rolling: at least a 1-point increase	0	14 (28)
Sitting: at least a 1-point increase	0	15 (30)
Crawling: at least a 1-point increase	0	3 (6)
Standing: at least a 1-point increase	0	7 (14)
Walking: at least a 1-point increase	0	0
Achievement of any of the above in which there are more categories with improvement than with worsening (c)	0	29 (58)
Difference in percentages (50/28 mg nusinersen minus Sham control)		58.00
(95% CI) (d)		(39.46, 71.81)
p-value (compared to Sham control) (e)		<.0001

NOTE: (a) Subjects who died or who were withdrawn are considered non-responders. For any missing response at day 183, if the missing response is in between two immediate flanking visits then the response will be set to the worst of the 2 flanking visits, if this is not the case then the subject will be considered non-responder.
(b) Day 183 assessment is used.
(c) Endpoint used for analysis. For category of ability to kick, similar to the definition of improvement, worsening is defined as at least 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least 1-point decrease.
(d) Exact unconditional confidence interval.
(e) From Fisher exact test.
Abbreviation: CI=confidence interval.
Source: isis396443/232sm203-part-b-infant/csr/t-hmm-resp-d183-main.sas **Run Date:** 25JUL2024

Change From Baseline to Day 183 In HINE Section 2 Motor Milestones Total Score (Comparison of Higher Dose To Matched Sham Control)

A statistically significant greater improvement from baseline to Day 183 in HINE Section 2 motor milestone total score was observed in the 50/28-mg Group compared to the Matched Sham, indicating that nusinersen 50/28 mg improved motor function in participants with infantile-onset SMA. As a result, this key secondary endpoint was considered to be met.

Figure 3. Part B: Infantile-onset SMA: HINE 2: figure of mean change (+-SE) from baseline by visit ANCOVA analysis using MI: matched sham set



The change from baseline to Day 302 in HINE Section 2 motor milestone total score was numerically higher in the 50/28-mg Group than the 12-mg Group, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 6.12 [-2.693, 14.939]; joint-rank p = 0.1734)]. Change from baseline to Day 302 in HINE Section 2 motor milestone total score (LS mean [95% CI]) was numerically higher in the 50/28-mg Group (5.9 [4.6, 7.2]) than the 12-mg Group (5.3 [3.3, 7.4]) based on ANCOVA with MI (LS mean difference [95% CI] = 0.58 [-1.886, 3.042]; p = 0.6454). HINE 2 results were numerically favorable for the 50/28-mg Group than the 12-mg Group across post hoc analyses.

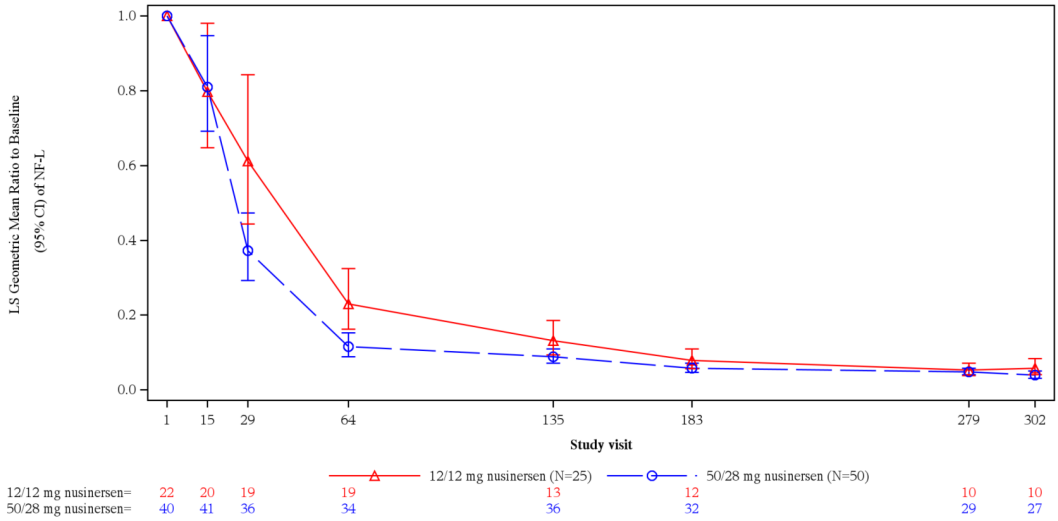
Change from baseline to Day 183 in plasma concentration of NF-L.

The reduction from baseline to Day 183 in plasma concentration of NF-L was significantly greater (e.g., lower ratio to baseline) in the 50/28-mg Group than the Matched Sham, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 29.58 [22.118, 37.042]; joint rank p < 0.0001).

Figure 4. Part B: Infantile-onset SMA: Plasma NF-L: figure of LS geometric mean ratio to baseline (95% CI) by visit: from ANCOVA analysis using MI: ITT set

Part B: Infantile-Onset SMA: Plasma NF-L: Figure of LS geometric mean ratio to baseline (95% CI) by visit: from ANCOVA analysis using MI: ITT set

Page: 1 of 1

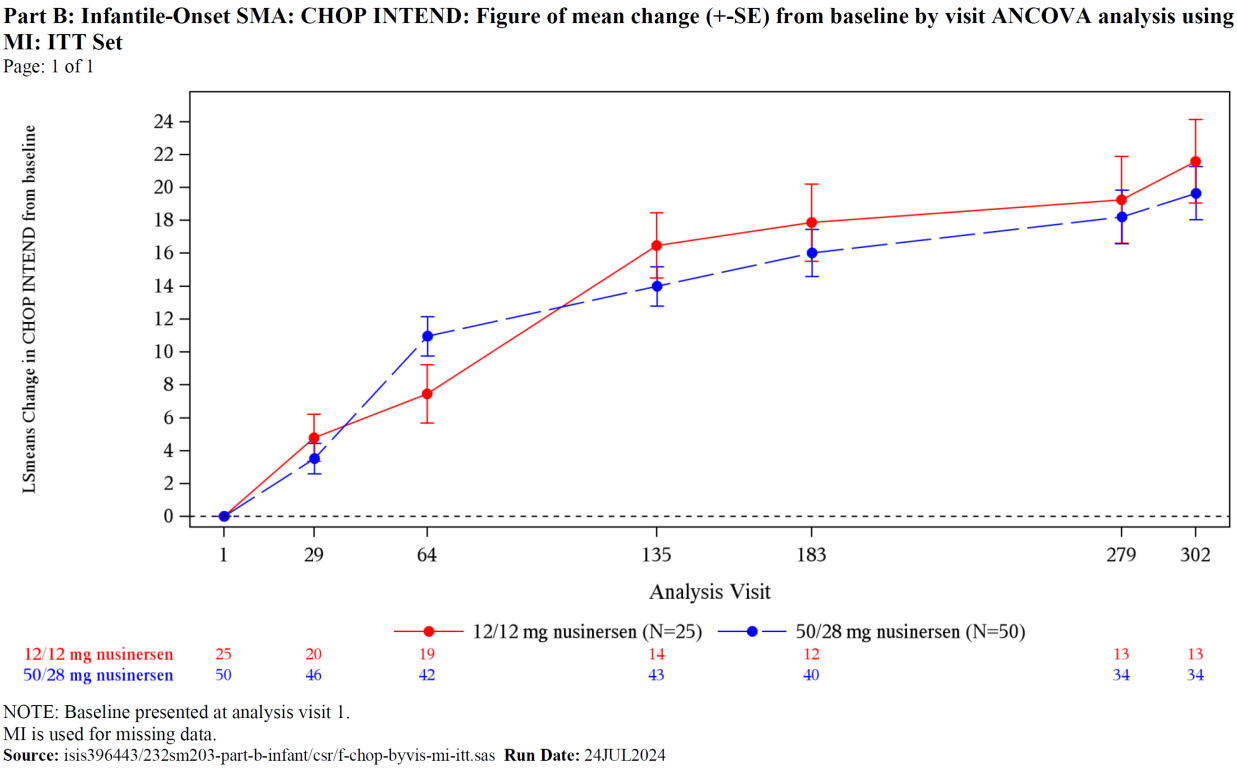


NOTE: Baseline presented at analysis visit 1.
LS means are obtained from the ANCOVA model with covariates: treatment as a fixed effect, disease duration at screening, baseline log Plasma NF-L and baseline CHOP INTEND total score. The n in the legend are subjects with observed data, Multiple imputation is used for missing data.
Lower limit of quantification (LLOQ) = 2.6 pg/mL
Values below limit of quantification (BLQ) are set to LLOQ/2,
Error bar is 95% confidence interval. Abbreviation: NF-L= neurofilament light chain
Source: isis396443/232sm203-part-b-infant/csr/f-nfl-plasm-rbase-vis-lsm-itt.sas **Run Date:** 03SEP2024

Change from baseline to Day 302 in CHOP INTEND total score

The change from baseline to Day 302 in CHOP INTEND total score was numerically higher in the 50/28-mg Group than the 12-mg Group based on the difference in ranks, but not statistically significant based on the JRT (LS mean difference [95% CI] = 1.00 [-9.290, 11.299]; joint rank p = 0.8484). Change from baseline to Day 302 in CHOP INTEND total score (LS mean [95% CI]) was numerically higher in the 12-mg Group (21.6 [16.6, 26.6]) than the 50/28-mg Group (19.6 [16.5, 22.8]) based on ANCOVA with MI (LS mean difference [95% CI] = -1.94 [-7.768, 3.884]; p = 0.5132).

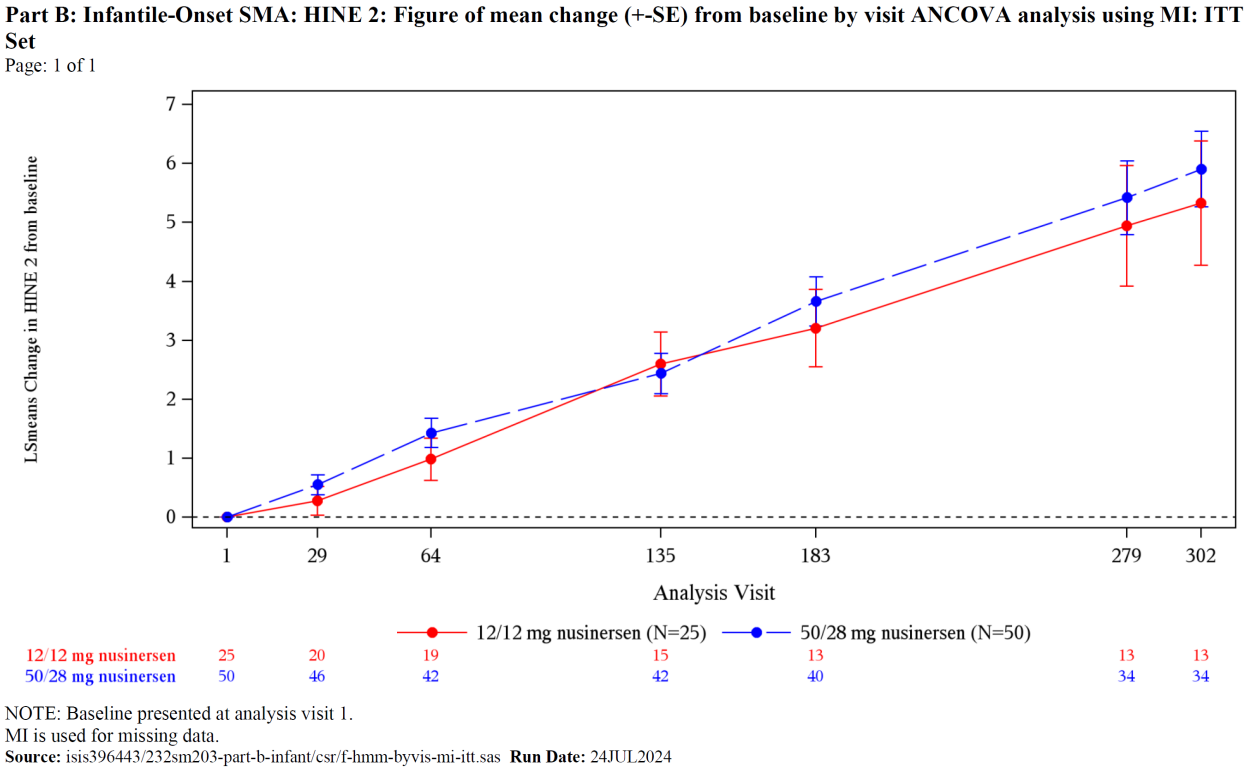
Figure 5. Part B: Infantile-onset SMA: CHOP INTEND: figure of mean change (+-SE) from baseline by visit ANCOVA analysis using MI: ITT set



Change from baseline to Day 302 in HINE Section 2 motor milestones total score

The change from baseline to Day 302 in HINE Section 2 motor milestone total score was numerically higher in the 50/28-mg Group than the 12-mg Group, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 6.12 [-2.693, 14.939]; joint rank p = 0.1734). Change from baseline to Day 302 in HINE Section 2 motor milestone total score (LS mean [95% CI]) was numerically higher in the 50/28-mg Group (5.9 [4.6, 7.2]) than the 12-mg Group (5.3 [3.3, 7.4]) based on ANCOVA with MI (LS mean difference [95% CI] = 0.58 [-1.886, 3.042]; p = 0.6454).

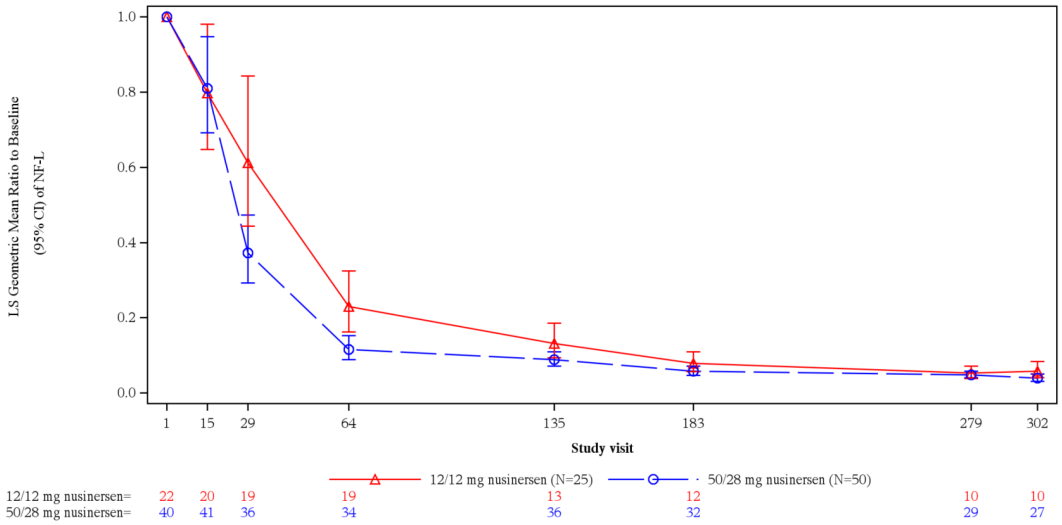
Figure 6. Part B: Infantile-onset SMA: HINE 2: figure of mean change (+-SE) from baseline by visit ANCOVA analysis using MI: ITT set



Change from baseline to Day 64 in plasma concentration of NF-L

The reduction from baseline to Day 64 in plasma concentration of NF-L (e.g., lower ratio to baseline) was nominally significantly greater in the 50/28-mg Group than the 12-mg Group, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 12.74 [3.840, 21.632]; p = 0.0050). The reduction from baseline to Day 64 in plasma concentration of NF-L (LS geometric mean ratio to baseline [95% CI]) was nominally significantly greater (e.g., lower ratio to baseline) in the 50/28-mg Group (0.12 [0.09, 0.15]) than the 12-mg Group (0.23 [0.16, 0.32]), based on ANCOVA with MI over time (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.51 [0.33, 0.78]; p = 0.0020).

Figure 7. Part B: Infantile-onset SMA: Plasma NF-L: figure of LS geometric mean ratio to baseline (95% CI) by visit: from ANCOVA analysis using MI: ITT set



NOTE: Baseline presented at analysis visit 1.
LS means are obtained from the ANCOVA model with covariates: treatment as a fixed effect, disease duration at screening, baseline log Plasma NF-L and baseline CHOP INTEND total score. The n in the legend are subjects with observed data, Multiple imputation is used for missing data.
Lower limit of quantification (LLOQ) = 2.6 pg/mL
Values below limit of quantification (BLQ) are set to LLOQ/2,
Error bar is 95% confidence interval. Abbreviation: NF-L= neurofilament light chain
Source: isis396443/232sm203-part-b-infant/csr/f-nfl-plasm-rbase-vis-lsm-itt.sas **Run Date:** 03SEP2024

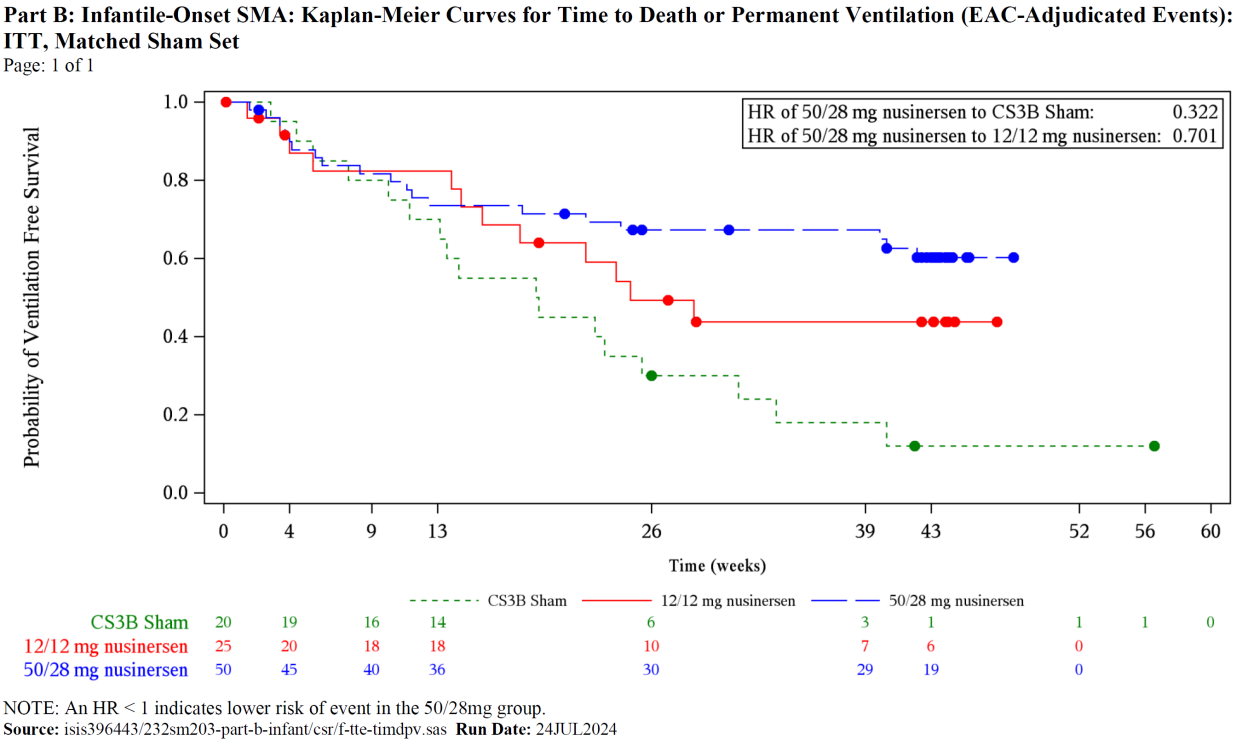
NFl at day 302

There was a greater decrease in plasma concentration of NF-L at Day 302 in the 12-mg Group and 50/28-mg Group compared to in the Matched Sham, with ratios to baseline (geometric mean [95%]) at Day 302 of 0.05 (0.04, 0.07), 0.04 (0.03, 0.05), and 0.49 (0.39, 0.62), respectively.

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) compared to matched sham set

The median (95% CI) time to death or permanent ventilation based on the Kaplan-Meier Method for the Matched Sham was 19.1 (10.00, 31.29) weeks and could not be estimated for the 50/28-mg Group. The time to death or permanent ventilation was nominally significantly higher in the 50/28-mg Group than the Matched Sham, based on the log-rank test stratified by disease duration (p = 0.0006). The hazard ratio (95% CI) of the 50/28-mg Group compared to the Matched Sham was 0.322 (0.158, 0.657) and was nominally significantly different between the groups (p = 0.0018).

Figure 8. Part B: Infantile-onset SMA: Kaplan-Meier curves for time to death or permanent ventilation (EAC-adjudicated events): ITT, matched sham set



NOTE: An HR < 1 indicates lower risk of event in the 50/28mg group.
Source: isis396443/232sm203-part-b-infant/csr/f-tte-timdpv.sas **Run Date:** 24JUL2024

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) compared to 12 mg nusinersen

A lower proportion of participants in the 50/28-mg Group (19 participants [38%]) died or required permanent ventilation than in the 12-mg Group (12 participants [48%]). The median (95% CI) time to death or permanent ventilation based on the Kaplan-Meier Method for the 12-mg Group was 24.7 (14.43, NA) weeks and could not be estimated for the 50/28-mg Group. The estimated time to death or permanent ventilation was numerically higher in the 50/28-mg Group than the 12-mg Group, based on the log-rank test stratified by disease duration (Figure 11; p = 0.2775).

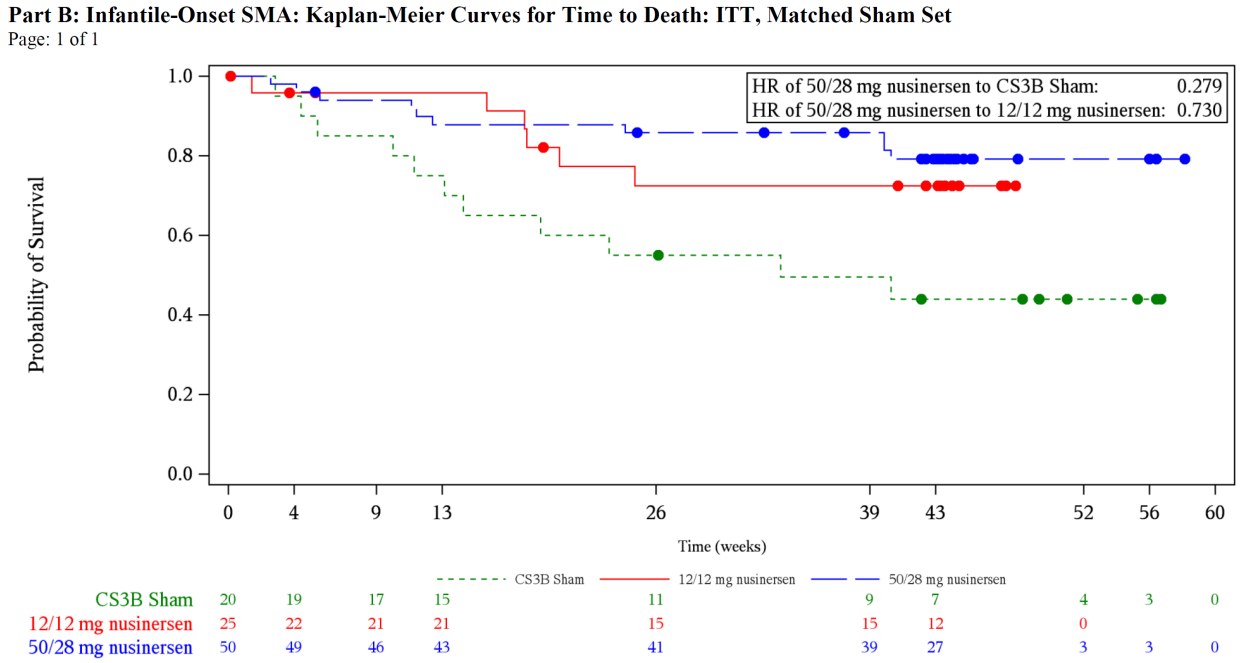
The hazard ratio (95% CI) was numerically lower in the 50/28-mg Group than the 12-mg Group (0.701 [0.338, 1.452]; p = 0.3386).

Time to death (overall survival) compared to matched sham set

A lower proportion of participants in the 50/28-mg Group (10 participants [20%]) died than in the Matched Sham (11 participants [55%]). The median (95% CI) time to death based on the Kaplan-Meier Method for the Matched Sham was 33.6 (11.29, NA) weeks and could not be estimated for the 50/28-mg Group. The time to death was nominally significantly higher in the 50/28-mg Group than the Matched Sham, based on the log-rank test stratified by disease duration (p = 0.0012).

The hazard ratio (95% CI) of the 50/28-mg Group compared to the Matched Sham was 0.279 (0.112, 0.696) and was nominally significantly different between the groups (p = 0.0062).

Figure 9. Part B: Infantile-onset SMA: Kaplan-Meier curves for time to death: ITT, matched sham set



NOTE: An HR < 1 indicates lower risk of event in the 50/28mg group.
Source: isis396443/232sm203-part-b-infant/csr/f-tte-timdth.sas **Run Date:** 24JUL2024

Time to death (overall survival) compared to 12 mg nusinersen

A lower proportion of participants in the 50/28-mg Group (10 participants [20%]) died than in the 12-mg Group (6 participants [24%]).

The median (95% CI) time to death based on the Kaplan-Meier Method could not be estimated for the 12-mg Group and the 50/28-mg Group. The estimated time to death was numerically higher in the 50/28-mg Group than the 12-mg Group, but not statistically significant based on the log-rank test stratified by disease duration (p = 0.4821).

The hazard ratio (95% CI) was numerically lower in the 50/28-mg Group than the 12-mg Group (0.730 [0.264, 2.015]; p = 0.5431).

Further data from Study SM203 Part B

Infantile onset

- When adjusted for disease duration at Screening and baseline CHOP INTEND score, the annualized rate of hospitalization (95% CI) was numerically lower in the 50/28-mg Group (1.9 [1.25, 2.82]) than the 12-mg Group (3.1 [1.78, 5.35]), based on binomial regression (p = 0.1522). The rate ratio (95% CI) of the adjusted rate of hospitalization of the 50/28-mg Group compared to the 12-mg Group was 0.6 (0.31, 1.20). The mean (SD) percentage of time in hospitalization was numerically lower for the 50/28-mg Group (16.2% [28.12%]) than the 12-mg Group (26.3% [37.11%]), based on ANCOVA (LS mean difference [95% CI] = -9.35 [-24.54, 5.84]; p = 0.2238).
- There was a greater improvement in the physician-rated clinical global impression in the 50/28-mg Group at Day 302, as indicated by a numerically higher proportion of CGIC responders in the 50/28-mg Group (28 participants [56.0%]) than in the 12-mg Group (10 participants [40.0%]), based on logarithmic regression (p = 0.2524). The odds ratio (50/28-mg / 12-mg; 95% CI) was 1.848 (0.646, 5.287). Similarly, there was a numerically higher proportion of caregiver-rated CGIC

responders in the 50/28-mg Group (31 participants [62.0%]) than in the 12-mg Group (10 participants [40.0%]), based on logarithmic regression (p = 0.1067). The odds ratio (50/28-mg / 12-mg; 95% CI) was 2.351 (0.832, 6.641).

- When adjusted for disease duration at Screening and baseline CHOP INTEND score, the annualized rate of serious respiratory events (95% CI) was numerically lower in the 50/28-mg Group (1.8 [1.17, 2.68]) than the 12-mg Group (2.1 [1.16, 3.72]), based on binomial regression (p = 0.6642). The rate ratio (95% CI) of the adjusted rate of serious respiratory events of the 50/28-mg Group compared to the 12-mg Group was 0.9 (0.42, 1.74).
- The mean (SD) proportion of time on ventilation was numerically higher in the 50/28-mg Group (26.4% [34.35%]) than the 12-mg Group (25.4% [34.08%]), based on ANCOVA (LS difference [95% CI] = 1.63 [-14.99, 18.25]; p = 0.8456).
- A numerically lower proportion of the 50/28-mg Group (22 participants [62.9%]) used ventilation at Day 302 than the 12-mg Group (9 participants [69.2%]).
- The following mean (SD) changes from baseline to Day 302 in PASA general feeding domain scores were numerically higher (indicating better retention of swallowing ability) in the 50/28-mg Group than the 12-mg Group:
- Had Difficulty Feeding Themselves: 12-mg Group, -1.6 (1.81); 50/28-mg Group, -0.6 (1.55)
- Had to Suction Excess Saliva or Drool: 12-mg Group, -1.7 (1.38); 50/28-mg Group, -0.2 (1.58)
- Not Able to Eat as Much as Would Like: 12-mg Group, -1.6 (1.72); 50/28-mg Group, -0.2 (1.45)
- Not Able to Eat Food Variety They Like: 12-mg Group, -1.6 (1.72); 50/28-mg Group, -1.0 (1.18)
- Been Tube-Fed: 12-mg Group, -1.8 (2.11); 50/28-mg Group, -0.9 (1.76)
- A lower proportion of participants in the 50/28-mg Group had decreased sucking/swallowing ability at Day 302 than in the 12-mg Group as assessed by HINE-1 (6% [2/35] versus 33% [4/12]), and a greater proportion of participants in the 50/28-mg Group had improved sucking/swallowing ability at Day 302 (26% [9/35] versus 8% [1/12], respectively) [5.3.5.3 ISE, Appendix 2.3.7, Output 1].
- The reduction from baseline to Day 15 in CSF concentrations of NF-L (LS geometric mean ratio to baseline [95% CI]) was numerically greater (e.g., lower ratio to baseline) in the 50/28-mg Group (0.94 [0.78, 1.15]) than the 12-mg Group (0.98 [0.74, 1.29]), based on ANCOVA with MI (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.97 [0.70, 1.34]; p = 0.8332). The reduction from baseline to Day 279 in CSF concentrations of NF-L (LS geometric mean ratio to baseline [95% CI]) was numerically greater (e.g., lower ratio to baseline) in the 50/28-mg Group (0.05 [0.04, 0.06]) than the 12-mg Group (0.06 [0.05, 0.08]), based on ANCOVA with MI (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.86 [0.62, 1.20]; p = 0.3785).

Later-Onset

- The change from baseline to Day 302 in HFMSE score (LS mean [95% CI]) was numerically higher (indicating improved motor function) in the 50/28-mg Group (3.3 [1.5, 5.0]) than the 12-mg Group (2.6 [0.2, 5.1]), based on ANCOVA with MI (LS mean difference [95% CI] = 0.63 [-2.5, 3.8]; p = 0.6949). The change from baseline to Month 9 in HFMSE score (LS mean [95% CI]) was nominally significantly higher in the 50/28-mg Group (2.9 [0.7, 5.0]) than the Matched CS4 Sham (-0.3 [-2.4, 1.7]), based on ANCOVA (LS mean difference [95% CI] = 3.2 [0.2, 6.2]; p = 0.0372). The change from baseline to Month 9 in HFMSE score (LS mean [95% CI]) was numerically higher in the 50/28-mg Group (3.3 [1.7, 4.9]) than the Matched CS4 12 mg (1.7 [0.6, 2.7]), based on ANCOVA (LS mean difference [95% CI] = 1.7 [-0.3, 3.6]; p = 0.0950).

- The change from baseline to Day 302 in RULM score (LS mean [95% CI]) was numerically higher (indicating improved upper limb function) in the in the 50/28-mg Group (2.4 [0.7, 4.2]) than the 12-mg Group (1.8 [-0.8, 4.4]), based on ANCOVA with MI (LS mean difference [95% CI] = 0.72 [-2.5, 4.0]; p = 0.6641). The change from baseline to Month 9 in RULM score (LS mean [95% CI]) was numerically higher in the 50/28-mg Group (2.1 [0.8, 3.4]) than the Matched CS4 Sham (0.4 [-0.9, 1.7]), based on ANCOVA (LS mean difference [95% CI] = 1.7 [-0.2, 3.5]; p = 0.0759). The change from baseline to Month 9 in RULM score (LS mean [95% CI]) was numerically higher in the 50/28-mg Group (2.3 [1.1, 3.5]) than the Matched CS4 12 mg (1.8 [1.0, 2.7]), based on ANCOVA (LS mean difference [95% CI] = 0.5 [-1.0, 1.9]; p = 0.5474).
- No participants in the 12-mg Group lost or achieved new WHO motor milestones during the study. One participant (6.3%) in the 50/28-mg Group achieved 1 new WHO motor milestones (e.g., standing with assistance) during the study. One participant (6.3%) in the 50/28-mg Group achieved 2 new WHO motor milestones (e.g., standing with assistance and walking alone) during the study. One participant (6.3%) in the 50/28-mg Group achieved 3 new WHO motor milestones (e.g., walking with assistance, standing alone, and walking alone). Two participants (12.5%) in the 50/28-mg Group lost 1 WHO motor milestone each (e.g., hands-and-knees crawling and standing with assistance; 1 participant [6.3%] each) during the study.
- The following ACEND domain total score changes from baseline to Day 302 were numerically higher (indicating reduced caregiver burden) in the 50/28-mg Group than the 12-mg Group, based on ANCOVA with MI (LS mean difference [95% CI]; p-value):
    - Feeding/Grooming/Dressing: 0.33 (-15.2, 15.8); p = 0.9668
    - Transfers: 9.94 (-3.3, 23.2); p = 0.1420
    - Mobility: 1.19 (-16.8, 19.2); p = 0.8969
    - Time: 16.27 (-0.2, 32.8); p = 0.0531
    - Finance: 15.49 (-0.7, 31.7); p = 0.0608
- The following ACEND domain total score changes from baseline to Day 302 were numerically lower (indicating greater caregiver burden) in the 50/28-mg Group than the 12-mg Group, based on ANCOVA with MI (LS mean difference [95% CI]; p-value):
    - Sitting/Play: -0.21 (-12.0, 11.6); p = 0.9725
    - Emotion: -0.06 (-13.8, 13.7); p = 0.9930
- The following changes from baseline to Day 302 in PedsQL total domain scores were numerically higher (indicating improved quality of life) in the 50/28-mg Group than the 12-mg Group, based on ANCOVA with MI (LS mean difference [95% CI]; p-value):
    - Inventory (participant rated): 8.82 (-3.4, 21.1); p = 0.1418
    - Inventory (parent rated): 2.72 (-6.7, 12.1); p = 0.5712
    - Neuromuscular (participant rated): 15.21 (6.4, 24.0); p = 0.0029
    - Neuromuscular (parent rated): 5.74 (-4.2, 15.7); p = 0.2573
- The reduction from baseline to Day 279 in CSF concentration of NF-L (LS geometric mean ratio to baseline) was similar in the 50/28-mg Group (0.33 [0.26, 0.41]) and the 12-mg Group (0.32 [0.23, 0.45]), based on ANCOVA with MI (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 1.02 [0.67, 1.57]; p = 0.9151).

- The reduction from baseline to Day 64 in plasma concentration of NF-L (LS geometric mean ratio to baseline [95% CI]) was nominally significantly greater (e.g., lower ratio to baseline) in the 50/28-mg Group (0.34 [0.25, 0.46]) than the 12-mg Group (0.58 [0.38, 0.89]), based on ANCOVA with MI (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.58 [0.34, 1.00]; p = 0.0495).
- When adjusted for age at Screening, the annualized rate of hospitalization (95% CI) was numerically higher in the 50/28-mg Group (1.6 [0.65, 4.07]) than the 12-mg Group (0.7 [0.15, 2.96]), based on binomial regression (p = 0.3122). The rate ratio (95% CI) of the adjusted rate of hospitalization of the 50/28-mg Group compared to the 12-mg Group was 2.5 (0.43, 14.20). The mean (SD) percentage of time in hospitalization for the 50/28-mg Group (1.9% [3.08%]) was numerically higher than the 12-mg Group (1.8% [2.96%]), based on ANCOVA (LS mean difference [95% CI] = 0.26 [-2.25, 2.77]; p = 0.8302).
- Three participants (37.5%) in the 12-mg Group and 6 participants (37.5%) in 50/28-mg Group were CGIC (physician) responders at Day 302 (logarithmic regression p = 0.6492). The odds ratio (50/28-mg / 12-mg; 95% CI) was 1.784 (0.147, 21.612). A numerically higher percentage of the 50/28-mg Group (8 participants [50.0%]) were CGIC (caregiver-rated) responders at Day 302 than the 12-mg Group (3 participants [37.5%]), based on logarithmic regression (p = 0.3651). The odds ratio (50/28-mg / 12-mg; 95% CI) was 2.706 (0.314, 23.337).
- The unadjusted annualized rate of serious respiratory events was numerically lower in the 50/28-mg Group (0.15) than the 12-mg Group (0.94).
- A numerically lower proportion of the 50/28-mg Group (5 participants [31.3%]) used ventilation at Day 302 than the 12-mg Group (4 participants [57.1%]).
- The following mean (SD) change from baseline to Day 302 in PASA general feeding domain scores was numerically higher (indicating better retention of swallowing ability) in the 50/28-mg Group than the 12-mg Group:
    - Had Difficulty Feeding Themselves: 12-mg Group, -0.4 (0.53); 50/28-mg Group, 0.3 (0.73)
- The following mean (SD) changes from baseline to Day 302 in PASA general feeding domain scores were numerically lower (indicating worse retention of swallowing ability) in the 50/28-mg Group than the 12-mg Group:
    - Not Able to Eat as Much as Would Like: 12-mg Group, 0.3 (0.95); 50/28-mg Group, 0.0 (0.39)
    - Not Able to Eat Food Variety They Like: 12-mg Group, 0.1 (0.69); 50/28-mg Group, -0.4 (0.93)
- The following mean (SD) changes from baseline to Day 302 in PASA general feeding domain scores were numerically similar in the 50/28-mg Group and the 12-mg Group):
    - Had to Suction Excess Saliva or Drool: 12-mg Group, 0.1 (0.38); 50/28-mg Group, 0.1 (0.36)
    - Been Tube-Fed: 12-mg Group, 0.00 (0.00); 50/28-mg Group, 0.00 (0.00)

Study SM203 Part A

Part A of Study SM203 was an open-label safety evaluation of a regimen consisting of nusinersen administered IT at loading doses of 28 mg on Days 1, 15, and 29, followed by 2 maintenance doses of 28 mg on Days 149 and 269; safety data were reviewed by the Independent Data Monitoring Committee

prior to exposing participants to the target higher dosing regimen in the pivotal portion of the study (Part B). Six treatment-naïve participants with later-onset SMA who were 6.1 to 12.6 years of age at Screening (mean age of 9.28 years) were enrolled in Part A, received all loading and maintenance doses per protocol, and completed the study. The majority (5 of 6 [83.3%]) of the participants were male. Four participants (66.7%) were White (1 Hispanic or Latino; 3 non-Hispanic or Latino), while the remaining 2 participants (33.3%) were Asian.

For Part A, the evaluation of efficacy data was secondary and exploratory only. There were no primary efficacy measures analyzed. Secondary objectives were to examine the clinical efficacy of a higher dose of nusinersen, with associated secondary efficacy endpoints focused on the change from baseline in motor function, quality of life, respiratory events, and ventilator use.

Conclusions on the Part A efficacy endpoints are as follows:

- For the majority of participants, there was stability or improvement in HFMSE scores over the duration of the study. Two participants experienced a decrease from baseline at the End of Study Visit that occurred between the Day 269 and Day 302 visits.
- For all participants, RULM total scores were stable or improved over the duration of the study.
- The majority of participants maintained the WHO motor milestones they had achieved at baseline throughout the study period. However, 1 participant who experienced tenotomies performed on Day 214 lost the ability to crawl on hands and knees at the Day 269 Study Visit.
- In general, ACEND and PedsQL scores remained stable throughout the study.
- At Day 302, the majority of Investigator-reported CGIC scores indicated minimal improvement relative to baseline, and the majority of caregiver-reported scores indicated minimal to much improvement relative to baseline. There was general stability in the Investigator and caregiver assessments throughout the duration of the study.
- No participants met the criteria for serious respiratory events, and no participants reported ventilator use at any point during the study.
- The 6MWT was not added to the Part A study design until Protocol Version 3 (05 June 2020), therefore, no baseline data are available for these participants. Two of the 3 ambulatory participants experienced general stability in 6MWT distance and percentage fatigue at the study visits where the 6MWT was conducted.

Study SM203 Part C

Part C of Study 203 was open-label and designed to evaluate the safety of transitioning participants from the 12 mg dosing regimen to the 50/28 mg dosing regimen in a representative patient population and enrolled a heterogenous population of participants, with a wide range of ages, phenotypes, ambulatory status, time on commercial nusinersen, and baseline HFMSE and RULM scores. In Part C, 40 participants who had already initiated treatment with nusinersen and received the approved dose of 12 mg for at least 1 year prior to entry (and with a median of 3.9 years) were enrolled to receive the higher dosing regimen via IT administration of a single bolus dose of 50 mg of nusinersen (administered 4 months ± 14 days after their most recent maintenance dose of 12 mg), with maintenance dosing of 28 mg on Days 121 and 241.

A total of 40 participants were enrolled and were dosed. Age at Screening ranged from 4 to 65 years. The mean age of the 2 participants with infantile-onset SMA was 4.8 years. Of the 14 participants < 18 years of age with later-onset SMA, the mean age was 10.7 years. Of the 24 participants ≥ 18 years of

age with later-onset SMA, the mean age was 37.4 years. Most participants were male (25 participants ([62.5%]), White (32 participants ([80.0%]), and not Hispanic or Latino (35 participants [87.5%]).

Baseline disease characteristics for infantile-onset and later-onset participants tended to present as expected based on respective disease severity.

In the 2 participants with infantile-onset SMA, age at symptom onset was 4 months for 1 participant and 6 months for 1 participant, and time from disease onset to enrollment was 4 years for 1 participant and 5 years for 1 participant. Age at SMA diagnosis was 1 year for both participants, and time from diagnosis to enrollment was 3 years for 1 participant and 4 years for 1 participant.

In later-onset SMA participants < 18 years of age, mean age at symptom onset was 16.3 months (range of 6 to 72 months), and mean time from disease onset to enrollment was 9.3 years (range of 4 to 17 years). Mean age at SMA diagnosis was 1.3 years (range of 0 to 3 years), and mean time from diagnosis to enrollment was 9.4 years (range of 4 to 17 years). In later-onset SMA participants ≥ 18 years of age, mean age at symptom onset was 76.2 months (range of 12 to 192 months), and mean time from disease onset to enrollment was 31.6 years (range of 8 to 59 years). Mean age at SMA diagnosis was 17 years (range of 2 to 54 years), and mean time from diagnosis to enrollment was 20.4 years (range of 4 to 50 years).

All participants with infantile-onset SMA had 3 copies of the SMN2 gene. In participants with later-onset SMA, the majority of participants < 18 years of age had 3 copies of SMN2, while the majority of participants ≥ 18 years of age had 4 copies of SMN2.

Conclusions on the efficacy endpoints are as follows:

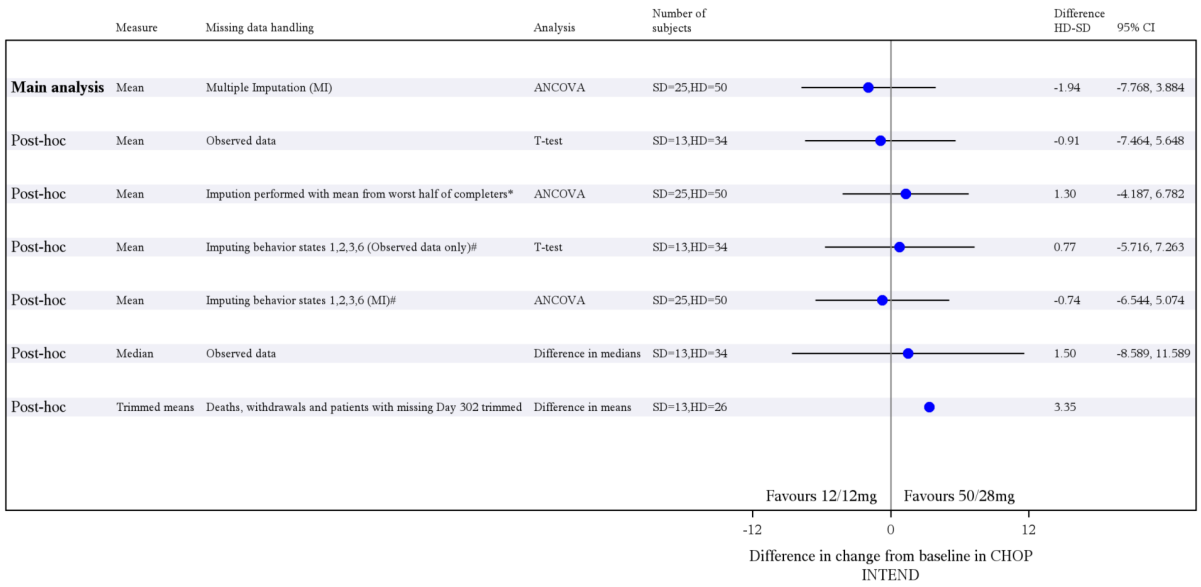
- Some participants (e.g., ambulatory adults) had scores at the upper end of HFMSE or RULM at baseline and thus did not have much opportunity for improvement. Regardless, for the majority of participants, HFMSE and RULM scores improved or were maintained over the duration of the study, with mean (SD) increases from baseline to Day 302 of 1.8 (3.99) points on HFMSE and 1.2 (2.14) points on RULM. In later-onset adults (> 18 years of age; n = 24), mean (SD) improvements of 2.3 (3.95) on HFMSE and 0.9 (1.89) on RULM were observed. These magnitudes of improvement are in line with what has been observed following the initiation of the approved nusinersen regimen (12 mg) in treatment-naïve patients in the literature and exceed what would be expected in a population that has been on nusinersen for several years.
- The majority of WHO motor milestones achieved by participants at baseline or gained during the study were maintained through the remainder of the study.
- In general, ACEND and PedsQL scores remained stable throughout the study.
- CHOP INTEND scores and HINE Section 2 motor milestones, which were assessed for 1 participant, remained stable throughout the study, with improvement in some HINE Section 2 motor milestones (kicking and rolling).
- At Day 302, the majority of Investigator-reported CGIC scores were assessed as minimally improved (19 participants [47.5%]) or no change (14 participants [35.0%]) relative to baseline, and the remaining scores were assessed as much improved (5 participants [12.5%]) and minimally worse (2 participants [5.0%]). The majority of caregiver-reported scores were assessed as minimally improved (9 participants [37.5%]) and much improved (6 participants [25.0%]) relative to baseline, and the remaining scores were assessed as no change (5 participants [20.8%]), very much improved (2 participants [8.3%]), and minimally worse (2 participants [8.3%]).

- A total of 29 hospitalizations were reported in 12 participants (30%). The majority of hospitalizations were for general observation following a dosing visit. Four participants were hospitalized for serious adverse events, none of which were related to study treatment or LP procedure as considered by the Investigator.
- There were no serious respiratory events reported during the study. Mean hours of ventilator use remained similar from baseline to Day 302. No participants required tracheostomies throughout the study.
- In general, ambulatory participants who completed the 6MWT maintained total distance walked at end of study compared to baseline, and fatigability remained stable throughout the study. Three participants were able to walk ≥ 30 meters past baseline value.
- The mean change in time to limitation increased by 60 seconds across 18 participants, indicating an increase in endurance.

Post-hoc analyses

Figure 10. Part B: Infantile-onset SMA: Forest plot for main and sensitivity analyses of change from baseline in CHOP INTEND to day 302: ITT set or observed data at day 302

Part B: Infantile-Onset SMA: Forest plot for main and sensitivity analyses of change from baseline in CHOP INTEND to Day 302: ITT Set or observed data at Day 302
Page: 1 of 1



* Impute missing Day 302 total scores including due to death/discontinuation with mean from worst half of completers (both arms)
# Imputing any behavior items of states 1,2,3,6 with most recent behavior item 4 or 5
Source: isis396443/232sm203-part-b-infant/csr/f-chop-fplot-d302.sas **Run Date:** 19SEP2024

Study SM302

A Long-Term Extension Study of Nusinersen (BIIB058) Administered at Higher Doses in Participants with Spinal Muscular Atrophy Who Previously Participated in an Investigational Study With Nusinersen

Study SM302 is an ongoing open-label, long-term extension study in which participants with SMA who completed Parts A, B, or C of Study SM203 could continue to receive higher dose nusinersen administered IT (or transition to higher dose) for up to 1921 days. Participants in Study SM203 who received maintenance doses of 28 mg nusinersen continued this dosing scheme in Study SM302. Those who received the currently approved maintenance dose of 12 mg nusinersen in Study SM203 were

administered a bolus dose of 50 mg nusinersen on Day 1 followed by 28 mg nusinersen maintenance doses every 4 months thereafter, which is identical to the regimen in Part C of Study SM203.

To maintain the double-blind for Part B of Study SM203, participants who were enrolled in Part B received a blinded first dose in Study SM302. During Study SM302, the participants together with Investigators, site staff, and the Sponsor study management team continued to be blinded to individual treatment assignments in Study 203.

As of the data cutoff date of 30 May 2024, 108 participants were enrolled and 103 participants were dosed, of which 9 participants discontinued study treatment and 8 participants withdrew from the study. No participants had completed the study as of the data cutoff date. Overall, 6 participants were from Part A, 35 participants were from Part B Infantile-Onset SMA, 23 participants were from Part B Later-Onset SMA, and 39 participants were from Part C of Study SM203.

Six participants from Part A, 26 participants with infantile-onset SMA from Part B, 16 participants with later-onset SMA from Part B, and 39 participants from Part C received maintenance doses of 28 mg approximately every 4 months; and 9 participants with infantile-onset SMA and 7 participants with later-onset SMA from Part B received a single loading dose of 50 mg nusinersen on Day 1, with all participants continuing to receive maintenance doses of 28 mg nusinersen approximately every 4 months.

Of the 6 participants in Part A, most were male (5 participants [83.3%]) and White (4 participants [66.7%]). Age at first dose in Study SM302 ranged from 7.23 to 13.67 years.

Of the 35 participants with infantile-onset SMA in Part B, most were male (16 participants [45.7%]) and White (24 participants [68.6%]). The mean age at first dose in Study SM302 was 1.49 years (range: 1.1 to 1.9 years).

Of the 23 participants with later-onset SMA in Part B, most were female (19 participants [82.6%]), White (10 participants [43.5%]), and not Hispanic or Latino (15 participants [65.2%]). The mean age at first dose in Study SM302 was 7.25 years (range: 3.2 to 10.9 years).

Of the 39 participants in Part C, most were male (24 participants [61.5%]), White (31 participants [79.5%]), and not Hispanic or Latino (35 participants [89.7%]). The 2 participants with infantile-onset SMA were 5.1 and 6.6 years of age at first dose in Study SM302. Of the 37 participants with later-onset SMA, the mean age at first dose in Study SM302 was 11.68 years (range: 5.9 to 18.4 years) in participants < 18 years of age and 38.99 years (range: 20.0 to 66.0 years) in participants ≥ 18 years of age.

Conclusions on the efficacy endpoints are as follows:

Part A

At the Study Day 841 Visit, 4 of 5 participants (80%) maintained the WHO motor milestones they achieved at baseline through the remainder of the study.

In the 5 participants who reached the Study Day 841 Visit, 4 participants had maintained or improved HFMSE total scores and 1 participant had a decrease in HFMSE total score.

In the 5 participants who reached the Study Day 841 Visit, 2 participants had maintained RULM total scores and 3 participants had decreased RULM total scores.

Part B Infantile-Onset SMA

Participants from the 50/28-mg Group continued to maintain or attained additional WHO motor milestones over time; at the Study Day 121 Visit, 12 of 19 participants (63.2%) achieved sitting without

support. Limited data were available for participants from the 12-mg Group; at the Study Day 121 Visit, 1 of 3 participants (33.3%) achieved sitting without support.

At the time of entry into Study SM302, 12 participants (34.3%) had met the endpoint of permanent ventilation. From baseline, 1 participant (3.8%) from the 50/28-mg Group and 2 participants (22.2%) from the 12-mg Group met the endpoint of death in Study SM302. No additional participants met the permanent ventilation definition in either group during Study SM302.

Participants from the 50/28-mg Group (n = 19) experienced improvement from baseline in CHOP INTEND total score at the Study Day 121 Visit (mean [95% CI] increase of 5.4 [2.31, 8.42] points), whereas participants from the 12-mg Group (n = 3) experienced a decline (mean [95% CI] change of -2.7 [-15.41, 10.08] points).

Participants from the 50/28-mg Group (n = 20) experienced improvement from baseline in HINE Section 2 motor milestones total score at the Study Day 121 Visit (mean [95% CI] increase of 1.2 [0.06, 2.24] points), whereas participants from the 12-mg Group (n = 3) experienced a decline (mean [95% CI] change of -1.7 [-11.07, 7.74] points).

There were insufficient HFMSE and RULM data at the time of the interim analysis to enable interpretation.

Part B Later-Onset SMA

Participants from both groups maintained over time the WHO milestone of sitting without support. At the Study Day 361 Visit, 16 of 16 participants (100.0%) from the 50/28-mg Group and 4 of 5 participants from the 12-mg Group had the ability to sit without support.

Participants from both groups experienced improvement from baseline in HFMSE total score at the Study Day 361 Visit, with mean (95% CI) increases of 1.0 (-0.71, 2.71) point in participants from the 50/28-mg Group (n = 16) and 0.5 (-2.55, 3.55) points in participants from the 12-mg Group (n = 4).

Participants from both groups experienced improvement from baseline in RULM total score at the Study Day 361 Visit, with mean (95% CI) increases of 0.9 (-0.51, 2.26) points in participants from the 50/28-mg Group (n = 16) and 1.8 (-3.51, 7.01) points in participants from the 12-mg Group (n = 4).

Part C

Nearly all participants (37 of 39 participants [94.9%]) had the ability to sit without support at baseline and maintained that ability at the Study Day 241 Visit (36 of 38 participants [94.7%]). A total of 20 of 39 participants (51.3%) were able to walk alone at baseline and 19 of 38 participants (50.0%) maintained that ability at the Study Day 241 Visit.

Participants generally maintained the prior improvements on functional measures (HFMSE and RULM) observed in Study SM203 following transition to the 50/28 mg dosing regimen over time in Study SM302, with a slight decline from baseline in HFMSE (mean [95% CI] change of -0.7 [-1.88, 0.55] points, driven by participants < 18 years of age with later-onset SMA) and no change from baseline in RULM (mean [95% CI] change of 0.0 [-0.59, 0.54] points) at the Study Day 241 Visit.

Participants with infantile-onset SMA (n = 2) experienced continued improvement from baseline in HFMSE (mean [95% CI] increase of 4.0 (-8.71, 16.71 points) and RULM (mean [95% CI] increase of 2.5 [-29.27, 34.27] points) at the Study Day 241 Visit.

Participants with later-onset SMA generally maintained the prior improvements observed in Study SM203 following transition to the 50/28 mg dosing regimen over time in Study SM302. Participants < 18 years of age with later-onset SMA (n = 14) experienced some decline from baseline in HFMSE (mean [95% CI] change of -2.4 [-4.78, -0.08] points) at the Study Day 241 Visit, but less decline in HFMSE than would be expected with the 12 mg dosing regimen based on experience in this age group in prior studies

(e.g., CS11). In contrast to HFMSE, these participants remained stable on RULM (mean [95% CI] increase of 0.3 [-0.98, 1.56] points at the Study Day 241 Visit). Participants ≥ 18 years of age with later-onset SMA (n = 23) remained stable from baseline in HFMSE (mean [95% CI] change of 0.0 [-1.37, 1.37] points) and experienced a slight decline from baseline in RULM (mean [95% CI] change of -0.4 [-0.88, 0.01] points) at the Study Day 241 Visit.

Ancillary analyses

The MAH has presented forest plot analyses and the probability to improve of the patients for different endpoints, and these also support the slight advantage of the 50/28 regimen, but the difference in the matched sham vs the 50/28 population preclude a clear justification of slight advantage of the 50/28 regimen.

Figure 11. Part B: Infantile-onset SMA: CHOP INTEND: Percentage of participants achieving thresholds of change from baseline to day 302: ITT set

Part B: Infantile-Onset SMA: CHOP INTEND: Percentage of participants achieving thresholds of change from baseline to Day 302: ITT Set

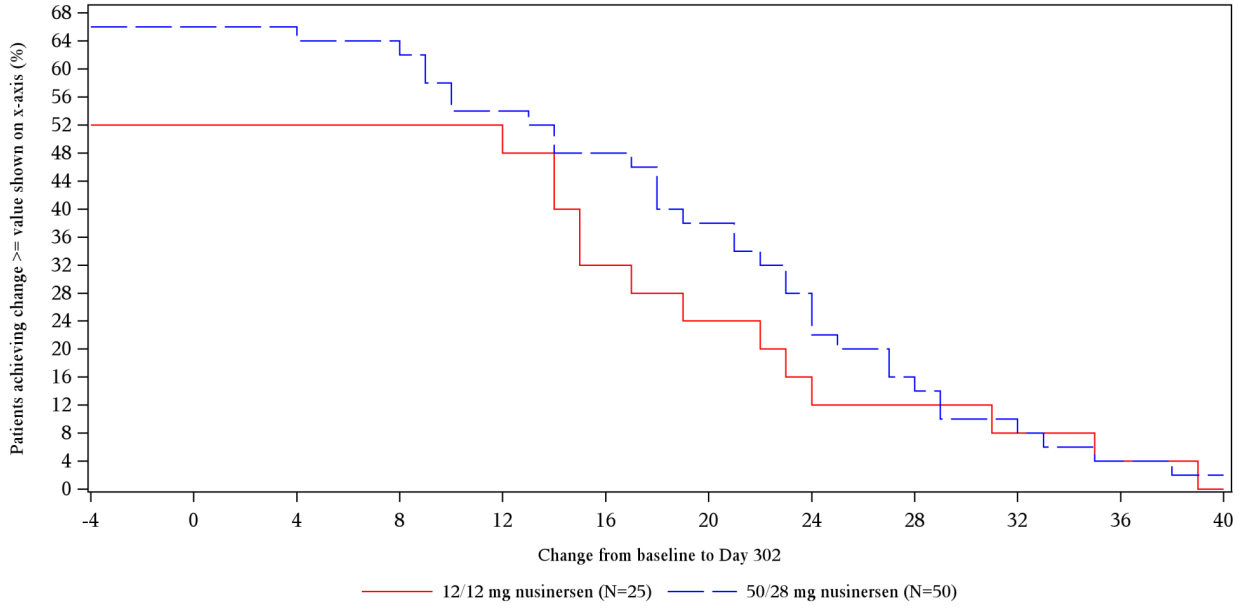


Figure 12. Part B: Infantile-onset SMA: HINE2: Percentage of participants achieving thresholds of change from baseline to day 302: ITT set

Part B: Infantile-Onset SMA: HINE2: Percentage of participants achieving thresholds of change from baseline to Day 302: ITT Set

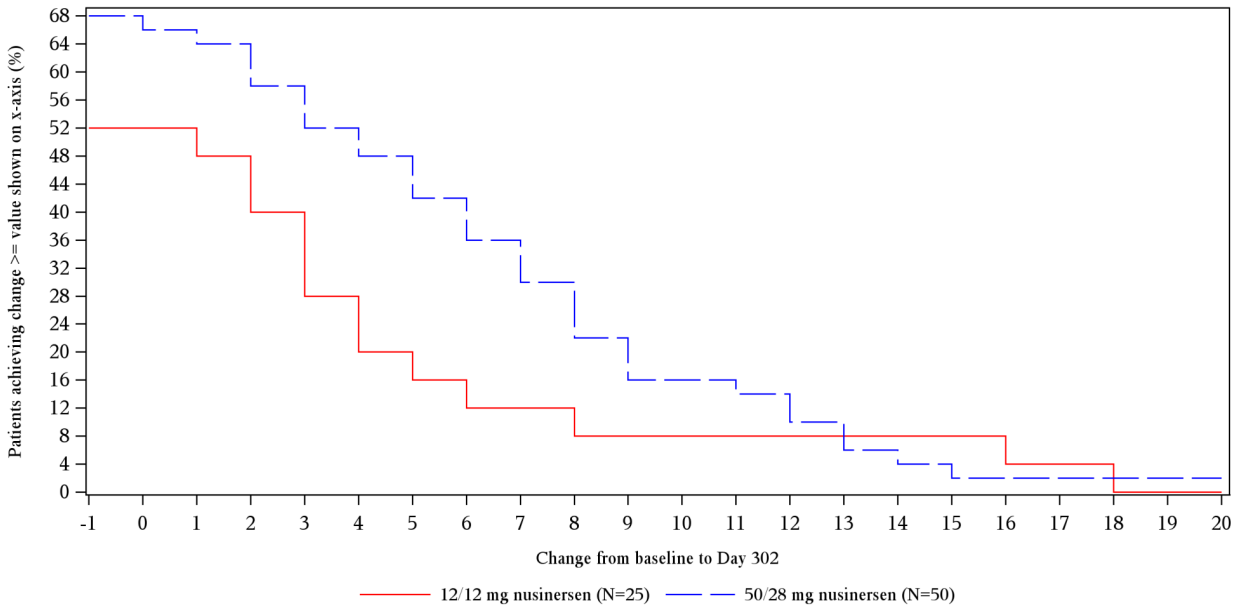
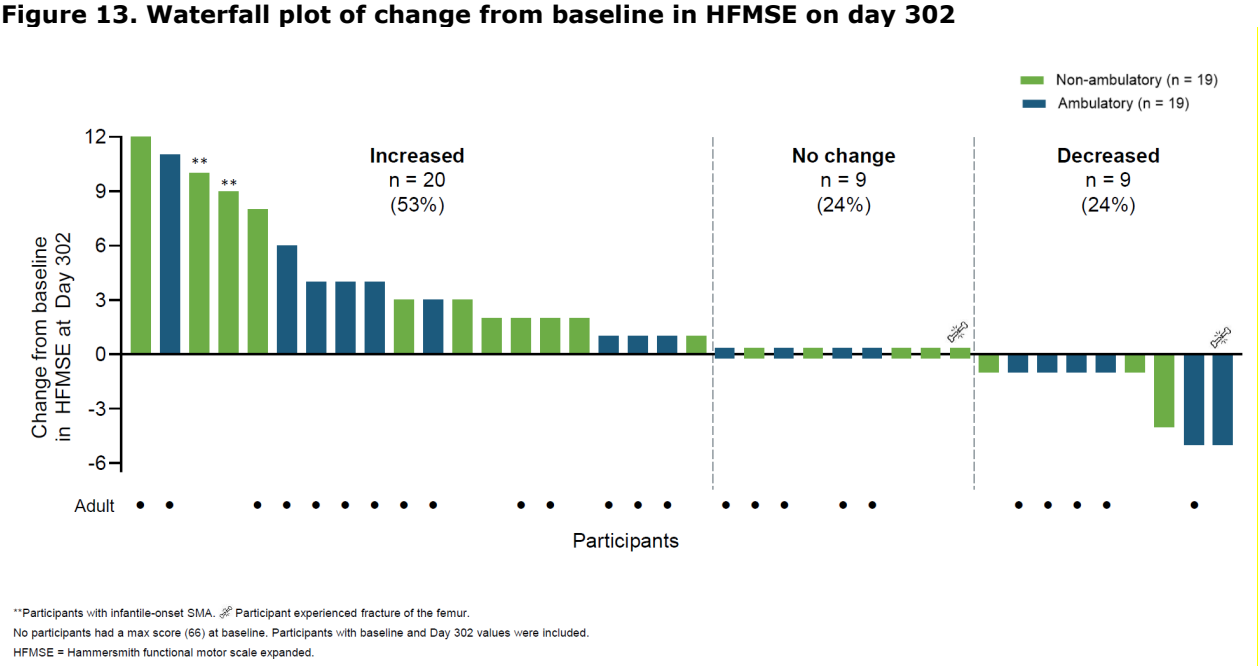


Figure 13. Waterfall plot of change from baseline in HFMSE on day 302



**Participants with infantile-onset SMA. Participant experienced fracture of the femur.
No participants had a max score (66) at baseline. Participants with baseline and Day 302 values were included.
HFMSE = Hammersmith functional motor scale expanded.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy			
Study identifier	Study number: 232SM203, Part B EudraCT number: 2019-002663-10 ISRCT number:		
Design	Part B of Study 232SM203 consisted of a pivotal, double-blind, active -controlled treatment period with either 2 or 4 loading doses of nusinersen (for the 50/28-mg Group and Control Group, respectively) administered IT followed by maintenance doses approximately every 4 months thereafter. 75 participants with infantile-onset SMA were randomized in a 1:2 ratio and received either the currently approved dosing regimen (12 mg) or higher dosing regimen (50/28 mg).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 323 to 420 days Not applicable Following completion of this study, all eligible participants were given the option to enrol in a separate, long term extension study (232SM302)
Hypothesis	Superiority of 50/28 mg versus Matched Sham from study CS3B (powered) Superiority of 50/28 mg versus 12/12mg (not formally powered)		
Treatment groups	Part B Infantile-Onset SMA, 50/28 mg Nusinersen		A total of 50 participants with infantile-onset SMA received 2 loading doses of 50 mg of nusinersen administered IT (Days 1 and 15) and 2 sham procedures on Days 29 and 64, followed by maintenance doses of 28 mg on Days 135 and 279 (and a sham procedure on Day 183).
	Part B: Infantile-Onset SMA: 12 mg Nusinersen		A total of 25 participants with infantile-onset SMA received 4 loading doses of 12 mg of nusinersen administered IT (Days 1, 15, 29, and 64), followed by maintenance doses of 12 mg on Days 183 and 279 (and a sham procedure on Day 135).
	Part B Infantile-Onset SMA, Matched Sham		The statistical testing of the primary endpoint and a subset of secondary endpoints used the Sham Control Group from Study CS3B. Within Study CS3B, there were 37 participants with an opportunity to attend the Day 183 visit. An algorithm was used to select a group of sham participants (n = 20) from the pool of 37 to achieve a closer match on baseline CHOP INTEND and disease duration.
Endpoints and definitions	Primary endpoint	CHOP INTEND total score change from baseline to Day 183	Change from baseline to Day 183 in CHOP INTEND total score, accounting for mortality/dropout using the joint rank test (comparison of higher dose to matched sham control)
	Key secondary endpoint	Proportion of HINE Section 2 motor milestone responders at Day 183	Proportion of HINE Section 2 motor milestone responders at Day 183 (comparison of higher dose to matched sham control)

	Key secondary endpoint	Change from baseline to Day 183 in HINE Section 2	Change from baseline to Day 183 in HINE Section 2 motor milestones total score, accounting for mortality/dropout using the joint rank test (comparison of higher dose to matched sham control)
	Key secondary endpoint	Change from baseline to Day 183 in plasma concentration of NF-L	Change from baseline to Day 183 in plasma concentration of NF-L, accounting for mortality/dropout using the joint rank test (comparison of higher dose to matched sham control)
	Key secondary endpoint	CHOP INTEND total score change from baseline to Day 302	Change from baseline to Day 302 in CHOP INTEND total score, accounting for mortality/dropout using the joint rank test (comparison of higher dose to 12 mg dose)
	Key secondary endpoint	Change from baseline to Day 302 in HINE Section 2	Change from baseline to Day 302 in HINE Section 2 motor milestones total score, accounting for mortality/dropout using the joint rank test (comparison of higher dose to 12 mg dose)
	Key secondary endpoint	Change from baseline to Day 64 in plasma concentration of NF-L	Change from baseline to Day 64 in plasma concentration of NF-L, accounting for mortality/dropout using the joint rank test (comparison of higher dose to 12 mg dose)
	Key secondary endpoint	Time to death or permanent ventilation (nusinersen 50/28 mg vs matched sham)	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) (comparison of higher dose to matched sham control)
	Key secondary endpoint	Time to death (overall survival) (nusinersen 50/28 mg vs matched sham)	Time to death (overall survival) (comparison of higher dose to matched sham control)
	Key secondary endpoint	Time to death or permanent ventilation (nusinersen 50/28 mg vs nusinersen 12 mg)	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) (comparison of higher dose to 12 mg dose)
	Key secondary endpoint	Time to death (overall survival) (nusinersen 50/28 mg vs nusinersen 12 mg)	Time to death (overall survival) (comparison of higher dose to 12 mg dose)
	Other secondary endpoint	Number and duration of hospitalizations	Number and duration of hospitalizations (comparison of higher dose to 12 mg dose)
	Other secondary endpoint	CGIC at Day 302	CGIC (physician, caregiver) at Day 302 (comparison of higher dose to 12 mg dose)

Database	20 July 2024		
Results and Analysis			
Analysis description	**Primary Endpoint Analysis**		
Endpoint: Change from baseline to Day 183 in CHOP INTEND total score			
Analysis population and time point description	Analysis Population: Matched Sham Set A total of 76 participants were randomized. 25 participants to 12/12mg and 51 to 50/28mg. One participant randomized to 50/28mg withdrew before receiving study treatment; therefore, the ITT Set included 25 in the 12/12 mg group and 50 in the 50/28mg group (participants were analysed in the treatment group to which they are randomized). Matched Sham Set: N=70, comprised of sham participants (N=20) identified by the matching algorithm and all 50/28 mg participants(N=50) in the ITT Set. Time point: Day 183		
Descriptive statistics and estimate variability	Treatment group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50
	Adjusted mean based on ranks	16.9	42.9
	95% CI	(10.1, 23.7)	(38.7, 47.2)
	Adjusted mean based on CHOP INTEND	-11.1	15.1
	95% CI	(-15.9,-6.2)	(12.4, 17.8)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Matched Sham	
	Adjusted mean difference based on ranks	26.06	
	95% CI	(17.941, 34.172)	
	Joint rank P-value	<0.0001	
	Adjusted mean difference based on CHOP INTEND	26.19	
	95% CI	(20.7, 31.7)	
Analysis description	**Key Secondary Endpoint Analyses**		
Endpoint: Proportion of HINE Section 2 motor milestone responders			
Analysis population and time point description	Analysis Populations: Matched Sham Set Time point: Day 183		
Descriptive statistics and estimate variability	Treatment group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50

	Proportion of HINE Section 2 motor milestone responders at Day 183 [n]	0% [0]	58% [29]
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Matched Sham	
	Difference in percentages	58.00%	
	95% CI	(39.46, 71.81)	
	P-value (from Fisher exact test, compared to sham)	<0.0001	
Endpoint: Change from baseline to Day 183 in HINE Section 2			
Analysis population and time point description	Analysis Populations: Matched Sham Set Time point: Day 183		
Descriptive statistics and estimate variability	Treatment group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50
	Adjusted mean based on ranks	16.5	43.1
	95% CI	(9.9, 23.0)	(39.0, 47.2)
	Adjusted mean based on HINE-2 Total Score	-0.2	3.7
	95% CI	(-1.5, 1.0)	(3.0, 4.4)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Matched Sham	
	Adjusted mean difference based on ranks	26.67	
	95% CI	(18.812, 34.526)	
	Joint rank P-value	<0.0001	
	Adjusted mean difference based on HINE-2 Total score	3.94	
	95% CI	(2.458,5.424)	
Endpoint: Change from baseline to Day 183 in plasma concentration of NF-L			
Analysis population and time point description	Analysis Populations: Matched Sham Set Time point: Day 183		
Descriptive statistics and estimate variability	Treatment group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50
	Adjusted mean based on ranks	14.4	44.0
	95% CI	(8.2, 20.6)	(40.1, 47.8)

	Adjusted GMR to baseline	0.70	0.06
	95% CI	(0.43, 1.12)	(0.05, 0.07)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg vs Matched Sham	
	Adjusted mean difference based on ranks	29.58	
	95% CI	(22.118, 37.042)	
	Joint rank P-value (compared to sham)	<0.0001	
	GMR (50/28mg: sham)	0.08	
	95% CI	(0.05,0.14)	
Endpoint: CHOP INTEND total score change from baseline to Day 302			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		
Descriptive statistics and estimate variability	Treatment group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Adjusted mean based on ranks	37.3	38.3
	95% CI	(29.1, 45.5)	(32.7, 44.0)
	Adjusted mean based on CHOP INTEND	21.6	19.6
	95% CI	(16.6, 26.6)	(16.5, 22.8)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Nusinersen 12-mg Group	
	Adjusted mean difference based on ranks	1.00	
	95% CI	(-9.290, 11.299)	
	Joint rank P-value (compared to 12 mg)	0.8484	
	Adjusted mean difference based on CHOP INTEND (50/28mg minus 12/12mg)	-1.94	
	95% CI	(-7.768, 3.884)	
Endpoint: Change from baseline to Day 302 in HINE Section 2			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		

Descriptive statistics and estimate variability	Treatment group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Adjusted mean based on ranks	34.3	39.8
	95% CI	(27.2, 41.4)	(34.9, 44.7)
	Adjusted mean based on HINE-2 Total Score	5.3	5.9
	95%CI	(3.3, 7.4)	(4.6, 7.2)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Nusinersen 12-mg Group	
	Adjusted mean difference based on ranks	5.48	
	95% CI	(-3.397, 14.357)	
	Joint rank P-value (compared to 12 mg)	0.2263	
	Adjusted mean difference based on HINE-2 Total Score	0.58	
	95% CI	(-1.886, 3.042)	
Endpoint: Change from baseline to Day 64 in plasma concentration of NF-L			
Analysis population and time point description	Analysis Population:ITT Set Time point: Day 64		
Descriptive statistics and estimate variability	Treatment group	Nusinersen 12-mg Group	Nusinersen 50-28-mg Group
	Number of subjects	25	50
	Adjusted mean based on ranks	29.5	42.2
	95% CI	(22.5, 36.5)	(37.5, 47.0)
	Adjusted GMR to baseline	0.23	0.12
	95% CI	(0.16, 0.32)	(0.09, 0.15)
Effect estimate per comparison	Comparison group	Nusinersen 50/28-mg Group vs Nusinersen 12-mg Group	
	LS mean difference	12.74	
	95% CI	(3.840, 21.632)	
	Joint rank P-value (50/28mg compared to 12 mg)	0.0050	
	GMR (50/28mg : 12/12mg)	0.51	
	95% CI	(0.33, 0.78)	

Endpoint: Time to death or permanent ventilation (nusinersen 50/28 mg vs matched			
Analysis population and time point description	Analysis Populations: Matched Sham Set Time point: All available follow-up.		
Descriptive statistics and estimate variability	Treatment Group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50
	Median (weeks)	19.1	Could not be estimated
	95% CI	(10.00, 31.29)	(39.86, NA)
	Number of patients who died or received permanent ventilation (%)	17 (85%)	19 (38%)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group vs Matched Sham	
	P-value based on log-rank test stratified by disease duration	0.0006	
	Hazard ratio	0.322	
	95% CI	(0.158, 0.657)	
Endpoint: Time to death (overall survival) (nusinersen 50/28 mg vs matched sham)			
Analysis population and time point description	Analysis Populations: Matched Sham Set Time point: All available follow-up.		
Descriptive statistics and estimate variability	Treatment Group	Matched Sham	Nusinersen 50/28-mg Group
	Number of subjects	20	50
	Median (weeks)	33.6	Could not be estimated
	95% CI	(11.29, NA)	(NA, NA)
	Number of patients who died (%)	11 (55%)	10 (20%)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group vs Matched Sham	
	P-value based on log-rank test stratified by disease duration	0.0012	
	Hazard ratio	0.279	
	95% CI	(0.112, 0.696)	
Endpoint: Time to death or permanent ventilation (nusinersen 50/28 mg vs nusinersen 12 mg)			

Analysis population and time point description	Analysis Populations: ITT Set Time point: All available follow-up.		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Median (weeks)	24.7	Could not be estimated
	95% CI	(14.43, NA)	(39.86, NA)
	Number of patients who died or received permanent ventilation (%)	12 (48%)	19 (38%)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group vs Nusinersen 12-mg Group	
	P-value based on long-rank test stratified by disease duration	0.2775	
	Hazard ratio	0.701	
	95% CI	(0.338, 1.452)	
Analysis description	**Other Secondary Endpoint Analyses**		
Endpoint: Number of hospitalizations			
Analysis population and time point description	Analysis Population: ITT Set Time point: Not applicable		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Number (%) of subjects with at least 1 hospitalization	19 (76.0)	26 (52.0)
	Adjusted annualized rate of hospitalizations	3.1	1.9
	95% CI	(1.78, 5.35)	(1.25, 2.82)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group vs Nusinersen 12-mg Group	
	Rate ratio	0.6	
	95% CI	(0.31, 1.20)	
	P-value (compared to 12 mg)	0.1522	
Endpoint: Duration of hospitalizations			

Analysis population and time point description	Analysis Population: ITT Set Time point: Not applicable		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Adjusted mean Percentage Of Time in Hospital	26.3	16.2
	Comparison groups	Nusinersen 50/28-mg Group vs Nusinersen 12-mg Group	
	Adjusted mean difference in percentages (50/28mg minus 12/12mg)	-9.35	
	P-value	0.2238	
Endpoint: CGIC (physician) at Day 302			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Number (%) of responders very much improved or much improved	10 (40.0)	28 (56.0)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group vs Nusinersen 12-mg Group	
	Odds ratio	1.848	
	95% CI	(0.646, 5.287)	
	P-value (compared to 12 mg)	0.2524	
Endpoint: CGIC (caregiver) at Day 302			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Number (%) of responders very much improved or much improved	10 (40.0)	31 (62.0)
	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12-mg Group	

	Odds ratio	2.351	
	95% CI	(0.832, 6.641)	
	P-value (compared to 12 mg)	0.1067	
Endpoint: Number of serious respiratory events			
Analysis population and time point description	Analysis Population: ITT Set Time point: Not applicable		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Adjusted annualized rate of serious respiratory events	2.1	1.8
	95% CI	(1.16, 3.72)	(1.17, 2.68)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12-mg Group	
	Rate ratio	0.9	
	95% CI	(0.42, 1.74)	
	P-value (compared to 12 mg)	0.6642	
Endpoint: Proportion of time on ventilation			
Analysis population and time point description	Analysis Population: ITT Set Time point: Not applicable		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	25	50
	Adjusted mean	24.98	26.61
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12-mg Group	
	Adjusted mean difference	1.63	
	95% CI	(-14.99, 18.25)	
	P-value (compared to 12 mg)	0.8456	
Endpoint: Ventilator use			

Analysis population and time point description	Analysis Population: ITT Set with response at Day 302 Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	13	35
	Number (%) of subjects who used ventilation support at Day 302	9 (69.2)	22 (62.9)
Notes	No statistical comparison of the groups was performed.		

Table 6. Summary of efficacy for study 232SM203 part B, later-onset

Title: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy		
Study identifier	Study number: 232SM203, Part B EudraCT number: 2019-002663-10 ISRCT number:	
Design	Part B of Study 232SM203 consisted of a pivotal, double-blind, active controlled treatment period with either 2 or 4 loading doses of nusinersen (for the 50/28-mg Group and Control Group, respectively) administered IT followed by maintenance doses approximately every 4 months thereafter. 24 participants with later-onset SMA were randomized in a 1:2 ratio to receive either the currently approved dosing regimen (12 mg) or higher dosing regimen (50/28 mg).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 323 to 420 days Not applicable Following completion of this study, all eligible participants were given the option to enrol in a separate, long-term extension study (232SM302)
Hypothesis	Exploratory – the following comparisons were performed (these comparisons were not formally powered): • Within 232SM203 - 50/28mg compared 12/12mg • 50/28mg will be compared to matched CS4 sham • 50/28mg will be compared to matched CS4 12mg	
Treatment groups	Part B Later-Onset SMA, 50/28 mg Nusinersen	A total of 16 participants with later-onset SMA received 2 loading doses of 50 mg of nusinersen administered IT (Days 1 and 15) and 2 sham procedures on Days 29 and 64, followed by maintenance doses of 28 mg on Days 135 and 279 (and a sham procedure on Day 183).
	Part B: Later-Onset SMA: 12 mg Nusinersen	A total of 8 participants with later-onset SMA received 4 loading doses of 12 mg of nusinersen administered IT (Days 1, 15, 29, and 64), followed by maintenance doses of 12 mg on Days 183 and 279 (and a sham procedure on Day 135).

	Matched nusinersen group from CS4 (50/28 mg)		Propensity score matching performed to match 232SM203 50/28mg arm to participants from the CS4 study 12mg arm (3 loading doses of followed by maintenance doses every 6 months)
	Matched Sham from CS4 (12 mg)		Propensity score matching performed to match 232SM203 50/28mg arm to participants from the CS4 study sham arm
Endpoints and definitions	Key Secondary endpoint	HFMSE change from baseline to Day 302	Change from baseline in HFMSE score for nusinersen 50/28-mg Group vs 12-mg Group
	Key Secondary endpoint	HFMSE change from baseline to Month 9	Change from baseline in HFMSE score 50/28-mg Group vs Matched Sham group
	Key Secondary endpoint	RULM score change from baseline to Day 302	Change from baseline in RULM score for nusinersen 50/28-mg Group vs 12-mg Group
	Key Secondary endpoint	RULM change from baseline to Month 9	Change from baseline in RULM score 50/28-mg Group vs Matched Sham group
	Key Secondary endpoint	Total number of new WHO motor milestones at Day 302	Total number of new WHO motor milestones at Day 302 score for nusinersen 50/28-mg Group vs 12-mg Group
	Key Secondary endpoint	Change from baseline in plasma concentration of NF-L	Plasma concentration of NF-L for nusinersen 50/28-mg Group vs 12-mg Group
Database lock	6th June 2024		

Results and Analysis

Analysis description	**Secondary Endpoint Analyses**		
Endpoint: HFMSE change from baseline			
Analysis population and time point description	Analysis Population: ITT Set A total of 24 participants were randomized and all went on to be dosed. The ITT Set comprises 8 participants randomized to 12/12mg and 16 randomized to 50/28mg (participants were analysed in the treatment group to which they are randomized). Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	8	16
	Adjusted mean	2.6	3.3
	95% CI	(0.2, 5.1)	(1.5, 5.0)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Nusinersen 12-mg Group	
	Adjusted mean difference	0.63	
	95% CI	(-2.5, 3.8)	

	P-value (compared to 12 mg)	0.6949	
Endpoint: HFMSE change from baseline			
Analysis population and time point description	Analysis Population: PS matched CS4 Sham Set. Formed from the ITT Set of sham control participants from CS4 using propensity score (PS) matching to select participants comparable to the 50/28mg group in 232SM203. The 50/28mg group will comprise participants from the ITT Set of 232SM203. Time point: 9 Months		
Descriptive statistics and estimate variability	Treatment Group	Matched Sham Set from CS4	Nusinersen 50/28-mg Group
	Number of subjects	16	16
	Adjusted mean	-0.3	2.9
	95% CI	-2.4, 1.7	(0.7, 5.0)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group minus Matched Sham Set from CS4	
	Adjusted mean difference	3.2	
	95% CI	(0.2,6.2)	
	P-value	0.0372	
Notes	Due to slightly different visit schedules between 232SM203 and CS4 the timepoint is labelled Month 9. This utilises Day 279 from 232SM203 and Day 274 from CS4.		
Endpoint: HFMSE change from baseline			
Analysis population and time point description	Analysis Population: PS matched CS4 nusinersen Set. Formed from the ITT Set of 12mg participants from CS4 using propensity score (PS) matching to select participants comparable to the 50/28mg group in 232SM203. The 50/28mg group will comprise participants from the ITT Set of 232SM203. Time point: 9 Months		
Descriptive statistics and estimate variability	Treatment Group	Matched Treatment Group from CS4	Nusinersen 50/28-mg Group
	Number of subjects	32	16
	Adjusted mean	1.7	3.3
	95% CI	0.6, 2.7	1.7, 4.9
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* matched 12mg nusinersen set from CS4	
	Adjusted mean difference	1.7	
	95% CI	-0.3, 3.6	
	P-value	0.0950	
Endpoint: RULM score change from baseline			

Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	8	16
	Adjusted mean	1.8	2.5
	95% CI	(-0.8, 4.4)	(0.7, 4.2)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12mg Group	
	Adjusted mean difference	0.72	
	95% CI	(-2.5, 4.0)	
	P-value	0.6641	
Endpoint: RULM change from baseline			
Analysis population and time point description	Analysis Populations: PS matched CS4 sham Set Time point: Month 9		
Descriptive statistics and estimate variability	Treatment Group	Matched Sham Set from CS4	Nusinersen 50/28-mg Group
	Number of subjects	16	16
	Adjusted mean	0.4	2.1
	95% CI	-0.9, 1.7	0.8, 3.4
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Matched Sham Set from CS4	
	Adjusted mean difference	1.7	
	95% CI	-0.2, 3.5	
	P-value	0.0759	
Endpoint: Total number of new WHO motor milestones			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	8	16

	Number (%) discontinued from study	1 (12.5)	0
	Number lost one motor milestone (%)	0	2 (12.5)
	No change (%)	7 (87.5)	11 (68.8)
	Number (%) gained 1 motor milestone	0	1 (6.3)
	Number (%) gained 2 motor milestones	0	1 (6.3)
	Number (%) gained 3 motor milestones		
	Adjusted mean	0.2	0.3
	95% CI	(-0.6, 1.0)	(-0.2, 0.8)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12-mg Group	
	Adjusted mean difference	0.10	
	95% CI	(-0.9, 1.1)	
	P-value	0.8244	
Endpoint: Change from baseline in plasma concentration of NF-L			
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 64		
Descriptive statistics and estimate variability	Treatment Group	Nusinersen 12-mg Group	Nusinersen 50/28-mg Group
	Number of subjects	8	16
	Adjusted geometric mean ratio to baseline	0.58	0.34
	95% CI	(0.38, 0.89)	(0.25, 0.46)
Effect estimate per comparison	Comparison groups	Nusinersen 50/28-mg Group *vs* Nusinersen 12-mg Group	
	Difference in geometric mean ratio (50/28 mg vs 12 mg)	0.58	
	95% CI	(0.34, 1.00)	
	P-value (compared to 12 mg)	0.0495	

Table 7. Summary of efficacy for 232SM203 part C

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

Study identifier	Study number: 232SM203, Part C EudraCT number: 2019-002663-10 ISRCT number:		
Design	In Part C of Study 232SM203, 40 participants who had already initiated treatment with nusinersen and had been receiving the approved dose of 12 mg for at least 1 year prior to entry were enrolled and received the higher dosing regimen. The initial cohort in Part C (i.e., Cohort 1) consisted of up to approximately 20 participants of any age and of any SMA status and an additional cohort (i.e., Cohort 2) consisting of up to approximately 20 adult participants (≥ 18 years of age).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 323 to 382 days Not applicable Following completion of this study, all eligible participants were given the option to enrol in a separate, long-term extension study (232SM302)
Hypothesis	Exploratory – estimate change from baseline to Day 302.		
Treatments groups	Part C, 50/28 mg Nusinersen		A total of 40 participants received a single 50 mg dose 4 months ± 14 days after their most recent maintenance dose of 12 mg followed by 2 maintenance doses of 28 mg on Days 121 and 241.
Endpoints and definitions	Key Secondary endpoint	HFMSE change from baseline to Day 302	Change from baseline in HFMSE total score
	Key Secondary endpoint	RULM score change from baseline to Day 302	Change from baseline in RULM score
	Key Secondary endpoint	Total number of new WHO motor milestones	Total number of new WHO motor milestones at Day 302
Database lock	17 November 2023		
Results and Analysis			
Analysis description	**Secondary Endpoint Analyses**		
Endpoint: HFMSE change from baseline			
Analysis population and time point description	Analysis Population: ITT Set: all participants who received at least 1 dose of nusinersen in Part C of Study 232SM203. Time point: Day 302		
Descriptive statistics and estimate variability	Treatment group		Nusinersen 50/28 mg
	Number of subjects		40
	Number of subjects with HFMSE scores		38
	Mean change from baseline		1.8
	SD		3.99

Endpoint: RULM score change from baseline to Day 302		
Analysis population and time point description	Analysis Population: ITT Set Time point: Day 302	
Descriptive statistics and estimate variability	Treatment group	Nusinersen 50/28 mg
	Number of subjects	40
	Number of subjects with RULM scores	37
	Mean change from baseline	1.2
	SD	2.14

2.6.6. Discussion on clinical efficacy

The primary support for the efficacy of a higher dosing regimen of nusinersen (50◦mg dose administered as 2◦loading doses at biweekly intervals and 28◦mg maintenance doses every 4◦months thereafter) is from the infantile-onset cohort of Part B of Study SM203.

The primary endpoint does not directly respond to the advantage of the 50/28 mg over the 12 mg dosing regimen, since it does not directly compare the two regimens, but a comparison of the 50/28 to the sham procedure performed in study CS3 was made instead. In this study, a comparison between the sham procedure and the 12 mg regimen had already been done, thus the possibility of an indirect comparison. Notwithstanding, the study population of study SM203 Part B was younger and with less disease duration than the population enrolled into CS3, including those in the sham study arm. Furthermore, the sham population was matched to the SM203 population, which decreased the sample size of the sham arm from 37 to 20 patients, but did not dim the difference in age at diagnosis and age of the patients in the matched CS and SM203. As a consequence, it is considered that the primary endpoint is not a robust comparison of the 50/28 regimen as compared to the 12 mg regimen to the point that the 50/28 dosing should be preferred over the 12 mg dosing. This was considered a major objection.

The development plan, did allow for a direct comparison of 50/28 *vs*. 12 mg, with two study arms in a 2:1 randomisation being used in the double-blind, active-controlled results for participants with later-onset SMA in Part B of Study SM203. Secondary analyses comparing the 50/28 mg dosing regimen with the approved 12 mg dosing regimen were also included to assess whether supportive trends in favor of the 50/28 mg dosing regimen could be observed. This plan included:

- The double-blind, active-controlled results for participants with later-onset SMA in Part B of Study SM203.
- The open-label transition (from the approved 12 mg dosing regimen to the 50/28mg dosing regimen) Part C of Study SM203.
- Integrated data across Study SM203 its long-term extension, Study SM302.

Although not powered to this direct comparison, the totality of the efficacy evidence points towards a possible minimal advantage of the 50/28 regimen. This is shown with the numerically more favourable behaviour of this regimen regarding the endpoints CHOP INTEND, HINE, RULM, the median (95% CI) time to death or permanent ventilation, measured at different timepoints including D64, D183 and D302.

Transition from the 12 mg regimen to the 50/28 mg regimen also point to the benign profile. The magnitude of effect is small though:

- The change from baseline to Day 302 in CHOP INTEND total score was numerically higher in the 50/28-mg Group than the12-mg Group, based on the difference in ranks, but not statistically significant based on the JRT (LS mean difference [95% CI] = 1.00 [-9.290, 11.299]; joint-rank p = 0.8484)
- The change from baseline to Day 302 in HINE Section 2 motor milestone total score was numerically higher in the 50/28-mg Group than the 12-mg Group, based on the difference in ranks and the JRT (LS mean difference [95% CI] = 6.12 [-2.693, 14.939]; joint-rank p = 0.1734)].
- The median (95% CI) time to death or permanent ventilation based on the Kaplan-Meier Method for the 12-mg Group was 24.7 (14.43, NA) weeks and could not be estimated for the 50/28-mg Group. The estimated time to death or permanent ventilation was numerically higher in the 50/28-mg Group than the 12-mg Group based on the log-rank test stratified by disease duration (p = 0.2775). The hazard ratio (95% CI) was numerically lower in the 50/28-mg Group than the 12-mg Group (0.701 [0.338, 1.452]; p = 0.3386).
- The median (95% CI) time to death based on the Kaplan-Meier Method could not be estimated for the 12-mg Group and the 50/28-mg Group. The estimated time to death was numerically higher in the 50/28-mg Group than the 12-mg Group based on the log-rank test stratified by disease duration (p = 0.4821). The hazard ratio (95% CI) was numerically lower in the 50/28-mg Group than the 12-mg Group (0.730 [0.264, 2.015]; p = 0.5431).
- When adjusted for disease duration at Screening and baseline CHOP INTEND score, the annualized rate of hospitalization (95% CI) was numerically lower in the 50/28-mg Group (1.9 [1.25, 2.82]) than the 12-mg Group (3.1 [1.78, 5.35]), based on binomial regression (p = 0.1522). The rate ratio (95% CI) of the adjusted rate of hospitalization of the 50/28-mg Group compared to the 12-mg Group was 0.6 (0.31, 1.20). The mean (SD) percentage of time in hospitalization was numerically lower for the 50/28-mg Group (16.2% [28.12%]) than the 12-mg Group (26.3% [37.11%]), based on ANCOVA (LS mean difference [95% CI] = -9.35 [-24.54, 5.84]; p = 0.2238).
- There was a greater improvement in the physician-rated clinical global impression in the 50/28-mg Group at Day 302, as indicated by a numerically higher proportion of CGIC responders in the 50/28-mg Group (28 participants [56.0%]) than in the 12-mg Group (10 participants [40.0%]), based on logarithmic regression (p = 0.2524). The odds ratio (50/28-mg / 12-mg; 95% CI) was 1.848 (0.646, 5.287). Similarly, there was a numerically higher proportion of caregiver-rated CGIC responders in the 50/28-mg Group (31 participants [62.0%]) than in the 12-mg Group (10 participants [40.0%]), based on logarithmic regression (p = 0.1067). The odds ratio (50/28-mg / 12-mg; 95% CI) was 2.351 (0.832, 6.641).
- When adjusted for disease duration at Screening and baseline CHOP INTEND score, the annualized rate of serious respiratory events (95% CI) was numerically lower in the 50/28-mg Group (1.8 [1.17, 2.68]) than the 12-mg Group (2.1 [1.16, 3.72]), based on binomial regression (p = 0.6642). The rate ratio (95% CI) of the adjusted rate of serious respiratory events of the 50/28-mg Group compared to the 12-mg Group was 0.9 (0.42, 1.74).
- The mean (SD) proportion of time on ventilation was numerically higher in the 50/28-mg Group (26.4% [34.35%]) than the 12-mg Group (25.4% [34.08%]), based on ANCOVA (LS difference [95% CI] = 1.63 [-14.99, 18.25]; p = 0.8456).

- A numerically lower proportion of the 50/28-mg Group (22 participants [62.9%]) used ventilation at Day 302 than the 12-mg Group (9 participants [69.2%]).
- Some mean (SD) changes from baseline to Day 302 in PASA general feeding domain scores were numerically higher (indicating better retention of swallowing ability) in the 50/28-mg Group than the 12-mg Group.

The incomplete matching baseline population decrease the certainty of the minimal efficacy advantage.

The MAH has presented forest plot analyses and probability to improve of the patients for different endpoints, and these may support the slight benefit of the 50/28 dose regimen over the 12/12.

2.6.7. Conclusions on clinical efficacy

In conclusion, although the primary endpoint, for which study SM203 part B was planned, did not allow a direct comparison, and is thus flawed by the differences in the sham procedure study population vs. the more recent studied population, it can be accepted that the totality of evidence provided support the efficacy of the 50/28 regimen to be similarly efficacious to the 12/12 regimen, and that the higher dose regimen may be advantageous to some patients (e.g., in SMA type 1 as a bridging treatment while waiting for gene therapy treatment) than the lower dose. Since no clear confirmation of the advantage of the higher regimen vs. the lower, it is considered that both regimens should be kept available. The decision to increase the dose should be left for the prescriber. Therefore, it was suggested that in SmPC section 4.2 regarding the posology, the treatment should start as early as possible and not positively discriminating the high dose regimen. As for switching "Patients on 12 mg dosing regimen ", the wording was requested to be changed to "Patients currently treated with Spinraza 12 mg may be transitioned to the 50/28 mg dosing regimen (…)". The MAH agreed with the proposal. From the clinical efficacy point of view the new proposed dosing regimen is approvable.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data is retrieved from a total of 10 clinical studies, including studies evaluating a higher-dose regimen of nusinersen (completed Study SM203 and an interim data cut off (30 May 2024) of its long-term extension, Study SM302. The proposed pooling safety data analysis by the MAH is considered acceptable. All in all, safety data from 2 key nusinersen higher-dose pools of interest included the following: a) *Pool G* consists of safety data from Study SM203 Part B, combined onset populations (infantile-onset and later-onset), separated by dose (higher-dose regimen [50/28 mg] and control 12 mg regimen), allowing for comparisons between the higher-dose and 12 mg regimens. Safety data from SM203 Part B were also presented separately for each onset population (infantile-onset and later-onset) by dose group to provide additional safety results by participant age; b) *Pool J* which consisted of all controlled and uncontrolled studies of nusinersen 28 mg or higher, across participants with infantile-onset and later-onset SMA.

Additional safety pools specific to Studies SM203 and SM302 (BI+, BL+, BEI, BEL, CEXT, and AEXT) provided supportive data, integrating data from participants in Study SM203 with data from Study SM302 for participants who continued in the long-term extension study. Furthermore, an additional data pool, Pool I, consisting of all controlled and uncontrolled studies of nusinersen 12 mg or lower, was provided

also as supportive data, which according to the MAH provides the largest safety experience of participants who received nusinersen 12 mg or lower.

For participants in Pool G (Study SM203 pivotal Part B), 66 of the 99 participants received the nusinersen 50/28 mg regimen, in a controlled study of both infantile-onset and later-onset SMA for a total of 61.34 participant-years, and 33 participants received the nusinersen 12 mg regimen for a total of 25.93 participant-years. In Pool J, a total of 128 participants were exposed to nusinersen 28 mg or higher across both controlled and uncontrolled studies. The mean (SD) time on study for participants on nusinersen 28 mg or higher was 689.1 (365.57) days, the total number of participant-years on study for participants on nusinersen higher dose was 241.48.

Regarding the supportive higher dose pools, in the study pool BEI, time on study ranged from 1 to 1206 days with a mean (SD) of 442.4 (316.53) days. Participants switching from nusinersen 12 mg to the nusinersen higher dosing regimen were on study for a mean (SD) of 312.4 (246.83) days, and participants remaining on the nusinersen higher dosing regimen were on study for a mean (SD) of 507.5 (329.42) days. Overall, 37 participants (49.3%) were on study for ≥ 360 days, and the mean (SD) number of doses received overall was 5.4 (2.68). The number of doses received was similar between the 2 groups in the BEI pool. The total person-years on study for the BEI pool was 90.85. In the study pool BEL, time on study ranged from 214 to 1290 days with a mean (SD) of 981.5 (232.47) days. Participants switching from nusinersen 12 mg to the nusinersen higher dosing regimen were on study for a median of 927.5 days, and participants remaining on the nusinersen higher dosing regimen were on study for a mean (SD) of 880.8 (331.98) days. Overall, 23 participants (95.8%) were on study for ≥ 360 days, and the mean (SD) number of doses received overall was 10.0 (1.99). The number of doses received was similar between the 2 groups in the BEL pool. The total person-years on study for the BEL pool was 64.49. In the study pool CEXT, time on study ranged from 312 to 1002 days with a mean (SD) of 818.2 (154.06) days. Overall, 39 participants (97.5%) were on study for ≥ 360 days, and the mean (SD) number of doses received overall was 7.5 (1.43). The total person-years on study for the CEXT pool was 89.61. In the study pool AEXT, time on study ranged from 1001 to 1521 days with a mean (SD) of 1365.2 (183.52) days. Overall, all 6 participants (100%) were on study for ≥ 360 days, and the mean (SD) number of doses received overall was 13.5 (1.76). The total person-years on study for the AEXT pool was 22.43.

In what concerns to supportive All Pooled nusinersen 12 mg or lower, the mean (SD) time on study for participants in Pool I (12 mg or lower) for both controlled and uncontrolled studies was 2034.0 (1048.01) days, and the total number of person-years on study was 2144.02 years. The mean (SD) total number of nusinersen doses received was 17.4 (7.55) for participants in Pool I.

2.6.8.2. Adverse events

Overall Adverse Events

Key Higher Dose Pooled Groups

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Overall Adverse Events

In Pool G, 28 (84.8%) participants receiving nusinersen 12/12 mg and 57 (86.4%) participants receiving the nusinersen 28 mg regimen (50/28 mg) experienced ≥ 1 AE. The number of participants experiencing ≥ 1 AE was similar across each dosing treatment group.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Overall Adverse Events

In Pool J, a total of 117 (91.4%) participants receiving nusinersen 28 mg or higher experienced ≥ 1 AE. For infantile-onset SMA, fewer participants switching from nusinersen 12 mg (7 participants [63.6%]) to the nusinersen 28 mg or higher experienced ≥ 1 AE than participants with infantile-onset SMA who were treatment-naïve at baseline (45 participants [90%]). For participants with later-onset SMA, the number experiencing ≥ 1 AE was similar between those who were switchers from nusinersen 12 mg and those who were treatment-naïve at baseline.

Supportive Higher Dose Pools Overall Adverse Events

The number of participants experiencing ≥ 1 AE was similar across each study pool. A total of 68 participants (90.7%) in the BEI pool and 22 participants (91.7%) in the BEL pool experienced ≥ 1 AE. In the CEXT and AEXT pools, 97.5% and 100% of participants experienced ≥ 1 AE, respectively. Overall, AE severity varied between groups. Within pools, most AEs were severe in the BEI pool (54.7%), mild in the BEL pool (41.7%), moderate in the CEXT pool (52.5%), and were evenly distributed across mild, moderate, and severe in the AEXT pool (33.3% each). The incidence of serious AEs (SAEs) was 69.3% in the BEI pool, 50.0% in the BEL pool, 32.5% in the CEXT pool, and 33.3% in the AEXT pool.

Comparatively, in study pools BI+ and BL+ (where each provides an additional 97 days of follow-up [to Day 1 of Study SM302]), most AEs were also severe in the BI+ pools (49.3%) and most AEs were also mild in the BL+ pool (50.0%). AEs with a fatal outcome related to study treatment as assessed by the Investigator were noted only in the BEI pool and included 8 (32.0%) participants on nusinersen12 mg and 12 (24%) participants on nusinersen 50/28 mg for each.

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

In Pool I, a total of 381 participants (99.0%) receiving nusinersen 12 mg or lower experienced ≥ 1 AE. The number of participants experiencing ≥ 1 AE was similar across each study group, with 25 participants (100%) with presymptomatic SMA, 160 participants (98.8%) with infantile-onset SMA, and 196 participants (99.0%) with later-onset SMA experiencing ≥ 1 AE.)

Common Adverse Events

Key Higher Dose Pooled Groups

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Most Common Adverse Events

The most common AEs by PT (occurring in ≥ 10% of participants) across both the nusinersen 12 mg and the nusinersen higher dose groups were pneumonia (18.2% and 15.2%), upper respiratory tract infection (15.2% and 13.6%), atelectasis (12.1% and 3.0%), pyrexia (12.1% and 15.2%), cough (9.1% and 10.6%), COVID-19 (9.1% and 13.6%), respiratory failure (9.1% and 12.1%), and pneumonia aspiration (6.1% and 10.6%).

For the infantile-onset participant population, AEs reported by ≥ 15% of participants in the nusinersen 12 mg group were pneumonia (5 participants [20.0%]), respiratory failure (4 participants [16.0%]), and pyrexia (4 participants [16.0%]). AEs reported by ≥ 15% of participants with infantile-onset SMA on nusinersen 50/28 mg were pneumonia (10 participants [20.0%]), respiratory failure (10 participants

[20.0%]), pyrexia (9 participants [18.0%]), COVID-19 (8 participants [16.0%]), and upper respiratory tract infection (8 participants [16.0%]).

In the later-onset participant population, AEs reported by ≥ 15% of participants with later-onset SMA on nusinersen 12 mg were procedural pain (3 participants [37.5%]) and upper respiratory tract infection (2 participants [25.0%]). AEs reported by ≥ 15% of participants on nusinersen 50/28 mg were procedural headache (4 participants [25.0%]) and procedural pain (3 participants [18.8%]).

Table 8. Pool G - study SM203 part B combined onset populations pooled by dose most common adverse events by PT occurring in ≥ 10% of participants in either group (safety analysis set)

Preferred Term	12/12 mg Nusinersen (N = 33)	50/28 mg Nusinersen (N = 66)
Number of participants with any event	28 (84.8)	57 (86.4)
Pneumonia	6 (18.2)	10 (15.2)
Upper respiratory tract infection	5 (15.2)	9 (13.6)
Atelectasis	4 (12.1)	2 (3.0)
Pyrexia	4 (12.1)	10 (15.2)
Cough	3 (9.1)	7 (10.6)
COVID-19	3 (9.1)	9 (13.6)
Respiratory failure	3 (9.1)	8 (12.1)
Pneumonia aspiration	2 (6.1)	7 (10.6)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA Version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Most Common Adverse Events

The most common AEs by PT (occurring in ≥ 10% of participants) in Pool J were COVID-19 (27.3%), procedural pain (19.5%), upper respiratory tract infection (17.2%), pneumonia (16.4%), pyrexia (16.4%), procedural headache (15.6%), nasopharyngitis (15.6%), fall (13.3%), cough (11.7%), vomiting (11.7%), headache (10.9%), and constipation (10.2%). While Pool J (28 mg or higher nusinersen) and Pool I (12 mg or lower nusinersen) cannot be directly compared due to the extent of exposure and other variables, the emerging data do show some similarities in terms of common AEs by SOC.

Table 9. Pool J - all pooled Nusinersen 28 mg or higher controlled and uncontrolled studies most common adverse events by PT occurring in ≥ 10% of participants (safety analysis set)

Preferred Term	Pool J 50 mg or 28 mg nusinersen (N = 128)
Number of participants with any event	**117 (91.4)**
COVID-19	35 (27.3)
Procedural pain	25 (19.5)
Upper respiratory tract infection	22 (17.2)
Pneumonia	21 (16.4)
Pyrexia	21 (16.4)
Nasopharyngitis	20 (15.6)
Procedural headache	20 (15.6)
Fall	17 (13.3)
Cough	15 (11.7)
Vomiting	15 (11.7)
Headache	14 (10.9)
Constipation	13 (10.2)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each and PT (MedDRA Version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Supportive Higher Dose Pools Most Common Adverse Events

The most common AEs by PT (occurring in ≥ 10% of participants in any group) across the supportive higher dose pools included, but were not limited to, COVID-19, procedural pain, headache, nasopharyngitis, upper respiratory tract infection, fall, tonsillitis, vomiting, pneumonia, and pyrexia.

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

The most common AEs by PT (occurring in ≥ 10% of participants) in Pool I included, but were not limited to, pyrexia (61.8%), upper respiratory tract infection (51.7%), scoliosis (45.7%), vomiting (42.9%), nasopharyngitis (38.4%), cough (34.8%), pneumonia (34.0%), headache (30.1%), procedural pain (28.1%), constipation (27.5%), and muscle contracture (25.2%).

Table 10. Pool I - supportive all pooled Nusinersen 12 mg or lower controlled and uncontrolled studies most common adverse events by PT occurring in ≥ 10% of participants (safety analysis set)

Preferred Term	**Pool I 12 mg or Lower Nusinersen (N = 385)**
Number of participants with any event	**381 (99.0)**
Pyrexia	238 (61.8)
Upper respiratory tract infection	199 (51.7)
Scoliosis	176 (45.7)
Vomiting	165 (42.9)
Nasopharyngitis	148 (38.4)
Cough	134 (34.8)
Pneumonia	131 (34.0)
Headache	116 (30.1)
Procedural pain	108 (28.1)
Constipation	106 (27.5)
Muscle contracture	97 (25.2)
Joint contracture	96 (24.9)
Back pain	86 (22.3)
Post lumbar puncture syndrome	84 (21.8)
Diarrhea	81 (21.0)
Influenza	78 (20.3)
Ear infection	74 (19.2)
Fall	73 (19.0)
COVID-19	67 (17.4)
Otitis media	66 (17.1)
Gastroenteritis	64 (16.6)
Respiratory tract infection	62 (16.1)
Respiratory distress	61 (15.8)
Rhinorrhea	60 (15.6)
Gastroenteritis viral	54 (14.0)
Bronchitis	52 (13.5)
Rash	52 (13.5)
Viral infection	52 (13.5)
Acute respiratory failure	51 (13.2)

Preferred Term	Pool I 12 mg or Lower Nusinersen (N = 385)
Oxygen saturation decreased	51 (13.2)
Rhinovirus infection	51 (13.2)
Nasal congestion	50 (13.0)
Nausea	50 (13.0)
Pain in extremity	49 (12.7)
Respiratory failure	49 (12.7)
Urinary tract infection	48 (12.5)
Atelectasis	46 (11.9)
Respiratory syncytial virus infection	46 (11.9)
Oropharyngeal pain	45 (11.7)
Viral upper respiratory tract infection	45 (11.7)
Seasonal allergy	44 (11.4)
Arthralgia	40 (10.4)
Femur fracture	40 (10.4)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA Version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Adverse drug reactions

Key Higher Dose Pooled Groups Adverse Events Assessed as Related to Study Treatment

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose - Adverse Events Assessed as Related to Study Treatment

One participant (3.0%) on nusinersen 12 mg and 4 participants (6.1%) on nusinersen 50/28 mg experienced AEs considered by the Investigator to be related to study treatment. Of these, 1 participant (3.0%) on nusinersen 12 mg experienced nausea and respiratory failure, and 2 participants (3.0%) on nusinersen 50/28 mg experienced pyrexia considered to be related to study treatment. One event each of eosinophilia, dysphoria, productive cough, and rash erythematous considered related to study treatment occurred in the 2 remaining participants in the nusinersen 50/28 mg group.

In the infantile-onset participants, the overall incidence of AEs considered by the Investigator to be related to study treatment across the treatment groups was similar regardless of nusinersen dose received. In participants with infantile-onset SMA, 4 participants experienced AEs that were considered by the Investigator to be related to study treatment, of whom 1 participant (4.0%) was in the nusinersen 12 mg group and 3 participants (6.0%) were in the nusinersen 50/28 mg group. No related AE for infantile-onset participants was reported more than once in either dosing group.

In the later-onset participants, the overall incidence of AEs considered by the Investigator to be related to study treatment across the treatment groups was similar, regardless of nusinersen dose received. In participants with later-onset SMA, 1 participant (6.3%) on nusinersen 50/28 mg experienced an AE of pyrexia that was considered by the Investigator to be related to study treatment.

Table 11. Pool G – study SM203 part B combined onset populations pooled by dose - adverse events assessed as related to study treatment (safety analysis set)

	12/12 mg nusinersen (N=33)	50/28 mg nusinersen (N=66)
Number of subjects with any related event	1 (3.0) [3]	4 (6.1) [6]
General disorders and administration site conditions	0	2 (3.0) [2]
Pyrexia	0	2 (3.0) [2]
Blood and lymphatic system disorders	0	1 (1.5) [1]
osinophilia	0	1 (1.5) [1]
Psychiatric disorders	0	1 (1.5) [1]
Dysphoria	0	1 (1.5) [1]
Respiratory, thoracic and mediastinal disorders	1 (3.0) [2]	1 (1.5) [1]
Productive cough	0	1 (1.5) [1]
Respiratory failure	1 (3.0) [2]	0
Skin and subcutaneous tissue disorders	0	1 (1.5) [1]
Rash erythematous	0	1 (1.5) [1]
Gastrointestinal disorders	1 (3.0) [1]	0
Nausea	1 (3.0) [1]	0

Note 1: A cut-off date of 19FEB2020 and 30MAY2024 was used for studies 232SM201 and 232SM302 respectively.

Note 2: N (%) [n] refers to the number of subjects (incidence rate) [number of occurrences].

Note 3: A subject was counted only once within each system organ class and preferred term (MedDRA version 26.1) for number and incidence rate.

Note 4: System organ class and preferred term are presented in decreasing frequency of right most column.

Note 5: Related as assessed by the investigator. If captured as 'Possibly' then also considered as related.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Adverse Events Assessed as Related to Study Treatment

Table 12. Pool J - all pooled Nusinersen 28 mg or higher controlled and uncontrolled studies adverse events assessed as related to study treatment by PT (safety analysis set)

Preferred Term	Pool J 50 mg or 28 mg Nusinersen (N = 128)
Number of participants with any related event	**13 (10.2)**
Pyrexia	3 (2.3)
Crystal urine present	2 (1.6)
Anemia	1 (0.8)
Balance disorder	1 (0.8)
CSF protein increased	1 (0.8)
Disturbance in attention	1 (0.8)
Dizziness	1 (0.8)
Dysphoria	1 (0.8)
Eosinophilia	1 (0.8)
Headache	1 (0.8)
Myalgia	1 (0.8)
Nausea	1 (0.8)
Peripheral coldness	1 (0.8)
Post lumbar puncture syndrome	1 (0.8)
Procedural pain	1 (0.8)
Productive cough	1 (0.8)
Proteinuria	1 (0.8)
Rash erythematous	1 (0.8)
Viral infection	1 (0.8)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.
Note 5: Related as assessed by the Investigator. If captured as "Possibly," then also considered as related.

Supportive Higher Dose Pools Adverse Events Assessed as Related to Study Treatment

The overall incidence of AEs considered by the Investigator to be related to study treatment across the treatment groups was similar across the nusinersen pools.

Table 13. Supportive higher dose pools adverse events assessed as related to study treatment by SOC and PT occurring in ≥ 2% of participants in any group (safety analysis set)

System Organ Class Preferred Term	BEI (N = 75)	BEL (N = 24)	CEXT (N = 40)	AEXT (N = 6)
Number of participants with any related event	**5 (6.7)**	**1 (4.2)**	**8 (20.0)**	**0 (0.0)**
Respiratory, thoracic, and mediastinal disorders	2 (2.7)	0	0	0
Productive cough	1 (1.3)			0

System Organ Class Preferred Term	BEI (N = 75)	BEL (N = 24)	CEXT (N = 40)	AEXT (N = 6)
Respiratory failure	1 (1.3)			0
General disorders and administration site conditions	1 (1.3)	1 (4.2)	1 (2.5)	0
Pyrexia	1 (1.3)	1 (4.2)	1 (2.5)	0
Gastrointestinal disorders	1 (1.3)	0	1 (2.5)	0
Nausea	1 (1.3)	0	1 (2.5)	0
Injury, poisoning, and procedural complications	0	0	2 (5.0)	0
Post lumbar puncture syndrome	0	0	1 (2.5)	0
Procedural pain	0	0	1 (2.5)	0
Investigations	0	0	3 (7.5)	0
Crystal urine present	0	0	2 (5.0)	0
CSF protein increased	0	0	1 (2.5)	0
Musculoskeletal and connective tissue disorders	0	0	1 (2.5)	0
Myalgia	0	0	1 (2.5)	0
Nervous system disorders	0	0	2 (5.0)	0
Balance disorder	0	0	1 (2.5)	0
Disturbance in attention	0	0	1 (2.5)	0
Dizziness	0	0	1 (2.5)	0
Headache	0	0	1 (2.5)	0
Renal and urinary disorders	0	0	1 (2.5)	0
Proteinuria	0	0	1 (2.5)	0
Vascular disorders	0	0	1 (2.5)	0
Peripheral coldness	0	0	1 (2.5)	0

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each SOC and PT (MedDRA version 26.1) for number and incidence rate.
Note 4: SOC and PT are presented in decreasing frequency of the first column.
Note 5: Related as assessed by the Investigator. If captured as "Possibly," then also considered as related.

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

AEs related to study treatment in Pool I were minimal with related AEs experienced by participants most frequently in the SOCs of Nervous system disorders (6.2%); General disorders and administration site conditions (5.5%); and Investigations (5.5%). In Pool I, 19 (4.9%) of participants experienced related AEs of pyrexia, 13 (3.4%) experienced related AEs of headache, 12 (3.1%) experienced related AEs of proteinuria, and 8 (2.1%) experienced back pain.

Table 14. Pool I – supportive all pooled 12 mg or lower controlled and uncontrolled studies adverse events assessed as related by PT occurring in ≥ 2% participants (safety analysis set)

• **Preferred Term**	• **Pool I 12 mg or Lower Nusinersen (N = 385)**
• **Number of participants with any related event**	• **99 (25.7)**
Pyrexia	19 (4.9)
Headache	13 (3.4)
Proteinuria	12 (3.1)
Back pain	8 (2.1)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.
Note 5: Related as assessed by the Investigator. If captured as "Possibly," then also considered as related.

2.6.8.3. Serious adverse events, deaths, and other significant events

Serious Adverse Events

Key Higher Dose Pooled Groups

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Serious Adverse Events

Overall, 63.6% of participants on nusinersen 12 mg and 45.5% of participants on nusinersen 50/28 mg experienced at least 1 SAE. The most common SAE occurred in the SOC of Infections and infestations by participants in both treatment arms (48.5% and 36.4%, respectively). Both treatment arms also experienced SAEs involving Respiratory, thoracic, and mediastinal disorders (33.3% and 15.2%) and Cardiac disorders (9.1% and 4.5%). SAEs by PT occurring in both groups included, but were not limited to, pneumonia (15.2% and 10.6%); respiratory failure (9.1% in each group); acute respiratory failure (9.1% and 3.0%); pneumonia aspiration (6.1% and 10.6%); and cardiac arrest (6.1% and 4.5%).

In infantile-onset participants, a total of 48 participants (64.0%) with infantile-onset SMA experienced SAEs. SAEs were similar in infantile-onset participants across the 2 treatment arms (18 participants [72.0%] on nusinersen 12 mg and 30 participants [60.0%] on nusinersen 50/28 mg). For the infantile-onset population, ≥ 10% of participants on nusinersen 12 mg experienced the following SAEs: pneumonia (5 participants [20.0%]), respiratory failure (4 participants [16.0%]), and acute respiratory failure (3 participants [12.0%]). All other SAEs were reported in < 10% of the infantile-onset participant population. In participants on nusinersen 50/28 mg, ≥ 10% of infantile-onset participants experienced the following SAEs: pneumonia (7 participants [14.0%]), pneumonia aspiration (7 participants [14.0%]), and respiratory failure (8 participants [16.0%]). All other SAEs were reported in < 10% of the infantile-onset participant population.

In later-onset participants, a total of 6 participants (25.0%) experienced SAEs. Four participants (50.0%) with later-onset SMA on nusinersen 12 mg experienced at least 1 SAE, and 2 participants (12.5%) on nusinersen 50/28 mg experienced SAEs. For the later-onset population, ≥ 10% of participants on nusinersen 12 mg experienced the following SAEs: pneumonia respiratory syncytial viral (1 participant [12.5%]), gastroenteritis rotavirus (1 participant [12.5%]), pneumonia aspiration (1 participant [12.5%]), pneumonia mycoplasmal (1 participant [12.5%]), pneumonia pneumococcal (1 participant

[12.5%]), asthma (1 participant [12.5%]), and atelectasis (1 participant [12.5%]). All SAEs reported in participants on nusinersen 50/28 mg were reported in < 10% of the later-onset participant population.

Table 15. Pool G – study SM203 part B combined onset populations pooled by dose serious adverse events by PT occurring in 2 or more participants in either group (safety analysis set)

Preferred Term	12/12 mg Nusinersen (N = 33)	50/28 mg Nusinersen (N = 66)
Number of participants with any serious event	**21 (63.6)**	**30 (45.5)**
Pneumonia	5 (15.2)	7 (10.6)
Acute respiratory failure	3 (9.1)	2 (3.0)
Atelectasis	3 (9.1)	0
Respiratory failure	3 (9.1)	6 (9.1)
Cardiac arrest	2 (6.1)	3 (4.5)
Cardio-respiratory arrest	2 (6.1)	0
Pneumonia aspiration	2 (6.1)	7 (10.6)
Respiratory tract infection	2 (6.1)	0
Bronchiolitis	1 (3.0)	3 (4.5)
Pneumonia respiratory syncytial viral	1 (3.0)	2 (3.0)
Pneumonia viral	1 (3.0)	2 (3.0)
Sudden infant death syndrome	1 (3.0)	2 (3.0)
COVID-19	0	4 (6.1)
Oxygen saturation decreased	0	2 (3.0)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Serious Adverse Events

In Pool J, SAEs were experienced by participants most frequently in the SOCs of Infections and infestations (29.7%); Respiratory, thoracic, and mediastinal disorders (12.5%); and Injury, poisoning, and procedural complications (7.8%). By PT, the only SAEs occurring in ≥ 5% of participants in Pool J were pneumonia (11.7%), respiratory failure (6.3%), and pneumonia aspiration (5.5%).

Table 16. Pool J – all pooled Nusinersen 28 mg or higher controlled and uncontrolled studies serious adverse events by PT occurring in ≥ 5% participants (safety analysis set)

Preferred Term	Pool J 50 mg or 28 mg Nusinersen (N = 128)
Number of participants with any serious event	**62 (48.4)**
Pneumonia	15 (11.7)
Respiratory failure	8 (6.3)
Pneumonia aspiration	7 (5.5)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Supportive Higher Dose Pools Serious Adverse Events

Overall, SAEs were experienced more frequently by participants in BEI (69.3%) and BEL (50.0%) than by participants in CEXT (32.5%) and AEXT (33.3%). SAEs involving Infections and infestations was the most common SOC of SAEs in both BEI (53.3%) and BEL (33.3%) and was experienced by 7.5% of participants in CEXT. No participants in AEXT experienced an SAE in the SOC of Infection or infestation. By PT, the most common SAE among participants in BEI was pneumonia (21.3%), which was also reported as an SAE in 8.3% of participants in BEL and 5.0% of participants in CEXT. SAEs of respiratory failure was reported in 16.0% of participants in BEI. Pneumonia aspiration SAEs were reported in 10.7% and 4.2% of participants in BEI and BEL, respectively. Scoliosis was reported as an SAE in 3 participants (12.5%) in BEL, and neuromuscular scoliosis was reported as an SAE 1 participant (4.2%) in BEL and 1 participant (16.7%) in AEXT. Additionally, 1 participant (16.7%) experienced an SAE of fall and femur fracture in AEXT, and 1 participant (1.3%) experienced an SAE of femur fracture in BEI. In the BEL Pool, 1 participant experienced an SAE of a fall (4.2%) and femur fracture (4.2%). In the CEXT Pool, 4 participants (10.0%) experienced SAEs of falls, 3 (7.5%) of whom had SAEs of femur fracture and 1 (2.5%) who had an SAE of lower limb fracture. All 4 participants were in the later-onset SMA group.

Table 17. Supportive higher dose pools serious adverse events by PT occurring in ≥ 10% of participants in any group (safety analysis set)

Preferred Term	BEI (N = 75)	BEL (N = 24)	CEXT (N = 40)	AEXT (N = 6)
Number of participants with any serious event	**52 (69.3)**	**12 (50.0)**	**13 (32.5)**	**2 (33.3)**
Pneumonia	16 (21.3)	2 (8.3)	2 (5.0)	0
Respiratory failure	12 (16.0)	0	0	0
Pneumonia aspiration	8 (10.7)	1 (4.2)	0	0
Femur fracture	1 (1.3)	1 (4.2)	3 (7.5)	1 (16.7)
Fall	0	1 (4.2)	4 (10.0)	1 (16.7)
Neuromuscular scoliosis	0	1 (4.2)	0	1 (16.7)
Scoliosis	0	3 (12.5)	0	0

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

In Pool I, participants experienced SAEs most frequently in the SOCs of Infections and infestations (49.4%); Respiratory, thoracic, and mediastinal disorders (35.1%); and Musculoskeletal and connective tissue disorders (18.7%). SAEs by PT occurring in ≥ 10% included pneumonia (24.7%); scoliosis (14.5%); respiratory distress (14.0%); acute respiratory failure (13.0%); and respiratory failure (12.2%).

Table 18. Pool I – supportive all pooled nusinersen 12 mg or lower controlled and uncontrolled studies serious adverse events by PT occurring in ≥ 10% participants (safety analysis set)

Preferred Term	Pool I 12 mg or Lower Nusinersen (N = 385)
Number of participants with any serious event	**273 (70.9)**
Pneumonia	95 (24.7)
Scoliosis	56 (14.5)
Respiratory distress	54 (14.0)
Acute respiratory failure	50 (13.0)
Respiratory failure	47 (12.2)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: N (%) refers to the number of participants (incidence rate).
Note 3: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 4: PT is presented in decreasing frequency of the first column.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

- ***Serious Adverse Events Related to Study Treatment***

Key Higher Dose Pooled Groups

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Serious Adverse Events Related to Study Treatment

Only 1 participant (3.0%) experienced an SAE considered by the Investigator to be related to study treatment among all participants in Pool G. The participant (infantile-onset SMA), who was on nusinersen 12 mg, experienced 2 occurrences of respiratory failure considered related to study treatment. There were no SAEs related to study treatment reported for participants on nusinersen higher dose.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Serious Adverse Events Related to Study Treatment

No participants in Pool J experienced an SAE assessed as related to study treatment.

Supportive Higher Dose Pools Serious Adverse Events Related to Study Treatment

Only 1 SAE was considered by the Investigator to be related to study treatment among all participants in the supportive high dose pools. In BEI, respiratory failure was experienced by 1 participant (1.3%). There were no other SAEs related to study treatment reported for any supportive higher dose pool.

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

In Pool I, there were 4 participants (1.0%) who experienced a total of 6 SAEs considered by the Investigator to be related to study treatment. Of these, 1 participant (0.6%) with infantile-onset SMA experienced respiratory failure on 2 occasions. The other 3 participants who experienced SAEs were in the later-onset population and had related SAEs of pyuria, back pain, syncope, and hematuria.

- ***Serious Adverse Events With a Fatal Outcome***

Key Higher Dose Pooled Groups

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Serious Adverse Events with a Fatal Outcome

Overall, the proportion of SAEs with a fatal outcome were similar between participants on nusinersen 12 mg (6 participants [18.2%]) and participants on the nusinersen 50/28 mg (10 participants [15.2%]). By PT, 2 participants (6.1%) on nusinersen 12 mg and 1 participant (1.5%) on nusinersen 50/28 mg had an SAE of cardiac arrest with a fatal outcome. Additionally, 2 participants (6.1%) on nusinersen 12 mg and 1 participant (1.5%) on nusinersen 50/28 mg had an SAE of pneumonia with a fatal outcome.

Table 19. Pool G - study SM203 part B combined onset populations pooled by dose serious adverse events with a fatal outcome by PT occurring in 2 or more of participants in either group (safety analysis set)

Preferred Term	12/12 mg Nusinersen (N = 33)	50/28 mg Nusinersen (N = 66)
Number of participants with any serious adverse events with a fatal outcome	**6 (18.2)**	**10 (15.2)**
Cardiac arrest	2 (6.1)	1 (1.5)
Pneumonia	2 (6.1)	1 (1.5)
Sudden infant death syndrome	1 (3.0)	2 (3.0)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 3: PT is presented in decreasing frequency of the first column.

Pool J - All Pooled Nusinersen 28 mg or Higher Controlled and Uncontrolled Studies Serious Adverse Events with a Fatal Outcome

Table 20. Pool J - all pooled Nusinersen 28 mg or higher controlled and uncontrolled studies serious adverse events with a fatal outcome by SOC (safety analysis set)

System Organ Class	Pool J 50 mg or 28 mg Nusinersen (N = 128)
Number of participants with any serious adverse events with a fatal outcome	**14 (10.9)**
Infections and infestations	6 (4.7)
Respiratory, thoracic, and mediastinal disorders	5 (3.9)
General disorders and administration site conditions	3 (2.3)
Cardiac disorders	1 (0.8)
Injury, poisoning, and procedural complications	1 (0.8)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: A participant was counted only once within each SOC (MedDRA version 26.1) for number and incidence rate.
Note 3: SOC is presented in decreasing frequency of the first column.

Supportive Higher Dose Pools Serious Adverse Events with a Fatal Outcome

Across the supportive high dose pools, only the BEI pool had participants who experienced SAEs with a fatal outcome (20 participants [26.7%]).

Supportive All Pooled Nusinersen 12 mg or Lower Controlled and Uncontrolled Studies Overall Adverse Events (Pool I)

In Pool I, SAEs with a fatal outcome were experienced in the SOCs of Respiratory, thoracic, and mediastinal disorders (4.9%); Cardiac disorders (1.8%); General disorders and administration site conditions (1.3%); Nervous system disorders (1.3%); and Infections and infestations (1.0%). By PT, 8 participants (2.1%) Pool I had an SAE of respiratory failure with a fatal outcome. Additionally, 5 participants (1.31%) had an SAE of cardio-respiratory arrest with a fatal outcome, and 4 participants (1.0%) had an SAE of acute respiratory failure. Other SAEs leading to a fatal outcome included, but were not limited to, hypoxic-ischemic encephalopathy (4 participants [1.0%]; pneumonia (3 participants [0.8%]); cardiac arrest (2 participants [0.5%]); death (2 participants [0.5%]); and respiratory arrest (2 participants [0.5%]).

Table 21. Pool I – supportive all pooled Nusinersen 12 mg or lower controlled and uncontrolled studies serious adverse events with a fatal outcome by PT in 2 or more participants (safety analysis set)

Preferred Term	Pool I 12 mg or Lower Nusinersen (N = 385)
Number of participants with any serious adverse events with a fatal outcome	**40 (10.4)**
Respiratory failure	8 (2.1)
Cardio-respiratory arrest	5 (1.3)
Acute respiratory failure	4 (1.0)
Hypoxic-ischemic encephalopathy	4 (1.0)
Pneumonia	3 (0.8)
Cardiac arrest	2 (0.5)
Death	2 (0.5)
Respiratory arrest	2 (0.5)

Note 1: A cutoff date of 19FEB2020 and 30MAY2024 was used for Studies 232SM201 and 232SM302, respectively.
Note 2: A participant was counted only once within each PT (MedDRA version 26.1) for number and incidence rate.
Note 3: PT is presented in decreasing frequency of the first column.

- ***ADRs of special interest - Adverse Drug Reactions Infantile-Onset***

Study SM203 Part B consisted of a higher dose arm (50/28 mg) and a control arm (12 mg). ADRs could be assessed only from the pivotal (infantile-onset) population in Part B of Study SM203, as there was no prespecified matching algorithm for the later-onset population in Part B. Therefore, for the purposes of ADR assessment, the analysis focused on the pivotal infantile-onset cohort. For both efficacy and safety analyses, a prespecified matching algorithm was used to identify 20 sham participants from Study CS3B who matched the Study SM203 50/28 mg group based on baseline CHOP INTEND score and disease duration. The review focused on AEs which occurred in greater than 10% of participants receiving nusinersen 50/28 mg who also had a frequency at least 5% greater in the nusinersen 50/28 mg group compared to Matched Sham. These frequencies were selected and considered adequate based on sample size. Based on these provisions, 3 PTs were identified for evaluation: pneumonia (10 [20.0%] participants in the 50/28 mg group versus 1 [5.0%] participant in Matched Sham), COVID-19 (8 [16.0%] participants in the 50/28 mg group versus 0 participants in Matched Sham), and pneumonia aspiration (7 [14.0%] participants in the 50/28 mg group versus 1 [5.0%] participant in Matched Sham) [232SM203 Part B CSR]. COVID-19 was discarded as a potential ADR as it was not applicable at the time of Study CS3B (from which Matched Sham participants were identified), and therefore no events were expected for the control. Remaining PTs for consideration as possible ADRs included pneumonia and

pneumonia aspiration. All events were SAEs and were assessed as not related to study treatment by the Investigator.

Review of PT Pneumonia

In Study SM203 Part B, the frequency of AEs with the PT pneumonia was 20% in participants receiving the nusinersen 50/28 mg dosing regimen (n = 10), 20% in participants receiving the nusinersen 12 mg dosing regimen (n = 5), and 5% in participants on Matched Sham (n = 1). Pneumonia is a known common AE in SMA. An analysis was performed to adjust for exposure time utilizing the SMQ for pneumonia infective. Overall, for the SMQ, the exposure-adjusted incidence rate per 100 person-years was lower in participants receiving the nusinersen 50/28 mg dosing regimen (117.5 person-years) versus participants receiving the nusinersen 12 mg dosing regimen (165.4 person-years) and Matched Sham (203.2 person-years).

Review of PT Pneumonia Aspiration

Pneumonia aspiration is commonly seen in patients with SMA. The frequency of pneumonia aspiration in infantile-onset SMA participants receiving the nusinersen the 50/28 mg dosing regimen in SM203 Part B was 14% (n = 7) versus 5% (n = 1) for participants on Matched Sham. Given that exposure time may differ between participants on nusinersen 50/28 mg and participants on Matched Sham because participants receiving treatment are living longer, a similar exposure-adjusted analysis was performed for the PT pneumonia aspiration. With this analysis, a > 10% higher incidence rate of pneumonia aspiration was observed in participants on nusinersen 50/28 mg (21.8 person-years [n = 7]) versus participants on Matched Sham (8.5 person-years [n = 1]) remained. All 8 events with PT pneumonia aspiration occurred before the third dose. Of the 7 participants with events of pneumonia aspiration that occurred in the 50/28 mg group, 2 events occurred on study Day 1. One participant experienced a repeat event of pneumonia aspiration in extension study SM302. Therefore, pneumonia aspiration is classified as a serious ADR for nusinersen at the 50/28 mg dose.

Table 22. Study SM203 Part B Infantile-Onset SMA: Frequency of ADRs at least 5% greater in participants on Nusinersen 50/28 mg compared to matched sham control (matched sham set, safety set) and in > 10% of participants

	Matched CS3B Sham control (N = 20)	**SM203 Part B 12/12 mg nusinersen (N = 25)**	**SM203 Part B 50/28 mg nusinersen (N = 50)**
Number of participants with any AE	20 (100)	22 (88.0)	45 (90.0)
Pneumonia aspiration	1 (5.0)	1 (4.0)	7 (14.0)

Note 1: A subject was counted only once within each PT (MedDRA Version 26.1).

2.6.8.4. Laboratory findings

Clinical laboratory data was evaluated to determine the incidence of abnormalities that emerge during the time intervals reported. Laboratory data was analyzed and is being reported for only the supportive higher dose pools BI+, BL+, CEXT, and AEXT with changes in laboratory evaluations presented relative to baseline, Day 1, in Study SM203.

- ***Hematology, Blood Chemistry, Coagulation, CSF, and UA***

Overall, there were no clinically meaningful changes over time for the hematology analytes. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. AEs of anemia, leukocytosis, eosinophilia, hypofibrinogenemia, deficiency anemia, iron deficiency

anemia, microcytic anemia, normochromic normocytic anemia, secondary thrombocytosis, and thrombocytosis were reported. Only 1 AE of anemia and 1 AE of eosinophilia were assessed as related to study treatment, both in infantile-onset SMA. Overall, there were no clinically meaningful changes over time for the blood chemistry analytes. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. AEs of hyperglycemia, hypoalbuminemia, hypoglycemia, hypokalemia, blood albumin decreased, blood creatinine decreased, and hyponatremia were reported, but none of these AEs were assessed by the Investigator as related to study treatment.

Liver Function Tests

In participants on nusinersen 50/28 mg, ALT was elevated (> ULN) in 36.8% of participants in the BI+ pool and 14.3% of participants in the BL+ pool. Of these abnormal ALT values, 2 participants (5.3%) in the BI+ pool had ALT values > 3x ULN. In participants on nusinersen 12 mg, 2 participants (14.3%) had ALT values > 3x ULN. Results were similar for AST values. Overall, AST values were > ULN in 8 participants (18.6%) on nusinersen 50/28 mg in the BI+ pool and in 1 participant (6.7%) in the BL+ pool. In the CEXT pool, 11 participants (33.3%) on nusinersen 50/28 mg had elevated (> ULN) ALT and 9 participants (25.7%) had elevated AST (4.5%). No participants on nusinersen 50/28 mg in the CEXT pool had ALT or AST > 3x ULN. No participants in the AEXT pool (nusinersen 28 mg) had AST elevations, and 1 (16.7) had elevated ALT. Elevations in total bilirubin were noted in 2 pools. One participant (2.6%) on nusinersen 50/28 mg in the CEXT pool had total bilirubin > ULN, 1 participant (2.5%) in the BI+ pool had elevated bilirubin > ULN. No participants in any pool had elevations in AST or ALT > 3x ULN accompanied by concurrently elevated bilirubin.

Coagulation

Pool G - Study SM203 Part B Combined Onset Populations Pooled by Dose Coagulation Parameters

Overall, there were no clinically meaningful changes over time for the coagulation parameters. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. No coagulation AEs were recorded for any participant for either nusinersen dose in Pool G. In participants with infantile-onset SMA, shifts to high aPTT were noted in both dose groups (35.3% of participants on nusinersen 12 mg and 17.5% of participants on nusinersen 50/28 mg) (232SM203 Part B). In participants with later-onset SMA, shifts to low aPTT were noted in both dose groups (28.6% of participants on nusinersen 12 mg and 12.5% of participants on nusinersen 50/28 mg) [232SM203 Part B].

Supportive Higher Dose Pools Coagulation Parameters

Coagulation parameter shifts from baseline to minimum and maximum post-baseline in the supportive higher dose pools were assessed for study pools BI+, BL+, and CEXT. Overall, there were no clinically meaningful changes over time for the coagulation parameters. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. Across study pools BI+, BL+, and CEXT, no coagulation AEs were recorded. In the BI+ pool, the proportion of participants with baseline shifts to high aPTT and prothrombin time were similar between treatment groups. Two participants on nusinersen higher dose shifted to high INR post-baseline compared to no shifts to high INR in participants on nusinersen 12 mg.

CSF Parameters

Study SM203 Part B Infantile-Onset and Later-Onset Pools CSF Parameters

Overall, there were no clinically meaningful changes over time for the CSF parameters. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. No CSF parameter AEs were recorded for any participant on either nusinersen dose.

Supportive Higher Dose Pools CSF Parameters

CSF parameter shifts from baseline to minimum and maximum post-baseline in the supportive higher dose pools were assessed for study pools BI+, BL+, and CEXT. Overall, CSF parameter shifts from baseline to abnormal values were minimal. In the BI+ pool, 5 participants (1 participant on nusinersen 12 mg and 4 participants on nusinersen higher dose) experienced post-baseline shifts to high leukocytes. In the BL+ pool, 4 participants experienced post-baseline shifts to high protein (3 participants on nusinersen 12 mg and 1 participant on nusinersen 50/28 mg) and 8 participants experienced post-baseline shifts to high erythrocytes (2 participants on nusinersen 12 mg and 6 participants on nusinersen 50/28 mg).

Urinalysis

Study SM203 Part B Infantile-Onset and Later-Onset Pools Urine Protein and UA Shifts from Baseline

Overall, there were no clinically meaningful changes over time for the UA analytes. In general, parameter shifts from baseline to abnormal values for individual participants were mild and transient. One participant (4.0%) with infantile-onset SMA on nusinersen 12 mg experienced an AE of leukocyturia. A similar proportion of participants at both dose levels had at least 1 positive urine protein result post-baseline (nusinersen 12 mg: 12 participants [71%]; nusinersen 50/28 mg: 29 participants [69%]). In later-onset participants, 1 participant (6.3%) on nusinersen 50/28 mg experienced an AE of proteinuria. Five participants (83.0%) on nusinersen 12 mg had at least 1 positive urine protein result post-baseline, and 9 participants (64.0%) on nusinersen 50/28 mg had at least 1 positive urine protein result post-baseline.

Supportive Higher Dose Pools Urine Protein and UA Shifts from Baseline

Urine protein and UA parameter shifts from baseline to minimum and maximum post-baseline in the supportive higher dose pools were assessed for study pools BI+, BL+, and CEXT. There were no notable differences in urine protein and UA parameters across the pools or dose levels.

Vital Signs, Physical Findings, Immunogenicity, and Other Observations Related to Safety

Neurological Examinations

Supportive Higher Dose Pools Neurological Examinations

Post-Baseline Reflexes and Chronic Worsening Shifts

Overall, most participants across groups maintained reflexes over time. There was no loss or gain in post-baseline reflexes reported in the BL+ pool for the key parameters. In the CEXT pool (nusinersen 50/28 mg), post-baseline reflex loss was noted in left biceps (2 participants [5.1%]), right biceps (1

participant [2.6%]), left triceps (2 participants [5.1%]), right triceps (2 participants [5.1%]), left ankle (3 participants [7.7%]), and right ankle (3 participants [7.7%]). Additionally, in the CEXT pool, post-baseline reflex gain was noted in both the right brachioradialis and left brachioradialis (1 participant [2.6%] with predose reflex ≥ 1 and 1 participant [2.6%] with predose = 0 for each right and left), both of which had later-onset SMA.

Hammersmith Infant Neurological Examination

Overall, most participants in BI+ maintained reflexes over time, and any changes were minimal. Overall, most participants across groups maintained reflexes over time. All participants on nusinersen 50/28 mg with predose reflex = 0 maintained acute post-baseline reflexes for the key parameters. In participants on nusinersen 50/28 mg with predose reflex ≥ 1, arm protection gain was noted in 1 participant (2.3%) and arm protection loss was noted in 1 participant (2.3%). In this same group, there 2 participants (4.4%) who experienced vertical suspension loss and 2 participants (4.4%) who experienced lateral titling loss. Participants on nusinersen 12 mg with predose reflex = 0 also maintained acute post-baseline reflexes for the key parameters reported. In participants with predose reflex ≥ 1 on nusinersen 12 mg, acute post-baseline gain was noted in tendon reflexes (1 participant [4.3%]) and arm protection (1 participant [4.3%]). In the same group, there were losses noted in tendon reflexes, arm protection, and vertical suspension (1 participant [4.3%] for each parameter.

Electrocardiogram

Supportive Higher Dose Pools Analysis of ECG Shifts

In the BI+ pool, some abnormal ECG results were reported, including 4 reported as AEs (2 in each dose group). In the BL+ pool, some abnormal ECG results were reported, but none were reported as AEs (2 in participants on nusinersen 12 mg and 4 participants on nusinersen 50/28 mg). One abnormal ECG result was reported as an AE in the CEXT pool. The event occurred in a participant on nusinersen 50/28 mg with later-onset SMA.

Supportive Higher Dose Pools QT Interval QTcF Abnormalities (Outliers)

No participants in the BL+ pool met the endpoint criteria for QTcF. In the CEXT pool, 1 participant on nusinersen 50/28 mg met the endpoint criteria of having a post-baseline QTcF of > 500 msec and an increase from baseline to any post-baseline timepoint in QTcF of > 60 msec. The participant had later-onset SMA.

Vital Signs

Supportive Higher Dose Pools Vital Signs

Overall, there were no clinically significant changes in vital signs associated with study treatment. here was a noted increase (7% or more from baseline) in weight across all 3 study pools. In the BI+ pool, 75.5% of participants on nusinersen 50/28 mg and 78.3% of participants on nusinersen 12 mg had an increase in weight from baseline ≥ 7%. A decrease in weight ≥ 7% was noted in the BI+ pool in 4.1% of participants on nusinersen 50/28 mg and 21.7% of participants on nusinersen 12 mg. In the BL+ pool, 81.3% of participants on nusinersen 50/28 mg and 87.5% of participants on nusinersen 12 mg had a ≥ 7% increase in weight from baseline. A ≥ 7% decrease in weight was noted in the BL+ pool in 6.3% of participants on nusinersen 50/28 mg and 25.0% of participants on nusinersen 12 mg. In the CEXT pool, 50.0% of participants on nusinersen 50/28 mg had a ≥ 7% increase in weight from baseline.

A ≥ 7% decrease in weight was noted in 20% of participants on nusinersen 50/28 mg in the CEXT pool. There was a decrease in weight of ≥ 7% in 1 (4.3%) participant in the BL+ pool and in 5 (12.8%) participants in the CEXT pool.

Growth Parameters

Supportive Higher Dose Pools Growth Parameters

In the BEI pool, 4 participants (5.3%) experienced AEs of weight decreased (1 participant [4.0%] switching from 12 mg to 50/28 mg and 3 participants [6.0%] on nusinersen 50/28 mg).

2.6.8.4. Safety in special populations

Intrinsic Factors

- ***Participant Sex Subgroup Analysis***

Supportive Higher Dose Pools BI+ and BL+ Adverse Events by Sex

Overall, the frequency of AEs by most SOCs was similar between male and female participants. Differences were noted between sexes in Cardiac disorder AEs, where male participants experienced a higher percentage than female participants. Additionally, ≥ 5% of female participants experienced AEs in the SOCs of Psychiatric disorders; Renal and urinary disorders; Endocrine disorders; and Eye disorders while male participants did not experience AEs in these SOCs. By PT, while a higher percentage of female than male participants experienced upper respiratory tract infections, respiratory failure, constipation, and malnutrition, none of the AEs were assessed as related to study treatment by the Investigator, and firm conclusions cannot be made due to the small sample size in each subgroup.

- ***Infantile-Onset Participant Subgroup Analysis***

Supportive Higher Dose Pool BI+ Adverse Events and Serious Adverse Events by Disease Duration at Informed Consent in Infantile-Onset Participants

Overall, the number of participants with any AE was similar between the 2 disease duration subgroups (89.6% and 92.6%). A greater percentage of participants with disease duration > 12 weeks experienced AEs in the SOCs of Gastrointestinal disorders and Metabolism and nutrition disorders, while a greater percentage of participants with disease duration ≤ 12 weeks experienced AEs in the SOC of Investigations. By PTs, a greater percentage of participants with disease duration > 12 weeks experienced AEs of pneumonia (40.7% versus 14.6% in participants with disease duration ≤ 12 weeks); dysphagia (22.2% versus 4.2%); constipation (18.5% versus 6.3%), and malnutrition (18.5% versus 4.2%). Participants with disease duration > 12 weeks experienced a smaller percentage of AEs of COVID-19 (7.4% versus 20.8% in participants with disease duration ≤ 12 weeks) and upper respiratory tract infection (11.11% versus 20.8%).

Overall, the number of participants having SAEs was similar between the 2 disease duration subgroups. A greater percentage of participants with disease duration ≤ 12 weeks experienced SAEs in the SOCs of Cardiac disorders; Injury, poisoning and procedural complications; Investigations; Gastrointestinal disorders; and Nervous system disorders, while a greater percentage of participants with disease

duration > 12 weeks experienced AEs in the SOCs of General disorders and administration site conditions and Musculoskeletal and connective tissue disorders. By PTs, a greater percentage of participants with disease duration ≤ 12 weeks experienced SAEs of acute respiratory failure as well as cardiac arrest (8.3% versus 3.7% in participants with disease duration > 12 week, for each PT). Participants with disease duration ≤ 12 weeks also experienced SAEs of atelectasis (4.2%), cardio-respiratory arrest (4.2%), oxygen saturation decreased (4.2%), and dysphagia (4.2%), while none of these were reported as SAEs in participants with disease duration > 12 weeks. However, a greater percentage of participants with disease duration > 12 weeks experienced AEs of pneumonia (25.9% versus 12.5%) and pneumonia viral (7.4% versus 2.1%). Additionally, participants with disease duration > 12 weeks experienced SAEs of urinary tract infection (7.4%), respiratory distress (7.4%), and sudden infant death syndrome (11.1%), while none of these were reported as SAEs in participants with disease duration ≤ 12 weeks.

- ***Baseline CHOP INTEND Subgroup Analysis***

Supportive Higher Dose Pool BI+ Adverse Events and Serious Adverse Events by Baseline CHOP INTEND

Overall, the percentage of AEs experienced by participants with a baseline CHOP INTEND score ≤ 18.5 was slightly higher than participants with a baseline CHOP INTEND score > 18.5 (94.9% and 86.1%, respectively). A greater percentage of participants with baseline CHOP INTEND score ≤ 18.5 experienced AEs in the SOCs of Respiratory, thoracic and mediastinal disorders (61.5% versus 33.3%); Investigations (23.1% versus 11.1%); Musculoskeletal and connective tissue disorders (15.4% versus 5.6%); Cardiac disorders (12.8% versus 5.6%); and Nervous system disorders (7.7% versus 2.8%). Participants with baseline CHOP INTEND score of > 18.5 experienced AEs in the SOCs of Eye disorders (5.6%), while participants with baseline CHOP INTEND score ≤ 18.5 experienced no AEs in this SOC.

Overall, a greater percentage of participants with baseline CHOP INTEND score ≤ 18.5 experienced SAEs (79.5%) compared to participants with baseline CHOP INTEND score > 18.5 (52.8%). Participants with a baseline CHOP INTEND score ≤ 18.5 reported a higher percentage of SAEs of pneumonia (23.1% versus 11.1%), respiratory failure (17.9% versus 13.9%), acute respiratory failure (10.3% versus 2.8%), and cardiac arrest (10.3% versus 2.8%).

- ***Later-Onset Participant Subgroup Analysis***

Supportive Higher Dose Pool BL+ Age at Screening Subgroup Analysis

A greater percentage of participants aged < 6 years at Screening than participants aged ≥ 6 years to < 12 years experienced AEs in the SOCs of General disorders and administration site conditions (8.3% versus 0%), Gastrointestinal disorders (33.3% versus 8.3%), Investigations (16.7% versus 8.3%), and Cardiac disorders (8.3% and 0%). A greater percentage of participants aged ≥ 6 to < 12 years at Screening experienced AEs in the SOCs of Respiratory, thoracic and mediastinal disorders (41.7% versus 16.7%); Skin and subcutaneous tissue disorders (16.7% *versus* 8.3%); Blood and lymphatic system disorders (8.3% and 0%); and Musculoskeletal and connective tissue disorders (25.0% versus 8.3%).

By PTs, a greater percentage of participants aged < 6 years at Screening experienced AEs of tonsillitis, influenza, pneumonia respiratory syncytial viral, pyrexia, diarrhea, and vomiting, while a greater percentage of participants aged ≥ 6 years to < 12 years at Screening experienced AEs of nasopharyngitis, asthma, procedural headache, and scoliosis. No firm conclusions can be made due to the small sample size in each subgroup.

Supportive Higher Dose Pool BL+ Serious Adverse Events by Age at Screening

Overall, participants in the older age group experienced more SAEs (41.7%) than participants in the younger age group (25.0%). Both groups reported SAEs in the SOC of Infections and infestations (33.3% and 25.0%). However, participants aged ≥ 6 years to < 12 years reported SAEs by PT of pneumonia, pneumonia aspiration, COVID-19, atelectasis, and asthma, none of which were reported as SAEs by participants aged < 6 years. There were 2 (16.7%) participants < 6 years at the time of screening who experienced SAEs of pneumonia respiratory syncytial viral.

- ***Baseline HFMSE Subgroup Analysis***

Supportive Higher Dose Pool BL+ Adverse Events and Serious Adverse Events by Baseline HFMSE

Overall, the same percentage of participants in each baseline HFMSE group experienced at least 1 AE (91.7% in each group). For both the baseline HFMSE ≤ 13.5 participants and the baseline HFMSE > 13.5 participants, most AEs were Infections and infestations (83.3% and 66.7%). AEs in the SOC of Musculoskeletal and connective tissue disorders were reported with the same frequency in both groups (16.7% in each group). Skin and subcutaneous tissue disorders AEs were reported in the baseline HFMSE ≤ 13.5 group (25.0%), but not in the baseline HFMSE > 13.5 group. Investigations and Nervous system disorders AEs were experienced by participants in the baseline HFMSE > 13.5 group (25.0% and 16.7%) but were not reported in the baseline HFMSE ≤ 13.5 group. A greater percentage of participants with baseline HFMSE score ≤ 13.5 (50.0%) experienced SAEs than participants with baseline HFMSE score > 13.5 (16.7%). The majority of SAEs in the ≤ 13.5 group were in the SOC of Infections and infestations (41.7%).

Use in Pregnancy and Lactation

The use of nusinersen in pregnancy and lactation has not been studied.

Overdose

There was 1 accidental overdose of nusinersen across all studies. On Day 279 in Study SM203 Part B, a participant with infantile-onset SMA was administered 60 mg in error instead of the assigned dose. The cause was determined to be an unintentional human error. There were no reported AEs for this participant associated with the accidental overdose.

2.6.8.5. Immunological events

Integrated Higher Dose Studies SM203 and SM302 Immunogenicity

Of the 128 participants treated with nusinersen 28 mg or higher dose across Study SM203 and Study SM302, 117 participants had available post-baseline plasma samples and were evaluated for ADAs for nusinersen, with 11 participants having no evaluable sample post-baseline. In total, 11 of 117 participants (9.4%) developed treatment-emergent anti-nusinersen antibodies, of whom 5 of 117 participants (4.3%) had transient ADAs, and 6 of 117 participants (5.1%) had persistent ADAs. The incidence of AEs, including AEs with PTs in the SMQs of anaphylactic reaction, angioedema, and hypersensitivity reaction, was analyzed by anti-nusinersen antibody status in the 117 participants evaluated for ADAs across Study SM203 and Study SM302.

- *Anaphylactic Reaction:* AEs identified using the SMQ of anaphylactic reaction were reported in 2 of 11 nusinersen-treated participants (18.2%) with a positive ADA result, 27 of 106 nusinersen

participants (25.5%) with a negative ADA result, and 5 of 11 nusinersen-treated participants (45.5%) with no evaluable sample post-baseline. The frequency of events in the SMQ of anaphylactic reaction was similar in ADA-positive participants as compared to ADA-negative participants.

- *Angioedema:* AEs identified using the SMQ of angioedema were reported in 1 of 11 nusinersen-treated participants (9.1%) with a positive ADA result, 5 of 106 nusinersen-treated participants (4.7%) with negative ADA result, and 1 of 11 nusinersen-treated participants (9.1%) with no evaluable sample post-baseline. The frequency of events in the SMQ of angioedema was increased in the ADA-positive participants as compared to ADA-negative participants.
- *Hypersensitivity Reaction:* AEs identified using the SMQ of hypersensitivity reaction were reported in 1 of 11 nusinersen-treated participants (9.1%) with a positive ADA result, 29 of 106 nusinersen-treated participants (27.4%) with a negative ADA result, and 4 of 11 nusinersen-treated participants (36.4%) with no evaluable sample post-baseline. The frequency of events in the SMQ of hypersensitivity reaction was decreased in ADA-positive participants as compared to ADA-negative participants.

Overall, there were no notable imbalances seen in the PTs identified using SMQs of anaphylactic reaction, angioedema, and hypersensitivity reaction between nusinersen-treated participants with a positive ADA result and those with a negative ADA result. The majority of events reported for nusinersen-treated participants who were ADA-positive were mild to moderate in severity and assessed as not related to nusinersen by the Investigator. No safety concerns due to anti-nusinersen antibody positivity were identified.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.7. Discontinuation due to adverse events

No participants in Pool G, J, supportive higher dose pools and pool I had an AE leading to treatment discontinuation.

2.6.8.8. Post marketing experience

Nusinersen was first approved globally in the US in December 2016 and is now approved in over 70 countries. Estimated global postmarketing exposure is based on nusinersen market data available through 31 March 2024 with approximately 14,365 patients and 32,774 cumulative PY of exposure. During the interval of this reporting period (01 April 2023 to 31 March 2024) there were an estimated 6915 PY of global nusinersen exposure (PSUR Report 26 July 2024). During the most recent reporting period, there were no actions taken for safety reasons. Cumulatively, 571 participants have been exposed to nusinersen in interventional clinical studies.

Arachnoiditis was added to the list of identified risks for nusinersen during the reporting period (01 April 2023 to 31 March 2024) and the CDS was updated with the evidence that supports a causal association between arachnoiditis and the use of nusinersen. Nusinersen is administered IT, and the LP procedure is a known risk factor for arachnoiditis; therefore, an association is possible. Arachnoiditis was assessed as an Identified Risk and ADR.

Relevant new information reported during the most recent reporting period consisted of 1 important potential risk: hydrocephalus. In CDS, Version 16, dated 01 May 2024, hydrocephalus is included as an AE in PSUR Report 26 July 2024. During the reporting period, 9 events pertaining to high-level group term Increased intracranial pressure and hydrocephalus were received in 9 case reports (6 initial and 3 follow-up cases), comprising 9 healthcare professional-confirmed events. All 9 events were considered serious (PSUR Report 26 July 2024). Events of hydrocephalus in nusinersen-treated patients have been reported very rarely and, where reported, are considered to be manageable and nusinersen treatment has been continued in some cases.

2.6.9. Discussion on clinical safety

Safety data is retrieved from a total of 10 clinical studies, including studies evaluating a higher-dose regimen of nusinersen (completed Study SM203 and an interim data cut off (30 May 2024) of its long-term extension, Study SM302). The proposed pooling safety data analysis by the MAH is considered acceptable. All in all, safety data from 2 key nusinersen higher-dose pools of interest included the following: a) *Pool G* consists of safety data from Study SM203 Part B, combined onset populations (infantile-onset and later-onset), separated by dose (higher-dose regimen [50/28 mg] and control 12 mg regimen), allowing for comparisons between the higher-dose and 12 mg regimens. Safety data from SM203 Part B were also presented separately for each onset population (infantile-onset and later-onset) by dose group to provide additional safety results by participant age; b) *Pool J* which consisted of all controlled and uncontrolled studies of nusinersen 28 mg or higher, across participants with infantile-onset and later-onset SMA.

Additional safety pools specific to Studies SM203 and SM302 (BI+, BL+, BEI, BEL, CEXT, and AEXT) provided supportive data, integrating data from participants in Study SM203 with data from Study SM302 for participants who continued on the long-term extension study. Furthermore, an additional data pool, Pool I, consisting of all controlled and uncontrolled studies of nusinersen 12 mg or lower, was provided also as supportive data, which according to the MAH provides the largest safety experience of participants who received nusinersen 12 mg or lower.

For the key higher dose pooled groups, and specifically for participants in Pool G (Study SM203 pivotal Part B), 66 participants received the nusinersen 50/28 mg regimen, for a total of 61.34 participant-years, and 33 participants received the nusinersen 12 mg regimen for a total of 25.93 participant-years. For the 66 participants receiving the higher dosing nusinersen regimen, the median number of doses received was 4.0. Median time on study was 397.0 days and 86.4% were on study for ≥ 180 days. For the 33 participants receiving nusinersen 12 mg, the median number of nusinersen doses received was 6.0, median time on study was 331.0 days and 69.7% were on study for ≥ 180 days. In Pool J, 128 participants were exposed to nusinersen 28 mg or higher across both controlled and uncontrolled studies, being the mean (SD) time on study 689.1 (365.57) days (the total number of participant-years on study for nusinersen higher dose was 241.48). For supportive studies, specifically for participants on Pool I (12 mg or lower), the mean (SD) time on study for both controlled and uncontrolled studies was 2034.0 (1048.01) days, and the total number of person-years on study was 2144.02 years.

All things considered, and given the proposed extended indication submitted by the MAH to investigate an enhanced dosing regimen for nusinersen, the safety database can be considered acceptable in the context of SMA being a rare condition. Moreover, it should be also emphasized that more than 15,000 patients worldwide have received nusinersen in the postmarketing setting, Expanded Access program, and clinical studies where safety profile for SOC dose (mainly 12 mg or lower) has been characterized.

All-in-all, across all 3 parts of Study SM203 and across all cohorts of participants, including treatment naïve and previously treated participants, the 50/28 mg dosing regimen of nusinersen was overall generally well tolerated and broadly consistent with the known safety profile of nusinersen 12 mg. In general, reported AEs were broadly consistent with the types and severities of AEs seen in infants and children with SMA or were consistent with the events observed in the context of the LP procedure.

In Pool G, 28 (84.8%) participants receiving nusinersen 12/12 mg and 57 (86.4%) participants receiving the nusinersen 28 mg regimen (50/28 mg) experienced ≥ 1 AE. The proportion of participants experiencing ≥ 1 AE was similar across each dosing treatment group. Overall, no differences were observed between infantile-onset and later-onset participants. The most common AEs by PT (occurring in ≥ 10% of participants) across both the nusinersen 12 mg and 50/28 mg dosing regimens were pneumonia (18.2% and 15.2%), upper respiratory tract infection (15.2% and 13.6%), atelectasis (12.1% and 3.0%), pyrexia (12.1% and 15.2%), cough (9.1% and 10.6%), COVID-19 (9.1% and 13.6%), respiratory failure (9.1% and 12.1%), and pneumonia aspiration (6.1% and 10.6%). The overall incidence of AEs considered by the Investigator to be related to study treatment across the treatment groups was similar for infantile-onset participants regardless of nusinersen dose received. One participant receiving 12 mg (nausea and respiratory failure) and 4 participants receiving 50/28 mg (i.e., 2 participants experienced pyrexia; one event each of eosinophilia, dysphoria, productive cough, and rash erythematous considered related study treatment occurred in the remaining 2 participants).

In Pool J, a total of 117 (91.4%) participants receiving nusinersen 28 mg or higher experienced ≥ 1 AE. For infantile-onset SMA, fewer participants switching from nusinersen 12 mg (7 participants [63.6%]) to the nusinersen 28 mg or higher experienced ≥ 1 AE when compared with participants with infantile onset SMA who were treatment-naïve at baseline (45 participants [90%]). For participants with later onset SMA, the number experiencing ≥ 1 AE was similar between those who were switchers from nusinersen 12 mg and those who were treatment naïve at baseline. For the infantile-onset SMA participants and given the differences found between naïve to treatment and switchers, the MAH was requested to characterize these differences in terms of AE event severity, type of events and relatedness to the study drug by the investigator and discuss if appropriate warnings are needed in the product information. In the responses provided, the MAH justified that the AEs that were more frequently reported in the naïve-to-treatment group compared to the switchers group were events commonly seen in the SMA population, and these events were the main driver behind the overall differences found. The fact that the switchers had already been treated with 12 mg nusinersen and achieved some clinical benefit could explain this difference, given that the switchers did not report as many AEs related to the SMA disease compared to the naïve-to-treatment group with previously untreated SMA. A similar pattern to the overall incidence of severe AEs was also found among these subgroups, and the incidence of AEs considered by the Investigator to be related to study treatment was also similar among subgroups. The MAH committed to continue monitoring the safety profile of 50/28 mg nusinersen through routine pharmacovigilance activities in patients who are naïve to treatment and those who switch from 12 mg nusinersen.

The most common AEs by PT in Pool J (occurring in ≥10% of participants) were COVID-19 (27.3%), procedural pain (19.5%), upper respiratory tract infection (17.2%), pneumonia (16.4%); pyrexia (16.4%), procedural headache (15.6%), nasopharyngitis (15.6%), fall (13.3%), cough (11.7%), vomiting (11.7%), headache (10.9%), and constipation (10.2%). A total of 13 participants (10.2%) receiving nusinersen 28 mg or higher experienced at least 1 AE considered by the Investigator to be related to study treatment. The most common of these AEs by PT, occurring in more than 1 participant were pyrexia (3 participants [2.3%]) and crystal urine present (2 participants [1.6%]).

In what concerns to supportive higher dose pools, the number of participants experiencing ≥ 1 AE was overall similar across each study pool. The most common AEs by PT (occurring in ≥ 10% of participants

in any group) across the supportive higher dose pools included, were but not limited to, COVID-19, procedural pain, headache, nasopharyngitis, upper respiratory tract infection, fall, tonsillitis, vomiting, pneumonia, and pyrexia. In Pool I (12 mg or lower), 99.0% of participants experienced ≥ 1 AE, being similar across each study group (presymptomatic, infantile onset, and later-onset). The most common AEs by PT (occurring in ≥ 10% of participants) were not limited to, pyrexia (61.8%), upper respiratory tract infection (51.7%), scoliosis (45.7%), vomiting (42.9%), nasopharyngitis (38.4%), cough (34.8%), pneumonia (34.0%), headache (30.1%), procedural pain (28.1%), constipation (27.5%), and muscle contracture (25.2%).

Given the number of events of pyrexia found across the different study treatment pools, and the cases where these events were considered by the investigator to be related by to study treatment, the MAH was requested to discuss if a causal relationship between nusinersen and pyrexia was at least a reasonable possibility. Based on the review conducted by the MAH, it was concluded that there is biologic plausibility for pyrexia in nusinersen and that existent evidence supports a causal association between exposure to nusinersen and pyrexia. In clinical trials of 12 mg nusinersen, there were 1075 reported events of pyrexia, and 22 events in trials of 50/28 mg nusinersen. Of those, 103 events (91 in 12 mg, 12 in 50/28 mg) occurred within 3 days after dosing with Spinraza. A total of 16 events were assessed as related by the investigator and were medically reviewed by the MAH; of those 14 were found to have a possible causal relationship between pyrexia and nusinersen: 11 events in the 12 mg or lower group, and 3 events in the 50/28 mg group. Moreover, data from post-marketing setting retrieved a total of 940 events of pyrexia. Of those, 93 events in 87 cases occurred within 3 days of nusinersen dosing and had no alternative aetiology for fever. In view of available evidence, it is agreed with the MAH that a causal relationship between nusinersen and pyrexia is at least a reasonable possibility.

In what concerns to SAESs reported from the key Pool G, 63.6% of participants receiving nusinersen 12 mg and 45.5% of participants receiving nusinersen 50/28 mg experienced at least 1 SAE. SAEs by PT occurring in ≥ 5% of participants in either the 12 mg dosing regimen or the 50/28 mg dosing regimen were pneumonia (15.2% and 10.6%), acute respiratory failure (9.1% and 3.0%), respiratory failure (9.1% and 9.1%), cardiac arrest (6.1% and 4.5%), cardio-respiratory arrest (6.1% and 0%), pneumonia aspiration (6.1% and 10.6%), respiratory tract infection (6.1% and 0%), and COVID-19 (0% and 6.1%). Pneumonia aspiration was more frequent (almost the double) among higher nusinersen doses as compared with 12/12 mg nusinersen and is now reflected in the section 4.8 of the SmPC (please see below). Only 1 participant (3.0%) experienced an SAE considered by the Investigator to be related to study treatment and no SAEs related to study treatment reported for participants on nusinersen higher dose. In pool J, a total of 62 participants (48.4%) receiving nusinersen 28 mg or higher experienced at least 1 SAE. By PT, the only SAEs occurring in ≥ 5% of participants in Pool J were pneumonia (11.7%), respiratory failure (6.3%), and pneumonia aspiration (5.5%). No participants in Pool J experienced an SAE assessed as related to study treatment. In what concerns to supportive higher dose pools, only 1 SAE was considered by the Investigator to be related to study treatment among all participants in the supportive high dose pools. In BEI, respiratory failure was experienced by 1 participant (1.3%) in the switching group (12/12 mg to 50/28 mg). The participant was on nusinersen 12 mg at the time of the event. There were no other SAEs related to study treatment reported for any supportive higher dose pool.

For the key higher doses pooled results regarding SAEs with a fatal outcome the results were the following. For pool G, overall, the proportion of participants with SAEs with a fatal outcome was similar between those receiving nusinersen 12 mg (6 participants;18.2%) and those receiving nusinersen 50/28 mg (10 participants; 15.2%]). There were no SAEs with a fatal outcome reported in later-onset participants. By PT, 2 participants (6.1%) receiving nusinersen 12 mg and 1 participant (1.5%) receiving nusinersen 50/28 mg had an SAE of pneumonia with a fatal outcome. Additionally, 2 participants (6.1%)

receiving nusinersen 12 mg and 1 participant (1.5%) receiving nusinersen 50/28 mg had an SAE of cardiac arrest with a fatal outcome. In pool J, a total of 14 participants (10.9%) receiving nusinersen 28 mg or higher had an SAE with a fatal outcome. SAEs with a fatal outcome by PT occurring in more than 1 participant were pneumonia aspiration and sudden infant death syndrome (2 participants each PT [1.6%]). None of the SAEs with a fatal outcome for both pools G and J were considered by the Investigator to be related to study treatment, which is concurred.

The MAH presented a specific analysis for adverse events of special interest: pneumonia and pneumonia aspiration. Based on a review of AEs occurring in greater than 10% of infantile-onset participants receiving nusinersen 50/28 mg in Part B of Study SM203 and that also had a frequency at least 5% greater in the nusinersen 50/28-mg Group compared to the Matched Sham control group from Study CS3B, pneumonia aspiration was identified as an ADR for nusinersen at the 50/28 mg dose. When adjusting for exposure, a > 10% higher incidence rate of pneumonia aspiration was observed in participants on nusinersen 50/28 mg (21.8 participant years [n = 7]) versus participants on matched sham (8.5 participant years [n = 1]) remained.

The incidence of AEs with a PT of pneumonia aspiration in participants with infantile-onset SMA receiving the nusinersen 50/28 mg dosing regimen in Study 232SM203 Part B was 14.0% (7/50 participants) versus 5.0% (1/20 participants) for participants on matched sham. All AEs of pneumonia aspiration were serious AEs (SAEs), and all were assessed as unrelated to study treatment by the Investigator. In the infantile-onset population treated with 12 mg nusinersen in Study 232SM203 Part B, the frequency of pneumonia aspiration was 4.0% (1/25 participants) versus (5.0%, 1/20 participants) in matched sham. It is acknowledged that the higher exposure-adjusted incidence rate of pneumonia aspiration for participants receiving nusinersen 50/28 mg compared to matched sham had not a clear alternate explanation, thus, the reason for the mismatch between the frequency of pneumonia aspiration between 12 mg and 50/28 mg is not known. Both pneumonia and pneumonia aspiration occur frequently in the SMA population, and at present time a biological mechanistic rationale that justifies an increased prevalence of this ADR related to the higher dose cannot be established. Of note, it is acknowledged that a higher probability of post-lumbar puncture headache, postural pain, which are worse when upright (sitting or standing) and are relieved by lying down – especially supine - the patients, could also have played a role in these aspiration pneumonia cases. The adverse event reports of aspiration pneumonia almost exclusively emerged from one single study site. Taking all together, there is no clear evidence, at present, that pneumonia aspiration is an ADR for the higher doses. Nevertheless, given the imbalance observed (although derived from almost one site), aspiration pneumonia should be monitored through routine pharmacovigilance activities in clinical practice and presented separately for each dose in the next PSURs.

No participants in Pools G and J had an AE leading to treatment discontinuation. Similarly, no participants in supportive studies (supportive higher dose pools or all pooled nusinersen 12 mg or lower) had an AE leading to treatment discontinuation. All AEs that led to withdrawal from the study were fatal AEs across the integrated nusinersen higher dose study pools.

Clinical laboratory data was analysed and reported for only the supportive higher dose pools BI+, BL+, CEXT, and AEXT with changes in laboratory evaluations presented relative to baseline, Day 1, in Study SM203. Across all pooling groups, results of laboratory assessments, including haematology, blood chemistry, urinalysis, and coagulation, did not reveal any new clinically significant changes or patterns related to dosing with nusinersen. Results of vital signs, ECGs, neurological examinations, and growth parameters did not reveal any new safety concerns for the nusinersen higher 50/28 mg dosing regimen.

Global postmarketing exposure estimates provided by the MAH stated that through 31 March 2024 approximately 14,365 patients and 32,774 cumulative PY of exposure were observed. During the last

PSUR reporting period (01 April 2023 to 31 March 2024)), arachnoiditis was added to the list of identified risks for nusinersen and it is now adequately reflected in the product information. It should be also noted that a total of 9 cases of pertaining to high level group term Increased intracranial pressure and hydrocephalus were received during this reporting period (9 case reports: 6 initial and 3 follow-up cases), comprising 9 healthcare professional confirmed events. All 9 events were considered serious. Currently, hydrocephalus is an important potential risk defined in the RMP. Hence, and in this particular context, a concern on the safety of the higher loading regimen and the potential for patients to develop increased intracranial hypertension (e.g., hydrocephalus) cannot be excluded and is a matter of concern. The MAH was requested to provide a cumulative review of all hydrocephalus cases from all existent evidence, including clinical studies and spontaneous reporting data, as well as other routine pharmacovigilance activities (e.g., follow-up questionnaires). Based on the analysis of available data, a causal association between the development of hydrocephalus and exposure to nusinersen treatment could not be established. Hydrocephalus will remain an important potential risk with nusinersen in the RMP. Hydrocephalus is currently listed in the nusinersen reference safety information (CDS), as well as the Investigator Brochure and the Patient Safety Information used for Informed Consent Forms. It is also included in nusinersen SmPC (section 4.4 - special warnings and precautions for use; and section 4.8 - undesirable effects). Hydrocephalus will continue to be monitored via routine pharmacovigilance. At current time, these activities are considered sufficient to mitigate and further characterize the important potential risk of hydrocephalus.

2.6.10. Conclusions on clinical safety

The safety profile of nusinersen higher doses (28 mg or 50 mg) was characterized from pooled data from controlled and uncontrolled studies, including the pivotal and controlled Study SM203 Part B, and controlled and uncontrolled studies of nusinersen 12 mg or lower. Overall, no new major safety concerns were noted and the safety profile of nusinersen 50/28 mg appears to be well tolerated and consistent with the known safety profile of nusinersen 12 mg in participants with infantile-onset and later-onset SMA. No new safety concerns were observed with continued use of nusinersen in the LTE studies.

2.7. Risk Management Plan

2.7.1 Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Thrombocytopenia and coagulation abnormalities • Renal toxicity • Hydrocephalus
Missing information	• Safety profile in patients> 18 years of age • Safety profile in patients with severe and progressive scoliosis • Safety profile in patients receiving repetitive LPs

Summary of safety concerns	
	• Safety profile in patients receiving long-term treatment with nusinersen • Safety profile in pregnant or breastfeeding women • Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)

2.7.1.1. Discussion on safety specification

At the current time, no changes to the existent summary of safety specifications for the approved medicinal product was proposed by the MAH.

2.7.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the MAH are appropriate.

2.7.2. Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Mile-stones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
MDA US Neuromuscular Disease Registry Prospective longitudinal registry in a research agreement with the Muscular Dystrophy Association • Status: Ongoing	The objective of the registry is to accelerate translational research to improve clinical care and patient outcomes by gaining a better understanding of the course of illness for specific neuromuscular diseases, collecting longitudinal patient data that will allow benchmarking of best clinical practices, and collecting data on genotype-phenotype correlations to allow for better prediction of disease progression	• Thrombocytopenia and coagulation abnormalities • Renal toxicity • Hydrocephalus • Safety profile in patients > 18 years of age • Safety profile in patients with severe and progressive scoliosis • Safety profile in patients receiving repetitive LPs • Safety profile in patients receiving long-term treatment with nusinersen • Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the	Status reports	To be provided in PSURs.

Study Status	Summary of objectives	Safety concerns addressed	Mile-stones	Due dates
	based on genetic information.	nusinersen clinical programme (e.g., Type 0 and Type IV SMA)		
ISMAC natural history study Longitudinal natural history study with the 3 regional networks that comprise the ISMAC. • Status: Ongoing	The objective of the registry is to allow researchers studying the biological basis of SMA and potential therapies in SMA access to individuals interested in participating in research and/or experimental therapies.	• Thrombocytopenia and coagulation abnormalities • Renal toxicity • Hydrocephalus • Safety profile in patients > 18 years of age • Safety profile in patients with severe and progressive scoliosis • Safety profile in patients receiving repetitive LPs • Safety profile in patients receiving long-term treatment with nusinersen • Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	Status reports	To be provided in PSURs.
TREAT-NMD Alliance registries Longitudinal natural history studies in a research agreement with the TREAT-NMD Alliance • Status: Ongoing	The objectives of the MAH collaboration with the TREAT-NMD Global SMA Registry is to provide information on the natural history of SMA, provide context to understand the safety and effectiveness of new treatments, and support post-marketing surveillance for those new treatments.	• Thrombocytopenia and coagulation abnormalities • Renal toxicity • Hydrocephalus • Safety profile in patients > 18 years of age • Safety profile in patients with severe and progressive scoliosis • Safety profile in patients receiving repetitive LPs • Safety profile in patients receiving long-term treatment with nusinersen • Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	Status reports	To be provided in PSURs.

Abbreviations: ISMAC, International Spinal Muscular Atrophy Consortium; LP, lumbar puncture; MDA, Muscular Dystrophy Association; SMA, Spinal Muscular Atrophy; TREAT-NMD, Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases; US, United States

The pharmacovigilance plan remains unchanged in this procedure.

The pharmacovigilance plan is identical to the currently approved RMP for Spinraza version 13.0. This is endorsed.

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
• None	
Important Potential Risks	
• Thrombocytopenia and coagulation abnormalities	***Routine risk communication:*** • SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you or your child are given Spinraza: Warnings and precautions*) provides information relating to the observation of adverse events of thrombocytopenia and coagulation abnormalities in nusinersen-treated patients. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • SmPC Section 4.4 (*Special warnings and precautions for use*) suggests platelet and coagulation laboratory testing prior to initiation of treatment, if clinically indicated. ***Other routine risk minimisation measures beyond the Product Information:*** • None
• Renal toxicity	***Routine risk communication:*** • SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you or your child are given Spinraza: Warnings and precautions*) provides information relating to the observation of adverse events of renal toxicity in nusinersen-treated patients. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • SmPC Section 4.4 (*Special warnings and precautions for use*) suggests urine protein testing (preferably using a first morning urine specimen), if clinically indicated. ***Other routine risk minimisation measures beyond the Product Information:*** • None
• Hydrocephalus	***Routine risk communication:*** • SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you or your child are given Spinraza: Warnings and precautions*) provides information relating to the observation of adverse events of hydrocephalus in nusinersen-treated patients. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the Product Information:*** • None
Missing information	
• Safety profile in patients> 18 years of age	***Routine risk communication:*** • None ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the Product Information:*** • None

• Safety profile in patients with severe and progressive scoliosis	***Routine risk communication:*** • SmPC Sections 4.2 (*Posology and method of administration*) and 4.4 (*Special warnings and precautions for use*) , in addition to PL Section 2 (*What you need to know before you or your child are given Spinraza:* *Warnings and precautions*), advises that IT administration of nusinersen may be difficult in patients with scoliosis. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • SmPC Sections 4.2 (*Posology and method of administration*) and 4.4 (*Special warnings and precautions for use*) advises that the use of imaging can be considered to mitigate the difficulties of nusinersen administration in patients with scoliosis. ***Other routine risk minimisation measures beyond the Product Information:*** • None
• Safety profile in patients receiving repetitive LPs	***Routine risk communication:*** • SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*) lists the ADRs that have been reported in association with LP procedures in nusinersen-treated patients. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None. ***Other routine risk minimisation measures beyond the Product Information:*** • None
• Safety profile in patients receiving long-term treatment with nusinersen	***Routine risk communication:*** • None ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the Product Information:*** • None
• Safety profile in pregnant or breastfeeding women	***Routine risk communication:*** • SmPC Section 4.6 (Fertility, pregnancy and lactation) and PL Section 2 (*What you need to know before you or your child are given Spinraza:* Pregnancy and breastfeeding) provides advice on the avoidance of pregnancy and/or breastfeeding whilst receiving nusinersen. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the Product Information:*** • None

• Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	***Routine risk communication:*** • None ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the Product Information:*** • None

The Risk Minimisation Measures remain unchanged.

Part V remain unchanged from the previous RMP version and is also in line with the currently approved version 13.0. This is endorsed.

2.7.4. Additional risk minimisation measures

There are no additional risk minimisation measures considered necessary for nusinersen, and routine risk minimisation activities are considered sufficient to manage the current safety concerns.

No changes have been made to this section of the RMP, which thus is in line with the currently approved RMP version 13.0. This is endorsed.

2.7.5. Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

No changes have been made to the risk minimisation measures in this procedure. This is endorsed.

2.7.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 13.3 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk and neuromuscular weakness [Swoboda 2009]. In almost every case, SMA is caused by a deletion or mutation in the *SMN1* gene located on chromosome 5q, which is responsible for the majority of SMN protein production. This deletion or mutation results in a deficiency of SMN protein and degeneration of the motor neurons in the anterior horn of the spinal cord. In less than 5% of cases, a clinical diagnosis of SMA may be caused by non 5q forms of the disease [Farrar and Kiernan 2015].

A second gene (*SMN2*) located near *SMN1* is responsible for a small amount of SMN protein production. The best-known predictor of clinical phenotype is the *SMN2* copy number. Infants with the most severe phenotype of SMA (Type 0) are symptomatic at birth and die within the first few weeks of life. Patients with all other SMA phenotypes are asymptomatic at birth. The duration of the asymptomatic phase is variable but is usually correlated with disease severity, with more severe disease associated with earlier symptom onset and less SMN protein production.

Prior to the development of advanced molecular medicine techniques that allow genotyping of both *SMN1* and *SMN2* copy number, SMA was diagnosed based on clinical presentation and categorized retrospectively (Type I, II, III, or IV) based on the maximal motor milestone achieved and the age at symptom onset. Generally, symptom onset and severity of SMA correlate with *SMN2* gene copy number [Arnold 2015].

Type I SMA is the most common form of SMA and represents approximately 58% of the birth prevalence [Ogino 2004]. More than 90% of patients with 2 copies of *SMN2* will develop Type I SMA [Feldkötter 2002], and these infants usually present with hypotonia, loss of motor function, and failure to achieve new milestones within the first 6 months of life. These infants are never able to sit without support [De Sanctis 2016; Russman 2007; Wang 2007]. The major cause of morbidity and mortality in patients with

Type I SMA is pulmonary disease due to neuromuscular weakness [Wang 2007]. In the absence of respiratory support, only 1.3% of infants with Type I SMA survive beyond 24 months of age [Gregoretti 2013].

Type II SMA represents approximately 29% of the birth prevalence [Ogino 2004]. More than 80% of patients with 3 copies of *SMN2* will develop Type II SMA but the SMN2 gene number can vary between 2 and 4 copies [Feldkötter 2002]. Children fail to achieve motor milestones because of proximal weakness and hypotonia that typically develop within the first 18 months of life [Rudnik-Schöneborn 2001]. This group is generally defined by an ability to sit independently but inability to walk unaided [Rudnik-Schöneborn 2001]. However, the progressive nature of the disease means some of these patients will lose their ability to sit unaided over time [Faravelli 2015; Russman 2007; Wang 2007]. Orthopedic and respiratory complications are a major cause of morbidity and mortality, and only 70% of patients with Type II SMA are alive at 25 years [Faravelli 2015].

Type III SMA represents approximately 13% of the birth prevalence [Ogino 2004]. More than 80% of patients with 4 copies of *SMN2* will develop Type III SMA but the *SMN2* gene number can vary between 3 or 4 copies [Feldkötter 2002]. These patients are able to stand and walk without support, but may lose these abilities as the disease progresses [Zerres and Rudnik-Schöneborn 1995]. While these patients may have normal life expectancy, neuromuscular and orthopedic complications are similar to those of Type II SMA and are a major cause of morbidity [Arnold 2015; Haaker and Fujak 2013; Wang 2007].

Type IV SMA (adult-onset) is the mildest form of SMA, and its occurrence is rare (<1%). Patients with Type IV SMA usually have 4 or more copies of the *SMN2* gene. After symptom onset, which has been reported after 10 years of age but more commonly after 20 to 30 years of age [Wang 2007], patients experience mild to moderate muscle weakness and increasing disabilities. Patients are ambulatory and their life expectancy is normal [Faravelli 2015].

3.1.2. Available therapies and unmet medical need

The following other therapies have been authorized for the treatment of SMA:

The gene transfer agent onasemnogene abeparvovec-xioi (Zolgensma®) is an AAV9 vector expressing an *SMN1* gene delivered intravenously. Zolgensma is approved in the United States (May 2019), Japan (March 2020), the European Union (May 2020), and several other markets.

Risdiplam (Evrysdi™, formerly RG7916) is an oral SMN2 directed splicing modifier was first approved in the United States (August 2020) and has since received approval in several other markets.

In regions where nusinersen or other SMA therapies have not yet been approved, medical care is supportive once patients become symptomatic. Due to neuromuscular weakness, patients with SMA lose motor milestones or never achieve them, and the most affected patients die or require permanent ventilation by 2 years of age [Gregoretti 2013]. For patients with infantile onset SMA, supportive care is targeted to respiratory and nutritional support [Finkel 2018; Mercuri 2018; Wang 2007]. Respiratory support consists of noninvasive ventilation, such as bilevel positive airway pressure, cough assist, and oral suctioning, that can require multiple hours of treatment per day. Tracheostomy for chronic ventilation may be performed if additional respiratory support is required. Patients with SMA may develop difficulty swallowing and require assistance with food intake or supplemental feedings through a gastrostomy tube. Medical care of patients with later-onset SMA depends on the level of disease progression but can include nutritional support, physical and occupational therapy, pain management, orthotics, spinal surgery, and environmental controls and home modifications to facilitate safe mobility. However, despite even the most robust support, disease progression, including respiratory deficits and weakness in the more severe forms of the disease, is relentless, leading to premature death.

Patients with SMA and the families who care for them describe a significant need for therapies that improve motor function and increase survival [Qian 2015] and have expressed that stabilization of the current clinical state would represent therapeutic progress [Rouault 2017]. Furthermore, improvements in motor function would ease the significant burden of supportive care, offer greater independence, and improve the patient's quality of life as well as that of their caregivers.

3.1.3. Main clinical studies

Study 232SM203: Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy

3.2. Favourable effects

The key favourable aspects of the 50/28 are:

- Superiority in efficacy response over sham procedure from study CS3 of Early onset SMA, as measured by CHOP INTEND CHOP INTEND total score change from baseline to Day 183, statistically relevant
- A trend in better efficacy response over the 12 mg dosing regimen of Early onset SMA, as measured by CHOP INTEND total score change from baseline to Day 302, Change from baseline to Day 302 in HINE Section 2, albeit not being the study statistically powered for it.
- Ancillary analyses with stringent criteria (imputation of zero to data after death vs. MAR imputation approach) favoured the 50/28 dose regimen as compared to 12/12 regimen.
- The decrease in lumbar punctures in the first period of treatment.

3.3. Uncertainties and limitations about favourable effects

The primary support for the efficacy of a higher dosing regimen of nusinersen (50◦mg dose administered as 2◦loading doses at biweekly intervals and 28◦mg maintenance doses every 4◦months thereafter) is from the infantile-onset cohort of Part B of Study SM203.

The primary endpoint does not directly respond to the advantage of the 50/28 mg over the 12 mg dosing regimen, since it does not directly compare the two regimens, but a comparison of the 50/28 to the sham procedure performed in study CS3 was made instead. In this study, a comparison between the sham procedure and the 12 mg regimen had already been done, thus the possibility of an indirect comparison. Notwithstanding, the study population of study SM203 Part B was younger and with less disease duration than the population enrolled into CS3, including those in the sham study arm. Furthermore, the sham population was matched to the SM203 population, which decreased the sample size of the sham arm from 37 to 20 patients. As a consequence, it was considered that the primary endpoint is not a robust comparison of the 50/28 regimen as compared to the 12 mg regimen to the point that the 50/28 dosing should be preferred over the 12 mg dosing. Additional analyses on the probability of improvement as treatment regimens were administered in each arm, and imputation of zero to values after death in HINE and CHOP scores provide some assurance that the results are consistent. However, limitations do not allow to confirm that the 50/28 dosing regimen is surely better

than the 12/12 for the entre SMA population, thus both regimens should remain available. Furthermore, the convenient effect of sparing of lumbar punctures observed initially in the 50/28 regimen, decreases as time goes by, since the maintenance regimen requires 4mth interval LPs independently of the dosing regimen.

3.4. Unfavourable effects

The safety profile of nusinersen higher doses (28 mg or 50 mg) was characterized from pooled data from controlled and uncontrolled studies, including the pivotal and controlled Study SM203 Part B, and controlled and uncontrolled studies of nusinersen 12 mg or lower. In pool G, the most common AEs by PT (occurring in ≥ 10% of participants) across both the nusinersen 12 mg and 50/28 mg dosing regimens were PTs of pneumonia (18.2% and 15.2%, respectively), upper respiratory tract infection (15.2% and 13.6%), atelectasis (12.1% and 3.0%), pyrexia (12.1% and 15.2%), cough (9.1% and 10.6%), COVID-19 (9.1% and 13.6%), respiratory failure (9.1% and 12.1%), and pneumonia aspiration (6.1% and 10.6%). The most common AEs by PT (occurring in ≥10% of participants) in Pool J were COVID-19 (27.3%), procedural pain (19.5%), upper respiratory tract infection (17.2%), pneumonia (16.4%); pyrexia (16.4%), procedural headache (15.6%), nasopharyngitis (15.6%), fall (13.3%), cough (11.7%), vomiting (11.7%), headache (10.9%), and constipation (10.2%).

Overall, no new major safety concerns were noted and the safety profile of higher dosing regimen of nusinersen 50/28 mg, which appears to be well tolerated and consistent with the known safety profile of the approved nusinersen 12 mg in participants with infantile-onset and later-onset SMA. No new safety concerns were observed with continued use of nusinersen in the long-term-extension studies.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties and limitations about unfavourable effects are similar from the approved 12mg dose. There is a risk of adverse reactions occurring as part of the lumbar puncture procedure. Potential difficulties with this route of administration may be seen in very young patients and those with scoliosis.

Thrombocytopenia and coagulation abnormalities and renal toxicity are important potential risks for nusinersen. If clinically indicated, platelet, coagulation laboratory testing and urine protein testing is recommended prior to administration of nusinersen. It should be also mentioned that hydrocephalus is also an important potential risk in the RMP, being this safety specification in a context of the higher loading regimen a matter of concern.

3.6. Effects Table

Table 23. Effects table for Spinraza

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Change from baseline to Day 64 in plasma concentration of NF-L	Neurofilaments (namely the plasma neurofilament light chain (Nf-L))	% reduction	50/28 mg vs 12 mg LS mean difference [95% CI] = 12.74 [3.840, 21.632]; p = 0.0050 50/28 mg 0.12 [0.09, 0.15] 50/28 mg vs 12 mg ANCOVA with MI over time (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.51 [0.33, 0.78]; p = 0.0020)	12 mg 0.23 [0.16, 0.32]	Doubtful clinical relevance, since the proposal is to propose the 50/28 dosing regimen as primary treatment regimen instead of the 12 mg	Secondary SM203 - Part B, Infantile-Onset SMA
Change from baseline to Day 64 in plasma concentration of NF-L	Neurofilaments (namely the plasma neurofilament light chain (Nf-L))	% reduction	50/28 mg 0.34 [0.25, 0.46 50/28 mg vs 12 mg ANCOVA with MI (50/28-mg / 12-mg LS geometric mean ratio [95% CI] = 0.58 [0.34, 1.00]; p = 0.0495)	12 mg – 0.58 [0.34, 1.00]	Doubtful clinical relevance, since the proposal is to propose the 50/28 dosing regimen as primary treatment regimen instead of the 12 mg	Secondary SM203 – Part B, Later-Onset SMA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Change from Baseline to Day 302 in CHOP INTEND total score	CHOP INTEND total score	score	50/28 mg vs 12 mg LS mean difference [95% CI] = 1.00 [-9.290, 11.299]; joint-rank p = 0.8484 50/28 mg 19.6 [16.5, 22.8]	12 mg 21.6 [16.6, 26.6] 12 mg vs 50/28 mg ANCOVA with MI (LS mean difference [95% CI] = -1.94 [-7.768, 3.884]; p = 0.5132)		Secondary SM203 Part B 12 mg ITT set
Change from Baseline to Day 302 in HINE Section 2 total score	HINE Section 2 motor milestone total score	score	50/28 mg 5.9 [4.6, 7.2]	12 mg 5.3 [3.3, 7.4] ANCOVA with MI (LS mean difference [95% CI] = 0.58 [-1.886, 3.042]; p = 0.6454		Secondary SM203 Part B 12 mg ITT set
Time to death or permanent ventilation	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) (comparison of higher dose to 12 mg dose)	% patients	50/28 mg 38% median (95% CI) time to death or permanent ventilation based on the Kaplan-Meier Method - could not be estimated HR (50/2 mg vs 12 mg) 0.701 [0.338, 1.452]; p = 0.3386	12 mg 48% median (95% CI) time to death or permanent ventilation based on the Kaplan-Meier Method - 24.7 (14.43, NA) weeks		Secondary SM203 Part B 12 mg ITT set

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Time to death (overall survival)	proportion of participants who died	%	20% estimated time to death was numerically higher in the 50/28-mg Group than the 12-mg Group, but not statistically significant based on the log-rank test stratified by disease duration (p = 0.4821) HR (50/28 mg vs 12 mg) 0.730 [0.264, 2.015]; p = 0.5431)	24%		Secondary SM203 Part B 12 mg ITT set
Change in CHOP INTEND as compared to sham procedure	Adjusted mean based in CHOP INTEND by day 183	score	15.1	-11.1 (sham procedure)	Doubtful clinical relevance, since the proposal is to propose the 50/28 dosing regimen as primary treatment regimen instead of the 12 mg	Primary endpoint SM203
CHOP INTEND total score change from baseline to Day 302	Adjusted mean based in CHOP INTEND by day 302	score	19.6	21.6	Lack of statistical significance	Key secondary endpoint SM203
Unfavourable Effects						
There were no relevant differences in terms of safety between study arms. Comparison between studies (SM203 / CS3) to sham procedure not clinically relevant.						

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The magnitude of efficacy as compared to the presently approved regimen, and the evidence to support not an alternative regimen to the 12 mg but the primarily proposed dosing regimen was what required discussion. Of note, the relative advantage of one less IT injection in favour of 50/28 mg is small, and the magnitude of the benefit also

The SM203 and 302 safety data did not disclose new AEs or a difference in prevalence, as would be expected from the population and study duration (some previously treated, others treated for a short period). The higher doses seem to have been similarly tolerated to the 12 mg dose. Notwithstanding, it is known that symptoms difficult to detect in the very young, such as those caused by hydrocephalus, have been identified outside the clinical trial scope.

From the totality of evidence on the direct comparison, there is ground to consider that the 50/28 higher dosing regimen may be initially more convenient than the 12 mg regimen, but the 12/12 regimen may be better suited for some patients and its long-term safety is well known.

3.7.2. Balance of benefits and risks

The balance of the B/R allows to consider the 50/28 mg a similarly recommended regimen, but does not substitute or overcomes the 12 mg regimen.

3.8. Conclusions

The overall benefit /risk balance of the new dosing regimen of Spinraza is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Spinraza is not similar to Zolgensma within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity

Outcome

Based on the CHMP review of data on quality safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Spinraza new strength is favourable in the following indication(s):

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Spinraza subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.