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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR SPINRAZA™ (NUSINERSEN)

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ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

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Rationale for submitting an updated RMP

Version 13.0 of this EU RMP has been created in order to note the completion of Study ISIS 396443-CS11 (SHINE), which is listed in Part IV as a post-authorisation efficacy study. This study is an open-label extension for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443-CS11. The clinical trial and postmarketing exposure has been updated.

Summary of significant changes in this RMP

In consideration of the above rationale, a summary of the significant changes implemented in Version 13.0 of this EU RMP is provided in the table below:

Module	Rationale for update	Summary of significant changes
Part I	Change due to 5-year renewal discussion.	During the Spinraza EU 5-year renewal, the EU black triangle was removed.
Part II Module SI	Alignment with current wording.	Update to incidence, prevalence, and treatment options.
Part II Module SII	Not applicable	No changes made
Part II Module SIII	Study ISIS 396443-CS11 (SHINE) completed.	Clinical trial exposure updated.

Module	Rationale for update	Summary of significant changes
Part II Module SIV	Study ISIS 396443-CS11 (SHINE) completed.	Exposure values updated.
Part II Module SV	Study ISIS 396443-CS11 (SHINE) completed.	Postmarketing exposure data updated post study completion.
Part II Module SVI	Not applicable	No changes made
Part II Module SVII	Study ISIS 396443-CS11 (SHINE) completed.	Postmarketing safety information updated.
Part II Module SVIII	Not applicable	No changes made
Part III	Alignment with current wording.	Updated term to "annual" and clarified MD location.
Part IV	Study ISIS 396443-CS11 (SHINE) completed.	Study ISIS 396443-CS11 (SHINE) completed and removed from Table 18 for planned and ongoing post-authorisation efficacy studies.
Part V	Change in risk minimisation requirement	Additional risk minimisation measures updated for Hydrocephalus
Part VI	Change in risk minimisation requirement	Additional risk minimisation measures updated for Hydrocephalus and general formatting

Module	Rationale for update	Summary of significant changes
Part VII	Study ISIS 396443-CS11 (SHINE) completed.	Annex 2: Added SHINE to the list of completed studies Annex 3: Updated format Annex 4: Added DCT forms Annex 5: SHINE removal Annex 7: References updated Annex 8: Updated procedure number and changes over time

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PART VII - ANNEXES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ADR	Adverse drug reaction
BiPAP	Bi-level positive airway pressure
CDP	Clinical Development Plan
CSF	Cerebrospinal Fluid
CNS	Central nervous system
DCT	Data collection tool
EAP	Early access programme
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FVC	Forced Vital Capacity
HLT	High Level Term
IBD	International birth date
IT	Intrathecal
ISMAC	International Spinal Muscular Atrophy Consortium
IV	Intravenous
LP	Lumbar puncture
MAH	Marketing Authorisation Holder
MDA	Muscular Dystrophy Association
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
PT	Preferred Term
PSUR	Periodic Safety Update Report
PK	Pharmacokinetic
QoL	Quality of life
RoW	rest of world
RR	Relative risk
SD	Standard deviation
SMA	Spinal Muscular Atrophy
SmPC	Summary of Medicinal Product Characteristics
SMN	Survival motor neuron
TREAT-NMD	Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases
US	United States

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Nusinersen (formerly known as BIIB058 and ISIS 396443)
Pharmacotherapeutic group(s) (ATC Code)	M09AX07
Marketing Authorisation Holder	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	SPINRAZA™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Antisense oligonucleotide (ASO) **Mode of action:** Nusinersen is an ASO specifically designed to treat SMA, an autosomal recessive progressive neuromuscular disease, due to mutations in the chromosome 5q. These mutations lead to loss of function of the survival motor neuron 1 (SMN1) gene, resulting in deficiency of SMN protein. The SMN2 gene also produces SMN protein but at low levels. SMA is a clinical spectrum of disease, with age of onset and disease severity linked to the number of SMN2 gene copies present; fewer SMN2 gene copies are associated with earlier age of onset and increased severity of symptoms. Nusinersen increases the proportion of exon 7 inclusion in *SMN2* messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the *SMN2* pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the *SMN2* mRNA. Once *SMN2* mRNA is produced, it is translated into the functional full-length SMN protein.
Hyperlink to the Product Information (PI)	[Spinraza EU SmPC]
Indication(s) in the EEA	***Current*:** Nusinersen is indicated for the treatment of 5q Spinal Muscular Atrophy.
Dosage in the EEA	***Current*:** The recommended dosage is 12 mg (5 ml) per administration. Spinraza treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter.

Pharmaceutical form(s) and strengths	***Current*:** *Form:* Solution for injection. *Strength:* Each 5 ml vial contains nusinersen sodium equivalent to 12 mg nusinersen. Each ml contains 2.4 mg of nusinersen.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of Spinal Muscular Atrophy

Epidemiology data for the indicated patient population (5q Spinal Muscular Atrophy [SMA]) is provided in the sections below.

Incidence and Prevalence

SMA is an autosomal recessive neuromuscular disease characterised 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]. Despite being a rare disease, SMA is the most common monogenetic cause of death in infants.

As a genetic disease, new cases of SMA at birth (birth prevalence) are a subset of all cases incident at conception that survive gestation.

The estimated global birth prevalence is 10 per 100,000. Among four studies from the United States (US), Sweden and Poland that used modern case definitions with genetic confirmation, the birth prevalence of SMA ranged from 8.5 to 10.3 per 100,000 live births [Prior 2010; Sugarman 2012; Arkblad 2009; Jedrzejowska 2010]. In the United Kingdom, a study of SMA prevalence in the all-age population found approximately 1.9 cases per 100,000 population as of August 1, 2007 [Norwood 2009]. In the US, a recent estimate the prevalence of SMA Types I, II and III ranged from 8,526 to 10,333 cases in 2016 [Lally, 2017].

Demographics of the population in the authorised indication and risk factors for the disease

See under Natural history of the indicated condition.

Main existing treatment options

There are 3 approved treatments for SMA. Nusinersen (Spinraza®) is an ASO that targets the *SMN2* gene for the treatment of all SMA subtypes in all ages, delivered through IT administration. It was approved in the US in 2016 and has since been approved in multiple regions worldwide, including Canada, the EU, Japan, and China.

A gene therapy agent, onasemnogene abeparvovec (Zolgensma®), is an adeno-associated viral vector expressing an *SMN1* gene delivered IV. It was approved in the US in 2019 and Japan in 2020 for the treatment of SMA Type 1 in patients younger than 2 years of age, and in the EU in May 2020 and multiple regions worldwide for the treatment of patients with 5q SMA with dosing guidance for body weight of up to 21 kg.

Risdiplam (Evrysdi™) is an oral SMN2-directed splicing modifier indicated for the treatment of SMA patients. It was first approved in the US in 2020 and EU in 2021 and has since received approval in at least 5 other markets.

Although these therapies have dramatically improved survival and motor development in SMA patients, they do not represent a cure and unmet medical need remains. For example, infantile-onset SMA patients treated with nusinersen, onasemnogene abeparvovec, or risdiplam have residual motor deficits relative to peers [Al-Zaidy 2019; Audic 2020; Kirschner 2020; Mendell 2021; Mercuri 2022].

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Based on age of symptom onset and maximal achieved motor abilities [Finkel 2015], SMA has been categorised into Types 0, I, II, III, and IV. In general, symptom onset and severity of SMA correlate with *SMN2* gene copy number in this genetic disorder [Arnold 2015]. All comorbidities described are a part of the natural disease course found in patients with SMA and are, therefore, not compared to the general population.

Type 0

Type 0 or prenatal SMA is a rare type in which infants are born with clinical signs of disease such as major contractures and respiratory compromise that often leads to the need for mechanical ventilation at or shortly after birth [Dubowitz 1999; Finkel 2015; MacLeod 1999; Mercuri 2012]. These patients usually have 1 copy of the *SMN2* gene. Death or the permanent need for ventilation typically occurs within weeks after birth.

Type I

Type I SMA is the most common form of SMA at birth, occurring in approximately 58% of cases [Ogino 2004]. Patients with Type I SMA usually have 2 or 3 copies of the *SMN2* gene, with 2 copies of the *SMN2* gene being the most common genotype [Faravelli 2015]. Patients with Type I SMA usually have symptom onset within the first 6 months of life. The earlier the symptom onset, the worse the prognosis [Thomas and Dubowitz 1994]. Initial symptoms include hypotonia/floppiness, inability to lift head/poor head control, and reduced motor activity [Borkowska 2002; Cobben 2008; Farrar 2013; Rudnik-Schoneborn 2009]. Swallowing and clearing of oral secretions are affected by 1 year of age [Wang 2007]. These infants are never able to sit without support [Russman 2007; Wang 2007]. Typically, they also lose all movement apart from residual finger, toe, and facial movements by 18 months of age [Bach 2007]. Despite limited motor function and physical interaction with their surroundings, patients with Type I SMA have normal intelligence [Chung 2004; von Gontard 2002]. Infants with Type I SMA usually develop respiratory failure, with death occurring by the age of 2.

***Pulmonary*:** Pulmonary disease, secondary to neuromuscular weakness, is the major cause of morbidity and mortality in patients with Type I SMA [Wang 2007]. Reduced chest wall and pulmonary compliance increase the mechanical load on the weak respiratory muscles (in particular the diaphragm); this imbalance between load and capacity leads to muscle fatigue and respiratory failure [Sansone 2015]. Respiratory failure may begin as nocturnal only, with the patient unable to breathe when supine [Sansone 2015], with a gradually increasing need for daytime ventilation. Patients have problems clearing airway mucus secretions leading to aspiration pneumonia, a frequent cause of death in this patient population [Sansone 2015].

As per consensus guidelines in the US, the majority of patients with Type I SMA will use respiratory care, including use of an airway clearance device (e.g., CoughAssist™), at least once

daily; BiPAP, ≥12 hours/day; and suction use hourly to aid with oral secretions, as well as medications to reduce oral secretions [Davis 2014].

***Musculoskeletal*:** Limited motor function in children with SMA results in spinal deformity; limited mobility and activities of daily living; contracture formation; and increased risk of pain, osteopenia, and fractures. Congenital fractures are often seen in patients with Type I SMA As patients with Type I SMA age, they experience an increased prevalence of kyphoscoliosis, difficulty coughing, joint contractures, and voice/speech problems due to jaw contractures or inadequate ventilatory support of voice [Wang 2007]. Scoliosis is frequently diagnosed at an early age, with significant effect on the respiratory system [Haaker and Fujak 2013].

Gastrointestinal: Gastroesophageal reflux has been reported in almost 50% of patients with Type I SMA, and most patients use acid-reducing medication for reflux, as well as medication to improve gut motility [Davis 2014]. Many patients undergo a Nissen fundoplication, a procedure used to prevent reflux, and use bowel-regulating agents [Davis 2014].

***Nutrition and Failure to Thrive*:** Nutrition is a key concern for patients with Type I SMA; patients are frequently underweight as a result of bulbar dysfunction, dysphagia, and gastrointestinal dysmotility [Davis 2014; Poruk 2012]. Almost all patients eventually rely on essential nutritional support via feeding tube e.g., nasogastric tube and gastrostomy [Davis 2014; Poruk 2012; Rudnik-Schoneborn 2009]. In addition, there are changes in body composition with decreased lean body mass and increased fat mass [Davis 2014; Poruk 2012]. Approximately one-third of patients may meet the criteria for "failure to thrive" with a weight-for-age <third percentile [Poruk 2012]. Patients with Type I SMA have lower caloric intakes than recommended for their age group, perhaps due to a diminished metabolic rate related to their decreased muscle mass; caloric intake does not increase with age [Poruk 2012].

***Cardiovascular*:** *SMN2* number may be important for normal cardiac development in patients with Type I SMA [Rudnik-Schoneborn 2008].

Type II

Type II SMA represents approximately 29% of cases at birth [Ogino 2004]. Patients with Type II SMA usually have 3 copies of the *SMN2* gene but the number can vary between 2 and 4 copies [Feldkötter 2002]. Children fail to achieve motor milestones and exhibit proximal weakness and hypotonia within the first 18 months of life [Rudnik-Schoneborn 2001]. While there is a wide spectrum of clinical phenotypes among patients with Type II SMA, this group is generally defined by an ability to sit independently but an inability to walk unaided [Finkel 2015]. 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]. Orthopaedic complications are a hallmark of Type II SMA and include scoliosis, fractures, contractures of both the upper and lower extremities, as well as hip joint involvement [Haaker and Fujak 2013]. Such patients have a shortened life expectancy [Bladen 2014], ranging from 2 years to more than 40 years of age [Faravelli 2015].

***Pulmonary*:** Similar to Type I SMA, pulmonary disease, secondary to inspiratory and expiratory muscle weakness, is the primary cause of morbidity and mortality in patients with Type II SMA [Wang 2007]. Kyphoscoliosis, a common complication among patients with Type II SMA, further contributes to the development of restrictive lung disease [Gormley 2014]. The primary respiratory complications include ineffective cough with decreased airway clearance, nocturnal

hypoventilation, diminished lung and chest wall development, and increased risk for pulmonary infection [Wang 2007]. Regarding respiratory complications, Type II SMA is significantly variable across studies. Of 100 patients with Type II SMA, 38% needed non-invasive ventilation and 15% underwent tracheostomy (country was not specified) [Ioos 2004]. On the other hand, in an Italian SMA registry, of the 202 patients with Type II SMA, 26.0% required non-invasive ventilation and only 1.5% had a tracheostomy [Sansone 2015].

***Musculoskeletal*:** Children with SMA Type II fail to pass motor milestones because of proximal muscle weakness and hypotonia within the first 18 months of life [Rudnik-Schoneborn 2001]. While there is a wide spectrum of clinical courses among patients with SMA Type II, ranging from children who may have early difficulty sitting or rolling over to those who are able to crawl and even walk with support, this group is generally defined by their ability to sit independently and inability to walk independently [Rudnik-Schoneborn 2001]. The majority of patients will reach the independent sitter milestone by age 9 months. However, the progressive nature of the disease means that, over time, some of these patients will lose their ability to sit unaided. A study of 105 Chinese patients with SMA Type II found that the probability of maintaining independent sitter status was 91.1% at 1 and 2 years and 86.4% at 5 years [Ge 2012].

Orthopedic/Bone Density: For Types II and IIIA SMA, adequate and early treatment, including surgical interventions, can significantly decelerate the disease progression and improve quality of life (QOL). Characteristic symptoms of SMA, especially Types II and IIIA SMA, include contractures of the lower extremities (with hip subluxations and dislocations), as well as contractures and hypermobile joints in the upper extremities, and less frequently fine tremor of the fingers. There is a high risk for spontaneous fractures due to osteopenia and a possible interaction between the osteoclast-stimulating factor and the SMN protein [Haaker and Fujak 2013]. Scoliosis emerges in nearly 100% of non-ambulatory patients with SMA with a severe progression and it remains one of the major problems for orthopaedic therapy [Haaker and Fujak 2013]. Scoliosis is frequently diagnosed at an early age [Haaker and Fujak 2013]. In a large retrospective observational study in China of 105 patients with Type II SMA, the average age of onset was 9 months (SD 3.8, median 8 months, range 2 to 18 months) [Ge 2012].

***Gastrointestinal*:** No studies were found.

Nutrition, Growth, and Weight: In a recent systematic review [Moore 2016] of nutrition in SMA, the prevalence of feeding or swallowing difficulties ranged from 36 to 44% in Types II and III SMA; patients with Type II SMA are at greater risk of feeding or swallowing problems than Types III or IV SMA. The inability to sit, poor head control and reliance on mechanical ventilation were associated with feeding and swallowing difficulties.

Type III

Type III SMA occurs in approximately 13% of cases [Ogino 2004]. Patients usually have 3 or 4 copies of the *SMN2* gene, and are able to stand and walk without support, but may lose these abilities as the disease progresses [Zerres and Rudnik-Schoneborn 1995]. Orthopaedic complications may be similar to those of Type II SMA [Haaker and Fujak 2013]. It has been reported that these patients generally have a normal life expectancy [Arnold 2015; Wang 2007]. Type III SMA can be further divided into Type IIIA (diagnosed at 18 to 36 months; patients walk but never run or jump well) and Type IIIB (diagnosed at 3 to 10 years; patients are able to walk, run, jump, and participate in sports) [Finkel 2015]. In a large cohort study of 329 patients

with Type III SMA (195 Type IIIA and 134 Type IIIB) evaluated for a disease duration of up to 40 years, 10 patients died and the deaths were mainly unrelated to SMA [Zerres 1997].

***Pulmonary*:** Based on a literature review by Sansone [2015], patients with Type III SMA have normal or nearly normal pulmonary function, as assessed by forced vital capacity (FVC). Patients with Type III SMA can experience a slow decline in pulmonary function over time.

***Musculoskeletal*:** Patients with SMA Type III lose muscle strength over time. Motor milestone achievement can vary greatly in Type III SMA patients at the mild end of the spectrum show little disability, walk well, and easily climb stairs, while other patients show functioning that is borderline between Types II and III, where they are barely able to stand up and take steps without assistance and may be confined to a wheelchair early in their disease course [Rudnik-Schoneborn 2001]. The distinguishing milestone achieved for Type III SMA is the ability to walk unaided. The majority of patients with Type III SMA will reach the independent walker milestone by the age of 15 months. The progressive nature of the disease means the majority of these patients will lose their ability to walk unaided around puberty. A study of 25 Chinese patients with SMA Type III found that the probability of maintaining the ability to walk was 92% at 1, 2, or 5 years, but dropped to 76.7% at 10 years [Ge 2012].

***Orthopaedic/Bone Density*:** Patients with Type IIIa SMA have orthopaedic problems that are comparable to those experienced by patients with Type II SMA, although generally with later onset and decreased severity of the disease, whereas patients with Type IIIb SMA have only mild orthopaedic disturbances. SMA-attendant fractures are a significant complication for Type IIIa SMA. Nearly 100% of patients with Type IIIa SMA have scoliosis. For patients with Type IIIb SMA, preserved standing ability can decelerate the progression of scoliosis [Haaker and Fujak 2013]

Type IV

Type IV SMA is the mildest form of SMA and its occurrence is rare. Patients 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].

SI.2 Important co-morbidities found in the target population

See under Natural history of the indicated condition.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 Summary of key safety findings from non-clinical data

Nusinersen has been evaluated in a comprehensive nonclinical programme to support its use in treating patients with SMA including studies to evaluate the pharmacology, pharmacokinetic (PK) and tissue distribution, and nonclinical safety of nusinersen. Humans are the only species known to have the SMN2 gene; therefore, the preclinical pharmacological effects of nusinersen could only be studied in genetically modified animal models or human cells. The field has developed several different mouse models of SMA ranging in disease severity. The general approach has been to use genetic engineering to remove the endogenous mouse gene and add a variable number of copies of the human SMN2 gene. Models with more copies typically have milder disease than those with fewer copies. The pharmacological properties of nusinersen were assessed in multiple models with varying degrees of disease severity. For PK/pharmacodynamic relationships, a mild model expressing 4 copies of the human SMN2 gene was used [Hsieh-Li 2000]. For mild SMA mouse models, the only recognised phenotype is loss of the tail and ear necrosis. Mouse models with more severe disease, impacting motor function and survival, were used to assess efficacy of nusinersen.

The cynomolgus monkey was chosen as the species for repeat-dose intrathecal (IT) toxicology studies for 2 major reasons. First, based on other programmes using intravenous or subcutaneous (SC) dosing, the monkey is most representative of humans with regard to ASO tissue distribution, cellular uptake, metabolism, and sensitivity to class toxicities (e.g., proinflammatory effects) [Henry 2008]. Second, the neuroanatomy of non-human primates is closer to humans compared to other commonly used toxicology species. Thus, the ability to repeatedly administer the drug in a clinically relevant manner (IT dosing) in monkeys provides the most relevant safety and exposure information for IT dosing in patients.

Based on the results of the nonclinical programme, the pharmacology, PK, and safety profiles of nusinersen have been appropriately characterised in animal and in vitro studies. The calculated safety margin for IT doses in monkeys to IT doses in humans is based on the total dose administered either in the loading or maintenance phase of dosing and different cerebrospinal fluid (CSF) volumes in the 2 species (approximately 10-fold greater absolute CSF volume in adult humans).

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2 below.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity studies	
In repeat-dose toxicity studies (14-weeks and 53-weeks) of IT administration to juvenile cynomolgus monkeys, nusinersen was well tolerated. The exception was an acute, transient deficit in lower spinal reflexes which occurred at the highest dose levels in each study (3 or 4 mg per dose; equivalent to 30 or 40 mg per IT dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours. In the 53-week IT dosing study in cynomolgus monkeys no toxicity effects were seen at levels up to 14-fold the recommended annual clinical dose.	None, given the minimal severity of the findings, lack of neurotoxicity or progression, trend toward recovery, and lack of adverse neurobehavioural effects, these findings are not considered an adverse toxic response to nusinersen.
Reproductive/developmental toxicity	
Reproductive toxicology studies were conducted using subcutaneous administration of nusinersen in mice and rabbits. Results of the 3 developmental and reproductive toxicity studies using SC dosing were negative for drug-related effects on fertility, embryo-foetal development, or prenatal and postnatal development. In 2 studies (a combined fertility/embryo-foetal development study in mice and an embryo-foetal development study in rabbits, the highest dose was 87.5 mg/kg/week. Biodistribution measurements indicated that ISIS 396443 does not cross the placenta, and therefore, maternal exposure did not lead to any toxicologically relevant exposure in the developing foetus. Parental female mice received up to 60 mg/kg/week in a study to evaluate prenatal and postnatal development effects. There were no adverse effects of ISIS 396443 in the parental females and no adverse effects on F1 animals. ISIS 396443 was detected at very low levels in milk.	No impact on male or female fertility, embryo-foetal development, or pre/post-natal development was observed. Nusinersen is considered to have a low risk for reproductive and developmental toxicity in humans.
Genotoxicity	
No evidence of genotoxicity was observed in the Ames bacterial mutagenicity and in vitro chromosomal aberrations in Chinese Hamster Ovary cells.	None, nusinersen demonstrated no evidence of genotoxicity.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Carcinogenicity	
Carcinogenicity studies have not been conducted.	Using a weight-of-evidence approach, nusinersen was found not to have carcinogenicity potential in humans and thus does not pose a meaningful carcinogenic risk for patients.
Safety Pharmacology	
In safety pharmacology studies, no pulmonary or cardiovascular effects were found in rats following continuous IT infusion for 25 days, and there were no effects on ECG in the repeat-dose IT toxicology studies in monkeys. The only safety pharmacology effects observed were transient postdose effects on lower spinal reflex that were observed at the highest doses tested in monkeys (i.e., ≥3 mg); equivalent to 30 or 40 mg per IT dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours.	None, given the minimal severity of the findings, lack of neurotoxicity or progression, trend toward recovery, and lack of adverse neurobehavioural effects, these findings are not considered an adverse toxic response to nusinersen.
Other toxicity-related information	
Drug-Drug Interactions*:* No clinical studies of interactions with other medicines have been performed. Nusinersen is metabolised via nucleases and not by the cytochrome P450 (CYP450) system. In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism. In vitro studies indicate that the likelihood for interactions with nusinersen due to competition for plasma protein binding, or competition with or inhibition of transporters is low.	None. Nusinersen is not a substrate, inhibitor, or inducer of CYP450 enzymes.

Abbreviations: IT, intrathecal; SC, subcutaneous; kg, kilogram; ECG, electrocardiogram

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Nusinersen (formerly ISIS 396443) was developed for the treatment of SMA. The nusinersen clinical development plan (CDP) was designed to evaluate nusinersen across a broad range of SMA phenotypes to address the unmet medical need in this patient population.

The nusinersen CDP includes 10 clinical studies including subjects with presymptomatic SMA, symptomatic infantile-onset SMA, and subjects with symptomatic later-onset SMA. Of the 10 clinical studies, 5 are in subjects with later-onset SMA, 2 in subjects with infantile-onset SMA, 1 in subjects with genetically diagnosed, presymptomatic SMA (presymptomatic SMA), and 2 in subjects with both infantile- and later-onset SMA. Unless stated otherwise, multiple doses of nusinersen were studied. The 10 clinical studies of nusinersen are summarised as follows:

- **Subjects with presymptomatic or infantile-onset SMA:**
    - **ISIS 396443-CS3B (CS3B)**: pivotal, multicentre, Phase 3, randomised, double-blinded, sham-procedure controlled study in symptomatic subjects with infantile-onset SMA
    - **ISIS 396443-CS3A (CS3A)**: supportive, multicentre, Phase 2, open-label (uncontrolled) study in symptomatic subjects with infantile-onset SMA
    - **232SM201 (SM201; CS5; NURTURE)**: supportive, multicentre, Phase 2, open-label (uncontrolled) study in subjects with genetically diagnosed, presymptomatic SMA
- **Subjects with later-onset SMA:**
    - **ISIS 396443-CS1 (CS1)**: Phase 1, first-in-human, single-dose, dose-escalation study
    - **ISIS 396443-CS2 (CS2)**: multicentre, Phase 1/2a open-label, dose-escalation study
    - **ISIS 396443-C10 (CS10)**: multicentre, Phase 1, single-dose, open-label extension study for subjects who participated in Study CS1
    - **ISIS 36443-CS12 (CS12)**: multicentre, Phase 1, open-label extension study in subjects who completed Studies CS2 or CS10
    - **ISIS 396443-CS4 (CS4)**: pivotal, multicentre, Phase 3, randomised, double-blinded, sham- procedure controlled study in subjects with later-onset SMA
- **Subjects with infantile- or later-onset SMA:**
    - **232SM202 (SM202; EMBRACE):** Phase 2, randomised, double-blinded, sham-procedure controlled study in subjects with SMA not eligible to participate in Studies CS3B or CS4
    - **ISIS 396443-CS11 (CS11; SHINE):** open-label extension study for subjects with SMA who previously participated in investigational studies of nusinersen, including Studies CS12, CS3B, and CS4

The evaluations of safety presented in this European Union (EU) RMP (in support of the overall benefit-risk assessment of nusinersen) focuses primarily upon the review of integrated data from these 10 studies.

In the data being reported, 9 completed studies and interim data from Study 232SM201 with cutoff date 19 Feb 2020 were used; the overall exposure to nusinersen was 2119.66 subject-years in 352 subjects. Overall exposure data are provided in Table 3, Table 4, and Table 5. Data stratified by gender/age group and race are presented in Table 6 and Table 7.

Table 3: Subjects diagnosed with SMA: Exposure to treatment (categorical)

	Infants diagnosed with SMA				
		Symptomatic infantile onset			
	Presymptomatic	Screened <= 7 months of age	Screened > 7 months of age	Later-onset SMA	All subjects treated
Number of subjects dosed	25	100	37	190	352
Number of subjects treated and followed for					
>=180 days	25 (100)	84 (84)	35 (95)	186 (98)	330 (94)
>=360 days	25 (100)	78 (78)	35 (95)	182 (96)	320 (91)
>=720 days	25 (100)	74 (74)	35 (95)	180 (95)	314 (89)
>=1080 days	25 (100)	73 (73)	34 (92)	174 (92)	306 (87)
>=1440 days	13 (52)	71 (71)	31 (84)	169 (89)	284 (81)
>=1800 days	0	68 (68)	28 (76)	160 (84)	256 (73)
>=2160 days	0	63 (63)	22 (59)	139 (73)	224 (64)
>=2520 days	0	39 (39)	7 (19)	104 (55)	150 (43)
>=2880 days	0	15 (15)	1 (3)	45 (24)	61 (17)

Note: Time on study calculated as date of last visit minus date of first dose plus one. For ongoing subjects in 232SM201, the cut-off date of 19Feb2020 was used for the last visit.

SOURCE: ISIS396443/ISS/ISS-SPRING-2024/T-EXP.SAS DATE: 26FEB2024

Table 4: Subjects diagnosed with SMA: Exposure to treatment (cumulative)

	Infants diagnosed with SMA				
		Symptomatic infantile onset			
	Presymptomatic	Screened <= 7 months of age	Screened > 7 months of age	Later-onset SMA	All subjects treated
Time on study (days)					
n	25	100	37	190	352
Mean	1438.8	1928.6	2076.8	2466.0	2199.4
SD	192.49	1113.61	680.21	841.61	939.85
Median	1471.0	2449.0	2325.0	2591.5	2444.5
25th, 75th percentiles	1273.0, 1603.0	529.5, 2674.5	1829.0, 2464.0	2122.0, 2855.0	1695.5, 2739.0
Min, Max	1114, 1737	6, 3531	65, 2883	31, 3940	6, 3940
Time on study (years)					
n	25	100	37	190	352
Mean	3.939	5.280	5.686	6.751	6.022
SD	0.5270	3.0489	1.8623	2.3042	2.5732
Median	4.027	6.705	6.366	7.095	6.693
25th, 75th percentiles	3.485, 4.389	1.450, 7.322	5.008, 6.746	5.810, 7.817	4.642, 7.499
Min, Max	3.05, 4.76	0.02, 9.67	0.18, 7.89	0.08, 10.79	0.02, 10.79
Total number of subject-years	98.48	528.02	210.38	1282.78	2119.66

Note: Time on study calculated as date of last visit minus date of first dose plus one. For ongoing subjects in 232SM201, the cut-off date of 19Feb2020 was used for the last visit.

SOURCE: ISIS396443/ISS/ISS-SPRING-2024/T-EXP.SAS DATE: 26FEB2024

Table 5: Subjects diagnosed with SMA: Number of doses received

	Infants diagnosed with SMA				
		Symptomatic infantile onset			
	Presymptomatic	Screened <= 7 months of age	Screened > 7 months of age	Later-onset SMA	All subjects treated
Number of subjects dosed	25 (100)	100 (100)	37 (100)	190 (100)	352 (100)
Number of doses received					
1	0	1 (1)	0	5 (3)	6 (2)
2	0	3 (3)	0	1 (<1)	4 (1)
3	0	6 (6)	1 (3)	4 (2)	11 (3)
4	0	9 (9)	1 (3)	2 (1)	12 (3)
5	0	2 (2)	0	0	2 (<1)
6	0	2 (2)	0	0	2 (<1)
7	0	3 (3)	0	2 (1)	5 (1)
8	0	0	0	0	0
9	0	2 (2)	0	3 (2)	5 (1)
10	0	0	1 (3)	2 (1)	3 (<1)
11	0	0	0	4 (2)	4 (1)
12	1 (4)	0	1 (3)	2 (1)	4 (1)
13	5 (20)	0	0	5 (3)	10 (3)
14	3 (12)	1 (1)	2 (5)	2 (1)	8 (2)
15	5 (20)	2 (2)	0	3 (2)	10 (3)
16	6 (24)	1 (1)	0	5 (3)	12 (3)
17	4 (16)	2 (2)	3 (8)	5 (3)	14 (4)
18	1 (4)	1 (1)	4 (11)	6 (3)	12 (3)
19	0	2 (2)	0	15 (8)	17 (5)
20	0	0	3 (8)	12 (6)	15 (4)
21	0	3 (3)	4 (11)	14 (7)	21 (6)
22	0	13 (13)	5 (14)	42 (22)	60 (17)
23	0	13 (13)	6 (16)	23 (12)	42 (12)
24	0	11 (11)	1 (3)	21 (11)	33 (9)
25	0	6 (6)	1 (3)	6 (3)	13 (4)
26	0	10 (10)	3 (8)	6 (3)	19 (5)
27	0	4 (4)	1 (3)	0	5 (1)
28	0	2 (2)	0	0	2 (<1)
29	0	1 (1)	0	0	1 (<1)
n	25	100	37	190	352
Mean	15.0	17.9	19.6	19.2	18.6
SD	1.62	8.93	5.51	5.94	6.80
Median	15.0	22.0	21.0	22.0	21.0
25th, 75th percentiles	14.0, 16.0	7.0, 24.0	18.0, 23.0	18.0, 23.0	16.0, 23.0
Min, Max	12, 18	1, 29	3, 27	1, 26	1, 29
Total amount received (mg)					
n	25	100	37	190	352
Mean	167.2	206.3	232.6	226.9	217.4
SD	18.90	106.34	66.23	71.86	82.05
Median	166.6	256.4	249.2	256.5	252.0
25th, 75th percentiles	154.8, 178.6	77.1, 281.1	212.5, 273.2	216.0, 273.2	179.0, 274.0
Min, Max	132, 202	11, 329	34, 321	6, 309	6, 329

NOTE 1: Numbers in parentheses are percentages.
2: Sham procedures performed on subjects in CS11 who have already had a loading phase in the index are not included as doses in this summary
3: Includes Final CS1, CS2, CS10, CS12, CS3A, CS3B, CS4, 232SM202, CS11 and interim data (cut-off date) for 232SM201 (19Feb2020).

SOURCE: ISIS396443/ISS/ISS-SPRING-2024/T-NUMDOSE.SAS DATE: 03APR2024

Table 6: Person-time by gender and age group - Total integrated trials

	Male		Female	
Age Group (at first dose)	N	Subject-year in study	N	Subject-year in study
<6 weeks	12	46.196	13	48.225
>=6 weeks and <2 years	66	344.715	70	393.347
>=2 years and <18 years	88	598.048	103	659.452
>=18 years	0	0.000	0	0.000

Note 1: Subjects treated with ISIS 396443 from first dose of ISIS 396443 to last known date of follow-up which may span more than one study.
2: Includes Final CS1, CS2, CS10, CS12, CS3A, CS3B, CS4, 232SM202, CS11 and interim data (cut-off date) for 232SM201 (19Feb2020).

SOURCE: ISIS396443/ISS/ISS-SPRING-2024/T-PTIME-GENDER-AGE-INTEGRATED.SAS DATE: 03APR2024

Table 7: Person-time by ethnic group - Total integrated trials

Ethnic Origin	N	Subject-year in study
American Indian or Alaska Native	3	13.229
Asian	39	221.528
Black or African American	9	49.175
White	242	1505.02
Multiple	11	69.648
Other	8	43.543
Not Reported due to Confidentiality	40	187.836

Note 1: Subjects treated with ISIS 396443 from first dose of ISIS 396443 to last known date of follow-up which may span more than one study.
2: Includes Final CS1, CS2, CS10, CS12, CS3A, CS3B, CS4, 232SM202, CS11 and interim data (cut-off date) for 232SM201 (19Feb2020).

SOURCE: ISIS396443/ISS/ISS-SPRING-2024/T-PTIME-ETHNIC-INTEGRATED.SAS DATE: 03APR2024

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The nusinersen clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (in order to protect trial patients from potential risks associated with investigational product administration), or were good clinical practice related (e.g., to ensure that proper follow-up was possible).

When evaluating the impact of these exclusion criteria in relation to the impact on the safety of patients receiving treatment with nusinersen in the post-marketing setting, key exclusion criteria pertaining to safety from pivotal studies included in the primary pooled safety dataset are addressed by the 'Contraindications' and 'Special warnings and precautions for use' sections of the SPINRAZA (nusinersen) Summary of Product Characteristics (SmPC).

Exclusion criteria from these pivotal studies that are considered as contraindications in the SmPC, and their rationale for not being considered as missing information, are discussed in Table 8.

Table 8: Exclusion criteria that remain as contraindications in relation to the assessment of missing information

Exclusion Criteria	Reason for being an exclusion criterion	Is it considered to be missing information?	Rationale
Hypersensitivity to medicinal product	Standard exclusion criterion in order to ensure patient safety.	No	The current SmPC contraindicates the use of nusinersen in patients with hypersensitivity to the active substance or to any of the excipients (as listed in SmPC Section 6.1). Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.

Abbreviations: SmPC, Summary of Medicinal Product Characteristics

A review of the key exclusion criteria in the pivotal studies which do not remain as contraindications for use, and the appropriate justifications in relation to their relevance to be considered as missing information are presented in Table 9.

Table 9: Discussion of exclusion criteria not remaining as contraindications in relation to the assessment of missing information

Criteria	Reason for being an exclusion criterion	Considered to be missing information?	Rationale
Hypoxemia (O2 saturation awake <96% or O2 saturation asleep <96%, without ventilation support) during screening evaluation.	To identify infants and children able to complete the rigors of a clinical study. Infants with hypoxemia during screening evaluation would require significant ventilator support and most likely meet the study-defined permanent ventilation criterion, which was one of the primary efficacy endpoints in studies conducted in infants with SMA.	No	Although patients with hypoxemia at screening were excluded, patients who developed respiratory compromise during the studies were allowed to receive respiratory support as needed and continued in the clinical studies, and no specific safety concern was identified in this patient population.
Signs or symptoms of SMA present at birth or within the first week after birth	These patients typically have Type 0 SMA (a rare type, in which patients usually have 1 SMN2 copy number), for which death or permanent ventilation typically occur within weeks of birth. This exclusion criterion was therefore applied for logistical reasons, in order to identify individuals physically able to complete the rigors of a clinical study.	Yes	As the mechanism of action of nusinersen is the same in all patients with SMA (regardless of SMN2 copy number), it is feasible that Type 0 patients could derive clinical benefit from nusinersen treatment. However, as this patient population was under-represented in the clinical development programme, exposure in this population is considered to be an area of missing information, and the safety of these patients will be further assessed in the post-marketing setting through routine pharmacovigilance, and through collaboration with existing disease registries.
History of brain or spinal cord disease that would interfere with the LP procedures or CSF circulation.	To avoid difficulty in administering the drug and to avoid confounding the safety assessments of nusinersen.	No	The exclusion was not due to a specific safety concern with nusinersen.

Criteria	Reason for being an exclusion criterion	Considered to be missing information?	Rationale
Presence of implanted shunt for the drainage of CSF or implanted CNS catheter	To avoid difficulty in administering the drug and to avoid confounding the safety assessments of nusinersen	No	The exclusion was not due to a specific safety concern with nusinersen.
Previous or current participation in a clinical study with an investigational gene therapy for SMA.	To avoid confounding the assessment of safety and efficacy of nusinersen.	No	The exclusion was not due to a specific safety concern with nusinersen.
Participation in a study with an investigational therapy for SMA within 6 months or five half-lives of the investigational drug, whichever is the longer, prior to the first dose of nusinersen.	To avoid confounding the assessment of safety and efficacy of nusinersen	No	The exclusion was not due to a specific safety concern with nusinersen.
Severe contractures or scoliosis as evident on X-ray.	To avoid difficulty in administering the drug and to avoid confounding the safety assessments of nusinersen.	Yes	Scoliosis does not have an impact on the mechanism of action of nusinersen, but more progressive scoliosis may potentially interfere with the intrathecal administration of the drug. The impact of scoliosis on nusinersen administration will be further assessed in the post-marketing setting through routine pharmacovigilance, through collaboration with existing disease registries, and in ongoing clinical studies.

Criteria	Reason for being an exclusion criterion	Considered to be missing information?	Rationale
Ongoing medical condition that according to the Site Investigator would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures	To identify individuals physically and mentally able to complete the rigors of a clinical study.	No	The exclusion was not due to a specific safety concern with nusinersen.

Abbreviations: O2, oxygen; SMA, Spinal Muscular Atrophy; LP, lumbar puncture; CSF, cerebrospinal fluid; CNS, central nervous system.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, due to prolonged and cumulative effects and adverse events (AEs) which have long latency; however a review of the limitations of exposure to nusinersen in the clinical development programme, and the ability to detect specific categories of adverse reactions, is provided in Table 10.

Table 10: Limitations common to clinical trial development programme

Ability to detect adverse reactions	Level of adverse reaction detection for the clinical trial programme and implications for target population
Which are rare	A total of 352 subjects with SMA were exposed to nusinersen, with 2119.66 person-years of exposure, in the clinical programme. The clinical trial database is therefore too small to detect ADRs with an incidence as low as 1/1000 person-years.
Due to prolonged exposure Due to cumulative effects	In total, 314 subjects were exposed to nusinersen for ≥ 720 days (~2 years), 306 subjects for ≥ 1080 days (~3 years), and 61 subjects have received treatment for ≥ 2880 days (over 7 years) in the clinical development programme.

Ability to detect adverse reactions	Level of adverse reaction detection for the clinical trial programme and implications for target population
Which have long latency	No evidence from the nusinersen clinical development programme of an increased risk of AEs with prolonged exposure has been obtained, and there was a trend where certain AEs decreased over time. Furthermore, no evidence for cumulative effects has been observed in the clinical study setting, and there are no known nusinersen -associated effects that have a long latency.

Abbreviations: AE, adverse event; ADR, adverse drug reaction; SMA, Spinal Muscular Atrophy.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 11 below.

Table 11: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Adult or elderly patients	At the time of enrollment in an index study, no adult patients (defined as 18-65 years of age) received treatment in the nusinersen clinical development programme. No elderly patients (defined as over 65 years of age) were included in the nusinersen development programme; however the most common form of SMA has a severely reduced life expectancy, and therefore this age cohort is not relevant to the disease.
Pregnant and/or breastfeeding women	There are no data from clinical studies on the use of nusinersen during pregnancy or lactation.
Patients with relevant comorbidities: • Hepatic impairment • Renal impairment	Patients with hepatic insufficiency and/or severe renal impairment were not studied in the nusinersen clinical development programme. Given the known PK of nusinersen and the 2′-MOE ASO class, the natural history of the target population, and the results of the clinical and nonclinical studies to date, hepatic and renal effects are not anticipated and specific hepatic or renal impairment studies were not conducted.
Patients with relevant comorbidities: • Safety profile in patients with hypoxemia	Patients with hypoxemia at screening were not studied in the nusinersen clinical development programme. Although patients with hypoxemia at screening were excluded, patients who developed respiratory compromise during the studies were allowed to receive respiratory support as needed and continued in the clinical studies.

Type of special population	Exposure
Patients with relevant comorbidities: • Safety profile in patients with severe and progressive scoliosis	Severe scoliosis as evident on X-ray was an exclusion criterion in the nusinersen clinical studies; however, there was 1 report of scoliosis and 1 case of spinal fusion surgery during the nusinersen clinical development programme.
Subpopulations carrying relevant genetic polymorphisms: • Non-5q SMA	No patients with non-5q SMA received treatment in the nusinersen clinical development programme. Cases of non-5q SMA are rare compared to 5q SMA, and they are genetically heterogeneous with diverse clinical presentations of the disease [Darras 2011]. Nusinersen does not target forms of the disease caused by mutations in genes located on chromosomes 11, 12, 14, 20, and on the X chromosome [Bertini 1989; DeLong and Siddique 1992; Harms 2010; Isozumi 1996; Mellins 1974; Ramser 2008; Takata 2004].
Subpopulations carrying relevant genetic polymorphisms: • Patients with low SMN2 copy numbers (e.g., 0 or 1) or higher SMN2 copy numbers (e.g., >4) (i.e. Type 0 or Type IV SMA patients)	No patients with Type 0 or Type IV SMA received treatment in the nusinersen clinical development programme.
Patients of different racial and/or ethnic origin	In an integrated analysis of data from the nusinersen clinical studies, of the 352 patients included in the ethnic group count, 242 were White, 39 were Asian, 9 were Black or African American, 3 were American Indian or Alaska Native, and 19 were reported as Other or Multiple. Forty participants were not reported due to confidentiality. Although the numbers of subjects with different racial and/or ethnic origins were small, no apparent difference in AE incidence was observed.

Abbreviations: ACO, antisense oligonucleotide; PK, pharmacokinetic; SMA, Spinal Muscular Atrophy.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Biogen collects data on sales, free, EAP and NPP data for exposure calculations for Spinraza from partners from several countries and regions. These data are housed in databases from the internal Biogen data provider (e.g., Biogen marketing division) and supplied to Epidemiology, upon request, by country and region. Total patient number for regional data is provided to Epidemiology as the patient number at quarter end. Discontinued and deceased patients are removed by the data provider and as a result, cumulative patient counts from the international birth date are not available.

SV.1.2 Exposure

Cumulative post-marketing exposure to nusinersen is presented in Table 12. Cumulative global patient exposure is approximately 14,869 patients representing approximately 31,079 cumulative patient-years.

This estimated exposure is based on nusinersen market data available from 23 Dec 2016 (IBD) through 31 Dec 2023.

Table 12: Estimated Post-marketing Patient Exposure by Region, IBD through 31 Dec 2023

Region	Patients Exposed in Dec 2023	Cumulative Person-Years
EEA market setting	4541	12,867
RoW market setting	8302	11,102
US marketing setting	2026	7110
Total exposed	**14,869**	**31,079**

Abbreviations: EEA = European Economic Area; IBD = International Birth Date; RoW = Rest of World; US = United States.

II: 6 PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Nusinersen has no psychoactive properties and produces no mood elevating side effects, thereby limiting the potential for abuse or misuse. Because of the different targeted mechanism of action, no potential for drug abuse is anticipated, and no formal studies were conducted to examine drug abuse. Nusinersen, an ASO, does not cross the blood-brain-barrier; thus there is no possibility of drug abuse potentially related to accidental or intentional intravenous (IV) or SC dose administration. Based on its specificity of binding to mRNA to modulate splicing of the SMN2 gene, nusinersen is not likely to bind to receptors known to be involved in drug abuse. In repeat dose toxicology studies in monkeys, neuro-behavioural assessments were within normal limits, consistent with the lack of abuse potential. Thus, nusinersen has a low potential for abuse and should not be considered a controlled substance.

Medical review of relevant AEs terms reported in the clinical studies of nusinersen was performed to identify AEs potentially related to drug abuse. This review demonstrated that the safety profile of nusinersen did not include AEs typical of drug abuse, such as mood elevation or hallucination.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

No new safety concerns have been identified since the previous version of this EU RMP (Version 12.0, dated 19 Nov 2019) was approved.

SVII.2.2 Reclassification of existing safety concerns

No safety concerns have been reclassified since the previous version of this EU RMP (Version 12.0, dated 19 Nov 2019) was approved.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks

None.

SVII.3.2 Presentation of important potential risks

SVII.3.2.1 Thrombocytopenia and coagulation abnormalities

Relevant Medical Dictionary for Regulatory Activities (MedDRA) terms: PTs: Thrombocytopenia, Coagulopathy, Coagulation factor decreased, Coagulation time prolonged, Coagulation factor IX level decreased, and Coagulation factor X level decreased.

Potential mechanisms

Whilst several different potential mechanisms for thrombocytopenic episodes have been proposed in the literature, there is no consensus of opinion on the mechanism causing such events, and it is proposed that these might differ between ASO treatments, pre-clinical test species, and in mild versus severe events observed during clinical use [Frazier 2014].

Evidence source(s) and strength of evidence

Thrombocytopenia and coagulation abnormalities have been observed after administration of some subcutaneously and intravenously administered ASOs. This topic is therefore categorised as an important potential risk based on class effects data.

Characterisation of the risk

This risk is characterised in Table 13 below.

Table 13: Characterisation of important potential risk: Thrombocytopenia and coagulation abnormalities

Frequency	**Pivotal clinical studies** ***(Source: Summary of Clinical Safety, dated 22 February 2017)*** No adverse events (AEs) of Thrombocytopenia or Coagulation abnormalities were reported in the pivotal nusinersen clinical studies. **Post-marketing setting** Cases of Thrombocytopenia (PT) and coagulation disorder (PTs) have been reported during postmarketing use in the Global Safety Database and reviewed on a periodic basis, no new safety signal was identified.
Seriousness and severity	**Pivotal clinical studies** Not applicable. **Post-marketing setting** The majority of AEs were considered non-serious.
Reversibility and long-term outcomes	**Pivotal clinical studies** Not applicable. **Post-marketing setting** The majority of AEs received were reversable and self-limiting.
Impact on quality of life (QoL)	Thrombocytopenia and coagulation abnormalities are asymptomatic conditions, and their occurrence do not impact the QoL of an individual patient *per se*. If particularly prolonged or severe, thrombocytopenia and/or coagulation abnormalities may be associated with an increased risk of bleeding/haemorrhage as adverse clinical outcomes; however, as these outcomes can range from uncomplicated bruising to severe bleeding, the impact on a patient's quality must be assessed on a case-by-case basis. Upon review of the limited number of AEs of thrombocytopenia and coagulation abnormalities received to date, there is no evidence to suggest these events have resulted in any adverse clinical consequences which would impact a patient's QoL.

Risk factors and risk groups

No specific risk factors or at-risk groups for the development of thrombocytopenia and coagulation abnormalities have been identified in patients receiving nusinersen.

Preventability

Platelet and coagulation laboratory testing may serve to mitigate the risk of developing adverse clinical consequences resulting from thrombocytopenia/coagulation abnormalities through early detection, and are recommended prior to administration of nusinersen (if clinically indicated).

Impact on the risk-benefit balance of the product

Thrombocytopenia and coagulation abnormalities are asymptomatic conditions; however, the adverse clinical consequences of such laboratory abnormalities can vary considerably, from mild symptoms of bruising to severe events of bleeding. Therefore, the impact of developing thrombocytopenia or coagulation abnormalities (if confirmed) on the risk-benefit balance of nusinersen treatment must be assessed on a case-by-case basis. Based on the analysis of available data from the post-marketing setting and the nusinersen clinical development programme, there is currently no evidence to suggest a causal association between thrombocytopenia and coagulation abnormalities and nusinersen treatment, and therefore no impact on the risk-benefit balance of the product is currently anticipated.

Nevertheless, based on data from other medications in the ASO class, the nusinersen SmPC provides information on the potential risk of thrombocytopenia and coagulation abnormalities to allow prescribers to make an adequate risk-benefit assessment for an individual patient, and to mitigate the development of any adverse clinical consequences by the early detection of such events to ensure the continuation of a favourable risk-benefit balance.

Public health impact

The frequency of AEs of thrombocytopenia and coagulation abnormalities (and haemorrhages, as a potential adverse clinical outcome measure of such abnormalities) observed to date in the post-marketing setting is low, and no conclusive evidence has been obtained which indicates a causal association with nusinersen treatment. Consequently, no impact on public heath on a population level is expected.

SVII.3.2.2 Renal toxicity

Relevant MedDRA terms: SMQs: Acute renal failure, Chronic Kidney Disease, and Proteinuria.

Potential mechanisms

Data obtained in the pre-clinical setting indicate that most renal toxicities with ASOs are generally considered to be due to accumulation of oligonucleotides within lysosomes of the proximal tubule, resulting in physiologic perturbation of tubular absorptive capacity and in some cases, increased tubular proteinuria [Henry 2008]. Cytoplasmic granule accumulation is commonly noted within particular epithelial cells with many of these molecules [Henry 2008; Marquis and Grindel 2000]), and when noted within kidney or liver epithelium, cytoplasmic granules are considered to reflect accumulation of drug-related material [Levin and Henry 2008; Monteith 1999; Monteith and Levin 1999]. At high doses, the prominence of the granules in epithelial cells correlates with an increased incidence or severity of degeneration in the kidney or liver. In chronic studies, ASO accumulation in the kidney has also been associated with an increase in chronic progressive nephropathy in rats, as occurred with mipomersen [FDA 2012].

Evidence source(s) and strength of evidence

Renal toxicity has been observed after administration of some subcutaneously and intravenously administered ASOs, and is therefore categorised as an important potential risk based on class effects data.

Characterisation of the risk

This risk is characterised in Table 15 below.

Table 14: Characterisation of important potential risk: Renal toxicity

Frequency	**Pivotal clinical studies** ***(Source: Summary of Clinical Safety, dated 22 February 2017)*** No adverse events of kidney toxicity were reported in the pivotal nusinersen clinical studies. **Post-marketing setting** In the post-marketing setting, as of a data-lock date of 30 May 2019, cumulatively 78 medically confirmed AEs of potential renal toxicity (within the SMQs used to identify relevant AEs) in 71 case reports were received. The majority (51 events; 65.4% of all reported PTs) were of PT Protein urine present (27 events; 34.6% of all reported PTs), and Proteinuria (24 events; 30.8% of all reported PTs). Of the remaining events reported, no clustering of specific PTs was noted.
Seriousness and severity	**Pivotal clinical studies** Not applicable. **Post-marketing setting** The majority of events were reported as non-serious.
Reversibility and long-term outcomes	**Pivotal clinical studies** Not applicable. **Post-marketing setting** The majority of AEs received were reversable and self-limiting.
Impact on quality of life (QoL)	As renal toxicity can manifest as a wide range of clinical conditions, with consequences ranging from sub-clinical effects to life-threatening events, the impact on a patient's quality of life is difficult to assess outside of a case-by-case basis. However, upon review of the AEs indicative of renal toxicity received to date, the majority of events were sub-clinical events of proteinuria, which were predominantly non-serious, reversable, and self-limiting, and which did not have a significant impact on the individual patient in relation to QoL.

Risk factors and risk groups

In general, drug-induced renal toxicity is more common amongst certain patients and in specific clinical situations. Patient-related risk factors for drug-induced renal toxicity applicable to the indicated patient population are underlying renal insufficiency (e.g., glomerular filtration rate of

less than 60 mL per minute per 1.73 m^2), volume depletion, diabetes, heart failure, and sepsis (Naughton 2008).

No specific risk factors for the development of renal toxicity have been identified in patients receiving nusinersen.

Preventability

Successful prevention of drug-induced renal toxicity requires an understanding of patient-related risk factors, drug-related risk factors, and pre-emptive measures, coupled with vigilance and early intervention (Naughton 2008). Urine protein testing provides an indicator of possible renal injury, and is recommended for nusinersen-treated patients (if clinically indicated) to aid in the early detection of any potential renal adverse events, and to mitigate the development of potentially more serious renal toxicity.

Impact on the risk-benefit balance of the product

Signs and symptoms of renal toxicity can vary considerably, from sub-clinical findings of proteinuria to a life-threatening compromise in renal function, therefore the impact of this safety concern (if confirmed) on the risk-benefit balance of nusinersen treatment is difficult to assess outside of an individual case-by-case basis. However, based on the analysis of available data from the post-marketing setting and the nusinersen clinical development programme, there is currently no evidence to suggest a causal association between renal toxicity and nusinersen treatment, and therefore no impact on the risk-benefit balance of the product is currently anticipated.

Nevertheless, based on data from other medications in the ASO class, the nusinersen SmPC provides information on the potential risk of renal toxicity to allow prescribers to make an adequate risk-benefit assessment for an individual patient, and to mitigate the development of any adverse clinical consequences by the early detection of such events to ensure the continuation of a favourable risk-benefit balance.

Public health impact

The frequency of AEs indicative of renal toxicity observed to date in the post-marketing setting is low, and no conclusive evidence has been obtained that indicates a causal association with nusinersen treatment. Consequently, no impact on public heath on a population level is expected.

SVII.3.2.3 Hydrocephalus

Relevant MedDRA terms: Hydrocephalus (Preferred Term [PT]), Hydrocephalic conditions (High Level Term [HLT]), Increased intracranial pressure disorders (HLT)

Potential mechanisms

Proposed mechanisms of hydrocephalus include reduced absorption or impaired flow of CSF [Beni-Adani 2006].

Evidence source(s) and strength of evidence

No events of hydrocephalus have been reported in the nusinersen clinical development programme or in nonclinical studies; however, based on the identification of 2 events of hydrocephalus in 2 patients in the post-marketing setting, a subsequent analysis of all available

data (including published literature) was performed. Subsequently, whilst a causal association between the development of hydrocephalus and exposure to nusinersen treatment by lumber puncture (LP) could not be established; on the basis of the IT mode of administration (which has been attributed to transient drug-induced inflammation and associated with chemical meningitis ([Keidan 2005; Chamberlain 2012]) and the sparse information on post-marketing reports received to date, a causal association to nusinersen could not be completely excluded. Therefore, hydrocephalus is considered to be an important potential risk of nusinersen treatment until further meaningful data can be obtained.

Characterisation of the risk

This risk is characterised in Table 15 below.

Table 15: Characterisation of important potential risk: Hydrocephalus

Frequency	**Pivotal clinical studies** ***(Source: Summary of Clinical Safety, dated 22 February 2017)*** No cases of hydrocephalus have been reported in nusinersen clinical studies. **Post-marketing setting** Cases of hydrocephalus have been reported during postmarketing use in the Global Safety Database and reviewed on a periodic basis, no new safety signal was identified and no change to risk is required.
Seriousness and severity	**Pivotal clinical studies** Not applicable. **Post-marketing setting** Of the events identified, a majority were considered serious.
Reversibility and long-term outcomes	No fatal events have been reported in nusinersen-treated patients, and in the majority of cases patients were managed by appropriate standard of care (e.g., VPS placement). Furthermore, in patients who received VPS implantation, nusinersen treatment was continued post-procedure, with no complications or sequelae reported and no complications of hydrocephalus noted.
Impact on quality of life (QoL)	Hydrocephalus can affect cognitive and physical abilities, all of which may impact QoL. However, as no data on the long-term outcomes or impact of events of hydrocephalus in nusinersen-treated patients have been received, this precludes the ability to assess any specific impact on patient QoL in relation to this safety concern.

Risk factors and risk groups

In several studies, risk factors for the development of hydrocephalus in the general population have been identified, including gender, gestational age, birth weight and maternal characteristics:

- In a Danish study of isolated and syndromic congenital hydrocephalus [Munch 2014], risk for both types increased with earlier gestational age, lower birth weight, male gender, foetal exposure to maternal diabetes, being a multiple, and delivery by caesarean-section. In addition, the rate ratios (RR) of isolated congenital hydrocephalus were increased

among children who were first-born compared with later-born (RR: 1.32, 95% Confidence Interval [CI]: 1.17-1.49) and who were exposed compared to unexposed to several maternal factors including pre-eclampsia (RR: 2.11, 95% CI: 1.50-2.97), and either antidepressant (RR: 2.52, 95% CI: (1.47-4.29)) or proton-pump inhibitor use (RR: 2.35, 95% CI: 1.26-4.41) during the first trimester of pregnancy.

- A US study [Jeng 2011] noted an increased incidence of congenital hydrocephalus among males compared with females (Odds Ratio [OR]: 1.2, 95% CI: 1.1-1.3), and patients with lower than normal birth weights (1500-2000g: OR:13.9, 95% CI: 12.3-15.8; < 1500g OR: 50.7, 95% CI: 46.8- 54.8). Asians were noted to have a lower incidence than Whites (OR: 0.7, 95% CI: 0.6-0.8), and the incidence was higher among patients with government insurance, with no insurance, or who were self-pay (OR: 1.3, 95% CI: 1.2-1.4).

Trends in gestational age and gender were also noted in other studies:

- Among the hydrocephalus cases reported in the study of 4 European countries [Garne 2010], the median gestational age among live births, foetal deaths and Termination of Pregnancy due to Foetal Anomaly were 37, 29, and 21 weeks, respectively. There was a preponderance of boys (54%) among the hydrocephalus cases (47 boys, 36 girls, and 4 with unknown gender).
- In a study of western Sweden [Persson 2007], the incidence of hydrocephalus was 2.6, 9.6, 85.0, and 231 per 10,000 children born after 36 weeks (at term), 32 to 26 weeks (moderately preterm), 28 and 32 weeks (very preterm), and before 28 weeks (extremely preterm), respectively. There were twice as many boys (64%; n = 25) as girls (36%; n = 14). Within the very preterm group, there were 10 boys (77%) and 3 girls (23%).

Additionally, risk factors for acquired hydrocephalus include haemorrhage into the subarachnoid space or ventricular system, by ruptured aneurysms, arteriovenous malformations, trauma, or systemic bleeding disorders. CNS tumours and CNS infections which both involve mechanisms that resulting in obstruction of CSF flow and/or impaired CSF absorption are also potential causes [Beni-Adani 2006].

Furthermore, studies that report the occurrence of hydrocephalus among patients following IT injection or LP have also been reported ([Keidan 2005; Chamberlain 2012]).

No specific risk factors for the development of hydrocephalus have been identified in patients receiving nusinersen.

Preventability

Not known.

Impact on the risk-benefit balance of the product

Nusinersen is approved for the orphan indication of SMA, a rare genetic disease with no other approved treatment options. Therefore, nusinersen continues to provide benefits to patients with a disease of unmet medical need.

Based on the analysis of available data from the post-marketing setting and the nusinersen clinical development programme, a causal association between the development of hydrocephalus and exposure to nusinersen treatment by LP could not be established. However, on the basis of the IT mode of administration and the post-marketing case reports received to

date, a causal association to nusinersen could not be completely excluded. Therefore, hydrocephalus is assessed as an important potential risk with nusinersen and its route of administration.

Due to the findings of hydrocephalus in infant patients, information regarding the development of hydrocephalus was added to the nusinersen reference safety information, as this event will continue to be monitored via routine pharmacovigilance activities. These activities are considered sufficient to mitigate and further characterise the important potential risk of hydrocephalus. Given the continued benefit of nusinersen treatment for patients with SMA, the benefit-risk balance of nusinersen treatment for patients with SMA remains positive.

Public health impact

Events of hydrocephalus in nusinersen-treated patients have been reported very rarely and, where reported, are considered to be manageable. Therefore, the public health impact is considered to be low.

SVII.3.3 Presentation of missing information

SVII.3.3.1 Safety profile in patients > 18 years of age

Evidence source

Real world clinical findings support the effectiveness of nusinersen to stablize or improve motor function in some SMA adult Type II and III patients.

Whilst there is no theoretical reason to suspect that patients over the age of 18 years will experience a differing safety profile to that observed in the indicated patient population, it is anticipated that adult patients with SMA may have more advanced disease, and/or additional co-morbidities not observed in paediatric patients. The safety data in the adult population are consistent with the known safety profile of nusinseren and with co-morbidities associated with the underlying disease of SMA.

Population in need of further characterisation

Safety data in patients over the age of 18 years.

SVII.3.3.2 Safety profile in patients with severe and progressive scoliosis

Evidence source

Severe scoliosis as evident on X-ray was an exclusion criterion in the nusinersen clinical studies in order to avoid difficulties in IT administration of nusinersen; however, scoliosis is an expected co-morbidity in patients with later-onset SMA. Therefore, due to their exclusion from clinical studies, the safety profile of nusinersen in patients with severe and progressive scoliosis is unknown.

Anticipated risk/consequence of the missing information

Scoliosis does not have an impact on the mechanism of action of nusinersen, but more progressive scoliosis may potentially interfere with the IT administration of the drug.

The impact of severe and progressive scoliosis on nusinersen administration will therefore be further assessed in the post-marketing setting.

SVII.3.3.3 Safety profile in patients receiving repetitive LPs

Evidence source

In the nusinersen clinical development programme, no adverse trends or patterns were identified with multiple LPs, no patients discontinued treatment due to AEs related to LPs, and no AEs such as fibrosis or arachnoiditis were reported in patients with long-term exposure (>1081 days).

Nevertheless, data are considered limited in patients with long term nusinersen treatment who have received repetitive LPs; therefore the safety profile in these patients is unknown.

Population in need of further characterisation

Safety profile in patients receiving repetitive LPs.

SVII.3.3.4 Safety profile in patients receiving long-term treatment with nusinersen

Evidence source

In the nusinersen clinical development programme 314 subjects were exposed to nusinersen for ≥ 720 days (~2 years), 306 subjects for ≥ 1080 days (~3 years), 256 subjects have received treatment for ≥ 1800 days (~5 years), 224 subjects have received treatment for ≥ 2160 days (~6 years), 150 subjects have received treatment for ≥ 2520 days (~7 years), and 61 subjects have received treatment for ≥ 2880 days (~8 years). Long-term administration of nusinersen by IT injection, in Study ISIS 396443-CS11, was safe and well tolerated in participants with infantile- and later-onset SMA and was consistent with the known safety profile of nusinersen. No new types of AEs or safety patterns or trends, or safety concerns were identified.

Nevertheless, although long-term exposure data will continue to accrue as infants and children continue to receive nusinersen, there is currently considered to be insufficient information to fully characterise the safety profile in patients receiving long-term treatment with nusinersen.

Population in need of further characterisation

The safety profile in patients receiving long-term treatment with nusinersen.

SVII.3.3.5 Safety profile in pregnant or breastfeeding women

Evidence source

Nusinersen had no adverse effects on reproductive organs or any effects on fertility, embryo-foetal development, or pre-/post-natal development in studies in rabbits and mice. However, since animal studies are not always predictive of human responses, the benefits of treatment and the potential risks should be assessed in women of childbearing potential or women who become pregnant.

Currently, no data are available to assess the safety of nusinersen use during pregnancy and/or lactation; therefore use is this population is considered to be missing information.

Population in need of further characterisation

Safety data pertaining to pregnant or breastfeeding women receiving nusinersen treatment.

SVII.3.3.6 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)

Evidence source

Patients with Type 0 and Type IV SMA are very rare and were excluded from the nusinersen clinical development programme.

The mechanism of action of nusinersen is the same across all patients, regardless of the number of SMN2 gene copies, age at onset of disease, or disease severity. However, no data are available yet in Type 0 and Type IV SMA patients, and therefore the safety profile of nusinersen in these patients is unknown.

Population in need of further characterisation

Safety data pertaining to patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme.

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The nusinersen safety specification includes the following important identified risks, important potential risks and areas of missing information (Table 16).

Table 16: 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 • 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)

Abbreviations: LP, lumbar puncture; SMA, Spinal Muscular Atrophy.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III: 1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP.

Routine Biogen pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to assess the ongoing safety profile of nusinersen throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed in order to provide further characterisation data for specific safety concerns:

- **Specific adverse reaction follow-up questionnaires for hydrocephalus:** Targeted data collection tools (DCTs) for case reports of hydrocephalus aim to collect detailed information relating to suspected hydrocephalus events in a standardised fashion, to enable timely and robust collection of data and thereby optimising risk evaluation. There are 2 DCTs issued following receipt of a case report of suspected hydrocephalus – the first aims to collect comprehensive data on the initial event (including details on risk factors, diagnostics, etc); the second is issued 6-months and 12-months after the initial event in order to collect follow-up information on clinical course and outcome information. These DCTs are provided in Annex 4.

III. 2 Additional pharmacovigilance activities

In addition to routine pharmacovigilance activities described above, the MAH will also utilise information collected in 3 existing registries to further characterise specific nusinersen safety concerns. These registries are summarised below:

- ***Registry name, including design and population:*** *Muscular Dystrophy Association (MDA) United States (US) Neuromuscular Observational Research (MOVR).* This is a prospective longitudinal registry designed to collect data in 7 disease areas — including amyotrophic lateral sclerosis, SMA, Duchenne muscular dystrophy and Becker muscular dystrophy.
  - ***Rationale and objectives:*** The registry captures clinical information on a subset (approximately 4,000) of the more than 100,000 individuals with neuromuscular diseases who are registered with the MDA. 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 based on genetic information.

Data collection in SMA patients generally include patient demographics, SMN copy numbers, motor milestones, vital status, surgical history, hospitalisations, medications, mobility, scoliosis, other comorbidities, nutritional therapies, pulmonary function and devices, and cause of death.

In relation to nusinersen, data from this registry will be used to aid in the further characterisation of the following safety concerns: 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; and 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).

- ***Milestones:*** Status updates to be provided PSUR.

- ***Registry name, including design and population:*** *International SMA Consortium (ISMAC) natural history study.* This is a longitudinal natural history study of SMA patients with the 3 regional networks that comprise the ISMAC (led by Dr. Francesco Muntoni at Great Ormond Street Hospital in the UK, Dr. Eugenio Mercuri at Universita Cattolica del Sacro Cuore in Italy, and Dr. Richard Finkel at St. Jude Children's Research Hospital in the US).
  - ***Rationale and objectives:*** The purpose 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.

    Outputs expected to include baseline characteristics of treated patients and longitudinal data on nusinersen treatment patterns, motor function, respiratory function, hospitalisations, and comorbidities.

    In relation to nusinersen, data from this registry will be used to aid in the further characterisation of the following safety concerns: 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; and 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).
  - ***Milestones:*** Status updates to be provided PSUR.

- ***Registry name, including design and population:*** *Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) Alliance registries.* This registry comprises data from multiple national longitudinal natural history studies combined under a research agreement with the TREAT-NMD Alliance. More than 7000 SMA patients worldwide have been enrolled in TREAT-NMD-associated registries. As part of this alliance exists the Global SMA Patient Registry, which consists of 37 national patient

registries representing 32 countries (20 countries in Europe), collecting data from genetically confirmed patients across the spectrum of SMA.

- ***Rationale and objectives:*** 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.

  Data are self-reported and/or provided by healthcare professionals.

  In relation to nusinersen, data from this registry will be used to aid in the further characterisation of the following safety concerns: 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; and 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).

- ***Milestones:*** Status updates to be provided PSUR.

III. 3 Summary table of additional pharmacovigilance activities

A summary of the activities included in the pharmacovigilance plan are summarised in Table 17. These activities, while listed individually, are part of a single project that is a multi-registry collaboration akin to a registry design, rather than a registry study design, as per definitions in the EMA Registry Discussion Paper, dated 05 November 2018.

Table 17: Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
• None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities that 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 based on genetic information.	• 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.

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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.

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

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 PSUR

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

A summary of the studies included in the post-authorisation efficacy studies plan are summarised in Table 18

Table 18: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study name and description Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Study 232SM201 (NURTURE) An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and presymptomatic SMA • **Status:** Ongoing	The primary objective of the study is to examine the efficacy of multiple doses of nusinersen administered IT in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA. The secondary objectives are to examine the effects of nusinersen in infants with genetically diagnosed and presymptomatic SMA on the following: development of clinically manifested SMA as determined by a composite of clinical features seen in subjects with SMA; growth and function; and safety, tolerability, and PK.	• Long term efficacy	Last patient completed	Q1 2025
			Final study report	Apr 2026

Abbreviations: IT, intrathecal; LP, lumbar puncture; PK, pharmacokinetics; SMA, Spinal Muscular Atrophy.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V: 1 Routine risk minimisation measures

Routine risk minimisation measures are in place in order to ensure the maintenance of a favourable risk-benefit balance to patients administered nusinersen.

In the post-marketing setting, routine risk minimisation measures are the SmPC and Patient Leaflet (PL), which are the primary tools to communicate information about the benefits and risks associated with the use of nusinersen. These documents provide information to the prescriber and to the patient about the identified safety concerns and relevant potential safety concerns, and how these concerns should be managed in certain circumstances.

A description of the routine risk minimisation measures per safety concern are discussed in Table 19 below.

Table 19: 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*** • 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.

Safety concern	Routine risk minimisation activities
	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 concern	Routine risk minimisation activities
• 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

Abbreviations: ADR, Adverse drug reaction; LP, lumbar puncture; PL, Patient Leaflet; SMA, Spinal Muscular Atrophy; SmPC, Summary of Medicinal Product Characteristics;.

V: 2 Additional Risk Minimisation Measures

There are no additional risk minimisation measures considered necessary for nusinersen, and routine risk minimisation activities (as described in Part V.1) are considered sufficient to manage the current safety concerns.

V: 3 Summary of risk minimisation measures

Pharmacovigilance activities and risk management activities are summarised in Table 20.

Table 20: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
• None		
Important potential risks		
• Thrombocytopenia and coagulation abnormalities	***Routine risk communication:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries
• Renal toxicity	***Routine risk communication:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries
• Hydrocephalus	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • DCT for collection of additional information relating to reported events of hydrocephalus ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
• Safety profile in patients >18 years of age	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries
• Safety profile in patients with severe and progressive scoliosis	***Routine risk minimisation measures:*** • Information and guidance in SmPC Sections 4.2 and 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries
• Safety profile in patients receiving repetitive LPs	***Routine risk minimisation measures:*** • Information in SmPC Section 4.8 and PL Section 4 ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries
• Safety profile in patients receiving long-term treatment with nusinersen	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries

Safety concern	Risk minimisation measures	Pharmacovigilance activities
• Safety profile in pregnant or breastfeeding women	***Routine risk minimisation measures:*** • Information in SmPC Section 4.6 and PL Section 2 ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • 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 minimisation measures:*** • None ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR SPINRAZA (NUSINERSEN)

Summary of Risk Management Plan for Spinraza (nusinersen)

The European (EU) Risk Management Plan (RMP) details important risks of SPINRAZA™ (nusinersen), and how more information will be obtained about the uncertainties (missing information) of administration of SPINRAZA to specific populations.

The SPINRAZA Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how SPINRAZA should be used.

This summary of the RMP for SPINRAZA should be read in the context of all available relevant information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current described safety concerns will be included in updates of the EU RMP for SPINRAZA.

I. The medicine and what it is used for

SPINRAZA is authorised for the treatment of 5q Spinal Muscular Atrophy (see SmPC for the full indication). It contains nusinersen as the active substance, and it is given by intrathecal administration by lumbar puncture.

Further information about the evaluation of the benefits of SPINRAZA can be found in the EPAR for SPINRAZA, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SPINRAZA, together with measures to minimise such risks and the proposed studies for learning more about the risks of SPINRAZA, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals, respectively;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly; and
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and

regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SPINRAZA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of SPINRAZA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be categorised as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SPINRAZA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that needs to be collected (e.g. on the long-term use of the medicine):

List of important risks and missing information	
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 • 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)

Abbreviations: LP, lumbar puncture; SMA, Spinal Muscular Atrophy.

II.B Summary of important risks

This section presents a summary of important potential risks and missing information.

Important Potential Risk: *Thrombocytopenia and coagulation abnormalities*	
Evidence for linking the risk to the medicine	Thrombocytopenia and coagulation abnormalities are categorised as an important potential risk based on class effects data with other ASO treatments.
Risk factors and risk groups	No specific risk factors or at-risk groups for the development of thrombocytopenia or coagulation abnormalities have been identified in patients receiving nusinersen.

Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: ***Renal toxicity***	
Evidence for linking the risk to the medicine	Renal toxicity is categorised as an important potential risk based on class effects data with other ASO treatments.
Risk factors and risk groups	In general, drug-induced renal toxicity is more common amongst certain patients and in specific clinical situations. Patient-related risk factors for drug-induced renal toxicity applicable to the indicated patient population are underlying renal insufficiency (e.g., glomerular filtration rate of less than 60 mL per minute per 1.73 m2), volume depletion, diabetes, heart failure, and sepsis (Naughton 2008). No specific risk factors for the development of renal toxicity have been identified in patients receiving nusinersen.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: ***Hydrocephalus***	
Evidence for linking the risk to the medicine	No events of hydrocephalus have been reported in the nusinersen clinical development programme or in nonclinical studies; however, based on the identification of 2 events of hydrocephalus in 2 patients in the post-marketing setting, a subsequent analysis of all available data (including published literature) was performed. Subsequently, whilst a causal association between the development of hydrocephalus and exposure to nusinersen treatment by lumbar puncture could not be established; on the basis of the intrathecal mode of administration (which has been attributed to transient drug-induced inflammation and associated with chemical meningitis) and the sparse information on post-marketing reports received to date, a causal association to nusinersen could not be completely excluded. Therefore, hydrocephalus is considered to be an important potential risk of nusinersen treatment until such time further meaningful data can be obtained.
Risk factors and risk groups	No specific risk factors for the development of hydrocephalus have been identified in patients receiving nusinersen.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None.
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Missing Information: ***Safety profile in patients >18 years of age***	
Risk minimisation measures	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Missing Information: ***Safety profile in patients with severe and progressive scoliosis***	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information and guidance in SmPC Sections 4.2 and 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Missing Information: ***Safety profile in patients receiving repetitive LPs***	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.8 and PL Section 4 ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Missing Information: ***Safety profile in patients receiving long-term treatment with nusinersen***	
Risk minimisation measures	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Missing Information: ***Safety profile in pregnant or breastfeeding women***	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.6 and PL Section 2 ***Additional risk minimisation measures:*** • None

Missing Information: ***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)***	
Risk minimisation measures	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

- **Study 232SM201 (NURTURE):** An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and presymptomatic SMA.
  - *Purpose of the study:* The primary purpose of this study is to examine the efficacy of repeated doses of nusinersen administered as intrathecal injections in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA.

II.C.2 Other studies in post-authorisation development plan

Other studies in the post authorisation development plan are as follows:

- **Muscular Dystrophy Association (MDA) United States (US) Neuromuscular Observation Research (MOVR) registry:** This is a prospective longitudinal registry designed to collect data in 7 disease areas — including amyotrophic lateral sclerosis, SMA, Duchenne muscular dystrophy and Becker muscular dystrophy.
  - *Purpose of the study:* 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..
- **International SMA Consortium (ISMAC) natural history study:** This is a longitudinal natural history study of SMA patients with the 3 regional networks that comprise the ISMAC (led by: Dr. Francesco Muntoni at Great Ormond Street Hospital in the UK, Dr. Eugenio Mercuri at Universita Cattolica del Sacro Cuore in Italy, and Dr. Richard Finkel at Nemours Children's Health System in the US).

- *Purpose of the study:* 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.

- **Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) Alliance registries:** This registry comprises data from multiple national longitudinal natural history studies combined under a research agreement with the TREAT-NMD Alliance.

Purpose of the study: 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.

ANNEX 4 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Adverse event follow up forms will be distributed for potential events of hydrocephalus (see Part III [*Pharmacovigilance Plan*] of the EU RMP for details).

The follow up forms for distribution are provided in this Annex below:

- Spinraza Initial Hydrocephalus Data Collection Tool (DCT)
- Spinraza Hydrocephalus DCT for Months 6 and 12 Follow-up

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Patient Information:

Name: _____

Date of Birth: _____ DD/MMM/YYYY **Age at time of onset of event:** _____

Weight at time of onset of event: _____ **Height at time of onset of event:** _____

Spinraza Administration Information: Provide the following information regarding Spinraza dosing - all administrations including up to the diagnosis of hydrocephalus and any following hydrocephalus

Indication for use: _____

Date of administration (DD/MMM/YYYY)	Dose administered (mg)	Batch/Lot number	Route	Describe any complications including bleeding, infection, multiple attempts, or other difficulties with administration
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____

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Date of administration (DD/MMM/YYYY)	Dose administered (mg)	Batch/Lot number	Route	Describe any complications including bleeding, infection, multiple attempts, or other difficulties with administration
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____

Relevant Medical History

Patient medical history of hydrocephalus	☐ None	☐ Yes, please describe/specify including onset dates: _____
Patient risk factors for hydrocephalus	☐ None	☐ Yes, please describe/specify including onset dates: _____
Family medical history of hydrocephalus or relevant risk factors	☐ None	☐ Yes, please describe/specify including onset dates: _____

Hydrocephalus Diagnostic Information

Describe the signs/symptoms/presentation and diagnostic tests that led to work-up/diagnosis of hydrocephalus including date(s) of onset in relation to Spinraza dose

_____

Type of hydrocephalus? ☐ Communicating ☐ Non-communicating ☐ Unknown

Provide details of diagnostic testing (include lab reports/radiology reports if available)

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	Date (DD/MMM/YYYY)	Results
Imaging reports (including MRI, CT, ultrasound)		Description:
CSF cell count		Result: _____ Units: _____ Reference Range: _____
CSF protein		Result: _____ Units: _____ Reference Range: _____
CSF glucose		Result: _____ Units: _____ Reference Range: _____
CSF opening pressure		Result: _____ Units: _____ Reference Range: _____
CSF culture data		Result: _____ Units: _____ Reference Range: _____
Additional CSF testing results, if applicable		Result: _____ Units: _____ Reference Range: _____ Result: _____ Units: _____ Reference Range: _____
Additional hydrocephalus diagnostic testing		Description:

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Hydrocephalus Clinical Course Information

Provide the patient's current location: ☐ Hospital ☐ Home

Provide Admission date(s) and Discharge date(s) of hospitalization

Admission Date: _____ (DD/MMM/YYYY)

Discharge Date: _____ (DD/MMM/YYYY)

Describe the patient's clinical course during hospitalization

_____

Consider providing/attaching a copy of the hospitalization/discharge summary

Hydrocephalus Treatment Information

Describe any treatments or interventions administered to the patient for hydrocephalus (i.e., including details regarding any surgical intervention)

_____

Was a ventriculoperitoneal shunt (VPS) placed? ☐ Yes ☐ No

If yes, comment on the status of VPS

_____

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For any medication treatments administered, provide the following:

Medication Name	Dose	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

Spinraza Relationship and Action Taken

In your assessment, was the event of Hydrocephalus related to Spinraza therapy?
☐ Yes ☐ No

If yes, please provide rationale for assessment:
_____

Is Spinraza therapy continuing? ☐ Yes ☐ No

If yes, please provide date of next planned dose: _____

If no, please provide stop date: _____ and reason for discontinuation: _____

If stopped and restarted, please provide stop date: _____ and restart date: _____

Signature: _____ **Date:** _____
(DD/MMM/YYYY)

Print name: _____

If relevant, any records should be faxed to Biogen Drug Safety at 888-549-1902

Biogen	Spinraza Hydrocephalus DCT for Months 6 and 12 Follow-up (Governed by DEV-SOP-836)	RD-FORM-2150 Version: 5.0 Page 1 of 6

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Patient Name: _____ **Date of Birth:** _____ DD/MMM/YYYY

Spinraza Follow-up Administration Information: Provide the following information regarding Spinraza dosing - specifically following hydrocephalus

Is Spinraza therapy continuing? ☐ Yes ☐ No

If yes, please provide date of next planned dose: _____

If no, please provide stop date: _____ and reason for discontinuation: _____

If stopped and restarted, please provide stop date: _____ and restart date: _____

Provide **date of the most recent dose**: _____ (DD/MMM/YYYY)

Provide the **administration details** for **Spinraza doses received following hydrocephalus**

Date of administration (DD/MMM/YYYY)	Dose administered (mg)	Batch/Lot number	Route	Describe any complications including bleeding, infection, multiple attempts, or other difficulties with administration
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____
			☐ Lumbar puncture ☐ Other (including but not limited to implanted devices), please specify: _____	☐ None ☐ Complication description: _____

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Hydrocephalus Clinical Course Follow-up Information

Describe the follow-up clinical course of this patient's hydrocephalus including any sequelae and / or complications of hydrocephalus or its treatment.

_____

Describe the patient's functional / mobility status

_____

Please complete and return the functional status scoring table on the following pages (HFMSE, HINE, CHOP-INTEND, WHO motor milestones)

Signature: _____ **Date:** _____
(DD/MMM/YYYY)

Print name: _____

**** If relevant, any records should be faxed to Biogen Drug Safety at 888-549-1902***

Biogen	Spinraza Hydrocephalus DCT for Months 6 and 12 Follow-up (Governed by DEV-SOP-836)	RD-FORM-2150 Version: 5.0 Page 3 of 6

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Hammersmith Functional Motor Scale-Expanded (HFMSE)

Was the Hammersmith Functional Motor Scale Assessment performed?	☐ Yes o Date and time of exam: o Evaluator: ☐ No o Reason not done:

	Score
1. Plinth/Chair sitting	
2. Long sitting	
3. One hand to head in sitting	
4. Two hands to head in sitting	
5. Supine to side lying	
6. Rolls prone to supine over R	
7. Rolls prone to supine over L	
8. Rolls supine to prone over R	
9. Rolls supine to prone over L	
10. Sitting to lying	
11. Props on forearms	
12. Lifts head from prone	
13. Prop on extended arms	
14. Lying to sitting	
15. Fourpoint kneeling	
16. Crawling	
17. Lifts head from supine	
18. Supported standing	
19. Stand unsupported	
20. Stepping	
21. Right hip flexion in supine	
22. Left hip flexion in supine	
23. High kneeling to right half kneel	
24. High kneeling to left half kneel	
25. High kneeling to standing, leading with left leg (through right half kneel)	
26. High kneeling to standing, leading with right leg (through left half kneel)	
27. Stand to sitting on the floor	
28. Squat	
29. Jumps 12 inches forward	
30. Ascends 4 stairs with railing	
31. Descends 4 stairs with railing	
32. Ascends 4 stairs without arm support	
33. Descends 4 stairs without arm support	
Total Score	
Comments:	

Biogen	Spinraza Hydrocephalus DCT for Months 6 and 12 Follow-up (Governed by DEV-SOP-836)	RD-FORM-2150 Version: 5.0 Page 4 of 6

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Hammersmith Infant Neurological Exam (HINE)

Was the Hammersmith Infant Neurological Exam performed?	☐ Yes o Date and time of exam: o Evaluator: ☐ No o Reason not done:

Section 1: Neurological Items			
	Score		Score
Cranial Nerve Function			
Facial Appearance		Eye Appearance	
Auditory Response		Visual Response	
Sucking/Swallowing			
Posture			
Head		Trunk	
Arms		Hands	
Legs		Feet	
Movements			
Quantity		Quality	
Tone			
Scarf Sign		Passive Shoulder Elevation	
Pronation/Supination		Adductors	
Popliteal Angle		Ankle Dorsiflexion	
Pulled to Sit		Ventral Suspension	
Reflexes and Reactions			
Tendon Reflexes		Arm Protection	
Vertical Suspension		Lateral Tilting	
Forward Parachute			
Section 1 Total Score:			

Section 2: Motor Milestones			
	Score		Score
Head Control		Sitting	
Voluntary Grasp		Ability to Kick	
Rolling		Crawling	
Standing		Walking	
Section 2 Total Score:			

Section 3: Behavior			
	Score		Score
State of Consciousness		Emotional State	
Social Orientation			
Section 3 Total Score:			

Biogen	Spinraza Hydrocephalus DCT for Months 6 and 12 Follow-up (Governed by DEV-SOP-836)	RD-FORM-2150 Version: 5.0 Page 5 of 6

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The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

Was the CHOP INTEND Assessment performed?	☐ Yes ○ Date and time of exam: ○ Evaluator: ☐ No ○ Reason not done:

Time from Last Feeding		Hours		Minutes

Test Item	Behavioral State	Left Side Score Left to Right Score	Right Side Score Right to Left Score	Best Score
01. Spontaneous movement (Upper extremity)				
02. Spontaneous movement (Lower extremity)				
03. Hand grip				
04. Head in midline with visual stimulation				
05. Hip adductors				
06. Rolling: elicited from legs				
07. Rolling: elicited from arms				
08. Shoulder and elbow flexion and horizontal abduction				
09. Shoulder flexion and Elbow flexion				
10. Knee extension				
11. Hip flexion and foot dorsiflexion				
12. Head control				
13. Elbow flexion				
14. Neck flexion				
15. Head/Neck extension (Landau)				
16. Spinal Incurvation (Galant)				
Total Score:				
Comments:				

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WHO (World Health Organization) Motor Milestones

Was the WHO Motor Milestones Assessment performed?	☐ Yes o Date and time of exam: o Evaluator: ☐ No o Reason not done:

	First Scale	Second Scale
Emotional State	1 - Drowsy 2 - Awake and alert	1 - Calm 2 - Fussy 3 - Crying

	Observed Examiner Report	Score
Sitting without support	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Hands and knees crawling	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Standing with assistance	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Walking with assistance	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Standing alone	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Walking alone	1 - No (inability) 2 - No (refusal) 3 - Yes 9 - Unable to test	
Comments:		

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.