COVER PAGE

Official Title:	Spinraza (Nusinersen) SMA Pregnancy Exposure Study Within Existing SMA Registries
Protocol ID:	232SM405
Study Condition:	Spinal Muscular Atrophy
Protocol Approval Date:	16 April 2025

PASS PROTOCOL

TITLE:	Spinraza (Nusinersen) SMA Pregnancy Exposure Study Within Existing SMA Registries
PROTOCOL VERSION IDENTIFIER:	232SM405
DATE OF LAST VERSION OF PROTOCOL:	27 January 2023
EU PAS REGISTER NUMBER:	EUPAS104368
ACTIVE SUBSTANCE:	Nusinersen
MEDICINAL PRODUCT:	Spinraza
PRODUCT REFERENCE:	EMEA/H/C/004312
PROCEDURE NUMBER:	N/A
MARKETING AUTHORISATION HOLDER:	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The purpose of this study is to characterize how nusinersen may affect pregnancy outcomes and infants born to women with SMA who were exposed to nusinersen during a relevant window. The primary objectives of the study are to prospectively evaluate pregnancy complications and outcomes in women with SMA who were exposed to nusinersen up to 14 months prior to the first day of their last menstrual period before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy, and to prospectively evaluate birth outcomes and adverse effects in infants born to those women. The secondary objective of the study is to evaluate pregnancy outcomes in women with SMA exposed to nusinersen as compared with women without SMA who were not exposed to nusinersen (e.g., women from external, general population comparators).
COUNTRIES OF THE STUDY:	United States, United Kingdom, [redacted], Germany, Austria, Switzerland
AUTHOR:	[redacted] ScD [redacted] Biogen

MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER (MAH):	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
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Biogen

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Protocol 232SM405 was approved by:

_____ _____

[redacted], MD Date (*DD MMM YYYY*)

[redacted] Medical Director, [redacted]

Biogen

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

AAV	adeno-associated virus
AE	adverse event
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CRO	contract research organization
EDD	estimated date of delivery
EMA	European Medicines Agency
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
FTT	failure to thrive
GSRS	Global Safety and Regulatory Sciences
GVP	Good Pharmacovigilance Practice
HCP	health care professional
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ISMAR	International Spinal Muscular Atrophy Registry
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Birth Defects Program
MCM	major congenital malformation
PK	pharmacokinetic(s)
SAE	serious adverse event
SGA	small for gestational age
SMA	spinal muscular atrophy
SMA-REACH	Spinal Muscular Atrophy Research and Clinical Hub
SMN	survival motor neuron (protein)
SMN1	survival motor neuron 1 (gene)
SMN2	survival motor neuron 2 (gene)
SMS	short message service
SOC	system organ class
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

A list of all registries, their sponsors and other key sites, with their contact information, is available upon request (see Section 14).

Qualified Person for Pharmacovigilance:

[redacted], MD

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Global Safety Officer:

[redacted], MD

Medical Director, [redacted]

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Main Author:

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Biogen

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

4. ABSTRACT

Protocol Title:	Spinraza (Nusinersen) SMA Pregnancy Exposure Study Within Existing SMA Registries
Version Number:	3.0
Date of Protocol:	16 April 2025
Name and Affiliation of Main Author:	[redacted], ScD [redacted] Biogen
Rationale and Background:	Given the current treatment landscape for SMA, those with SMA may reach fertile age and consider pregnancy. A recent literature review identified 100 reported pregnancies in a total of 67 patients with SMA. Of these patients, 18 had Type II SMA, 44 had Type III SMA, 2 had Type IV SMA, and 3 did not have SMA type reported [Abati and Corti 2018]. Therefore, it is important to evaluate how exposure to nusinersen may affect pregnancy and infant outcomes.
Research Question and Objectives:	The purpose of this study is to characterize how nusinersen may affect pregnancy outcomes and infants born to individuals with SMA who were exposed to nusinersen during a relevant window. For the purposes of this study, "relevant window" and "relevant exposure window" are defined as 14 months prior to the first day of the participant's last menstrual period before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy. **Objectives** The primary objectives of the study are: • To prospectively evaluate pregnancy complications and outcomes in individuals with SMA who were exposed to nusinersen up to 14 months prior to the first day of their last menstrual period before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy. • To prospectively evaluate birth outcomes and adverse effects in infants born to individuals with SMA who were exposed to nusinersen up to 14 months prior to the first day of their last menstrual period before conception,

	14.5 months before the date of conception, and/or at any time during their pregnancy. The secondary objective of the study is: • To evaluate pregnancy outcomes in individuals with SMA exposed to nusinersen as compared with individuals without SMA who were not exposed to nusinersen (e.g., individuals from external, general population comparators). **Pregnancy and Infant Outcome Measures** The outcome measures in nusinersen-exposed pregnant individuals and their infants include the following: • Pregnancy loss – Pregnancy termination; spontaneous abortion; fetal death (stillbirth) • Live birth – Premature birth; full-term birth • Major congenital malformations (interchangeably referred to as birth defects, congenital malformations, and congenital anomalies) • Small for gestational age birth • Ectopic pregnancy • Molar pregnancy • Maternal death occurring up to 12 weeks after delivery • Infant death occurring up to 52 weeks of age • Abnormal postnatal growth and development and neurobehavioral impairment up to 24 months of age
Study Design:	This is an observational cohort study that will utilize data prospectively collected by existing SMA registries in pregnant individuals with SMA who were exposed to nusinersen during the relevant window. There are no mandated physician visits for this study. Instead, it is expected that participants and HCPs will be contacted according to the recommended study contact schedule (Section 16). While contacts for this study are not mandated, registries will inform

	participants and HCPs of the expected contact schedule and make every effort to ensure data are entered for each expected contact. The registries will also utilize electronic medical record review to collect data when contacting participants/HCPs is not feasible. After the participant enrolled in the registry provides consent for the pregnancy study (if not already adequately covered by the existing registry consent), current demographic data, and pregnancy information, in addition to relevant medical history at the time the pregnancy is reported, will be collected. Thereafter, it is expected that the participant will be contacted once per trimester to update contact information and ascertain the occurrence of a pregnancy outcome as defined above. It is expected that the participant's obstetric HCP will be contacted at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the EDD for the Pregnancy Outcome Follow-Up. At approximately 1, 2, 6, 12, 18, and 24 months after birth, it is expected that the pediatric HCP (or the participant) will be contacted for a Pediatric Follow-Up. All data collected at the follow-up contacts will be entered into the registry.
Population:	This study will be conducted using data for pregnant individuals with SMA from the ISMAR-US, UK Adult SMA-REACH, and SMArtCARE (Austria, Germany, and Switzerland networks) registries who were exposed to nusinersen during the relevant window.
Variables:	See Section 9.3.
Data Sources:	The registries will collect data from participants with SMA who are enrolled in the registries if they become pregnant within the relevant exposure window for nusinersen. The registries will also collect data from the participants' HCPs (e.g., obstetrician, pediatrician). In addition, previously collected data on the participant from the registry will be used. If the sample size allows for comparative analysis, external population-based data sources (e.g., MACDP, EUROCAT) will provide data on background rates for pregnancy outcomes in individuals without SMA who were not exposed to nusinersen.
Study Size:	The goal of the research initiative is to enroll as many participants as possible with SMA who receive nusinersen within the relevant exposure window. Based on the estimated number of participants of

	childbearing potential currently enrolled in the registries, or who may age into childbearing years over the duration of the study, and the number of incident pregnancies observed in the registries to date, the estimated enrollment number over the 10-year study period is 20 pregnancies.
Data Analysis:	The prevalence and 95% CIs of spontaneous abortions, birth defects, SGA births, and abnormal postnatal growth and development will be calculated. Other negative pregnancy outcomes will be similarly examined as the sample size permits. The denominator for calculating reporting rates of negative pregnancy outcomes will include only prospective reports (i.e., reports received and enrolled before the outcome of the pregnancy is known). All analyses will be conducted on an overall basis as well as grouped by the earliest trimester of exposure. For birth defects, analysis will be conducted only for participants who had exposure to nusinersen in the first trimester. As appropriate and where sample size permits, MCM reporting rates, and spontaneous abortion, SGA birth, and abnormal postnatal growth and development rates may be compared with their respective rates in the MACDP and EUROCAT general population databases, acknowledging the limitations of the databases. Comparative analyses will include only prospective reports. These comparisons will be based on examination of point estimates and 95% CIs.
Milestones:	Milestone dates are provided in Section 6.

5. AMENDMENTS AND UPDATES

Table 1: Changes to Protocol 232SM405

Version No.	Date	Section of Study Protocol	Amendment or Update	Reason
2.0[a]	27 January 2023	Global	Transition from original protocol to Phase 4 Observational PASS protocol template.	To ensure alignment with the appropriate template for this EU voluntary PASS study.
3.0[a]	16 April 2025	Global	Remove [redacted] registry	[redacted]
			Replace "ISMAR-UK" with "UK Adult SMA-REACH"	The UK Adult SMA-REACH registry was misidentified as the ISMAR-UK registry in the previous versions of the protocol.
		Section 11: Safety Definitions, Recording, Reporting, and Responsibilities.	Revisions to clarify adverse event reporting	To align protocol with the procedure for adverse event reporting for this study.

[a] This protocol amendment was implemented before the initiation of data collection.

6. MILESTONES

Table 2: Milestones for Protocol 232SM405

Milestone	Planned Date
Start of data collection	September 2023
End of data collection	October 2032
Final report of study results	October 2033

7. RATIONALE AND BACKGROUND

Biogen is conducting a pregnancy study within existing SMA disease registries for patients with nusinersen exposure during pregnancy and a relevant exposure period prior to conception. For the purposes of this study, "relevant window" and "relevant exposure window" are defined as 14 months prior to the first day of the participant's last menstrual period before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy.

7.1. Profile of Previous Experience With Nusinersen

Nusinersen has been administered to 352 unique participants with SMA in 10 clinical studies, with a total of 2119.66 person-years of exposure. More than 15,000 patients have been treated with nusinersen in the postmarketing setting, Expanded Access program, and clinical trials worldwide. Nusinersen has been safe and well tolerated, as demonstrated though a long clinical development program with some patients treated for more than 10 years. The most frequent SAEs have been either in the Respiratory, thoracic and mediastinal disorders SOC or respiratory events in the Infections and infestations SOC. Overall, all SAEs reported in clinical studies have been considered unrelated to study drug and consistent with the events seen in infants and children with SMA.

The efficacy of nusinersen has been demonstrated via clinical trials across a broad range of SMA types and patients in all age groups. The primary support for the efficacy of nusinersen in the treatment of SMA derives from sham-controlled studies in participants with infantile-onset SMA and later-onset SMA [Finkel 2017a; Mercuri 2018]. Participants receiving nusinersen achieved robust and highly statistically significant improvements in motor function compared to participants in the control arm. There was also a statistically significant lower proportion of participants with infantile-onset SMA who died or reached an event of permanent ventilation in the nusinersen group; nusinersen significantly prolonged event-free survival relative to the sham-control-treated participants.

Since approval, nusinersen has also been widely used in clinical practice to treat adults with SMA. Several recent publications have provided data on the effectiveness and safety of real-world treatment with nusinersen in adults with SMA, showing beneficial effects from nusinersen treatment that are inconsistent with the natural history of the disease [Hagenacker 2020; Maggi 2020; Walter 2019].

7.1.1. Nonclinical Reproductive Toxicology Experience With Nusinersen

Reproductive toxicology studies were conducted with nusinersen in mice and rabbits.

When nusinersen (0, 3, 10, or 25 mg/kg) was administered by subcutaneous injection to mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on male or female fertility or embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

A pre- and postnatal development study in mice using nusinersen administered subcutaneously at dose levels of 5, 20, and 60 mg/kg/week was also conducted. When nusinersen was administered to pregnant female mice every other day throughout organogenesis and continuing once every 6 days throughout the lactation period, evidence of possible adverse neurobehavioral effects (sporadic statistical changes in some locomotor activities and a learning and memory deficit only in male offspring) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established. The interpretation of the findings differed from FDA; however, the FDA has requested monitoring based on their interpretation of the results. In addition, during this study systemic exposure was measured in parental females, and a dose-related increase in liver concentrations was seen (37, 111, and 251 µg/g tissue at 5, 20, and 60 mg/kg/week, respectively). In contrast, only small amounts of nusinersen were detected in the breast milk of the lactating mice. Concentrations were 0.0085, 0.025, and 0.05 µg/mL in dams exposed to 5, 20, and 60 mg/kg/week. Based on this, the potential for exposure of nursing offspring to nusinersen via breast milk is low.

7.1.2. Clinical Experience With Nusinersen in Pregnant Women

There are no adequate data on the developmental risk associated with the use of nusinersen in pregnant individuals. There are no data from clinical studies on the use of nusinersen during pregnancy in humans, and there are limited data on the use of nusinersen during pregnancy from the postmarketing setting.

There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the treatment on milk production. However, based on the available nonclinical data, the risk of nusinersen exposure through breast milk to breastfeeding children is low.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

7.2. Study Rationale

7.2.1. Overview of Spinal Muscular Atrophy

SMA is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk and neuromuscular weakness [Swoboda 2009]. Despite being a rare disease, prior to the availability of therapeutic treatment options, SMA was one of the most common genetic causes of death in infants, with a reported birth prevalence ranging from 8.5 to 10.3 per 100,000 live births [Arkblad 2009; Jedrzejowska 2010; Prior 2010; Sugarman 2012; Tassie 2013].

Infants with the most severe form of SMA are symptomatic at birth and die within the first few weeks of life. Patients with all other forms of SMA are asymptomatic following

birth. This asymptomatic phase lasts for a variable length of time but is usually correlated with disease severity; more severe disease is associated with earlier symptom onset. Historically, the natural history of SMA includes 4 major recognized phenotypes that are dependent on age at onset and achieved motor abilities. Type I SMA has a disease onset within the first few months of life; these children are never able to sit or walk and usually die from respiratory failure by 2 years of age. Patients with Type II SMA are able to sit but never walk unaided, with symptoms presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but may become severely and increasingly disabled. Patients with Type IV SMA typically have disease onset after the age of 18 years and may have normal life expectancies.

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

7.2.2. Current Therapies for Spinal Muscular Atrophy

There are several therapies available for the treatment of SMA. Nusinersen (also referred to as ISIS 396443 or Spinraza) is approved for the treatment of SMA in the US (December 2016), EU (5q SMA) [May 2017], and other major markets. It is a uniformly modified 2′-*O*-(2-methoxyethyl) antisense oligonucleotide administered intrathecally to activate continuous production of functional, full-length SMN protein within motor neurons and other cells of the central nervous system.

Risdiplam (Evrysdi; formerly RG7916), developed by Genentech, is an oral SMN2-directed splicing modifier indicated for the treatment of SMA in patients 2 months of age and older, and is approved in the US (August 2020), EU (March 2021), and Canada (April 2021). The gene transfer agent onasemnogene abeparvovec-xioi (Zolgensma), developed by AveXis and Novartis, is an AAV9 vector expressing an *SMN1* gene delivered intravenously. Zolgensma is approved in the US (May 2019) and Japan (March 2020) for the treatment of Type I SMA in patients younger than 2 years old and in the EU (May 2020) for the treatment of 5q SMA in patients who weigh up to 21 kg.

In countries where nusinersen and/or other therapies are not approved, current medical care is limited to supportive care focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery, with specific guidelines according to age at SMA onset [Finkel 2017b]; [Mercuri 2018].

7.2.3. Study Rationale

Given the current treatment landscape for SMA, individuals with SMA may reach childbearing age and consider pregnancy. Therefore, it is important to evaluate how exposure to nusinersen may affect pregnancy and infant outcomes.

In studies of SMA patients in the real-world setting, there is an approximately equal distribution of males and females with SMA [Kaufmann 2011]. Among adult patients, there is also an approximately equal distribution by sex [Kruitwagen-van Reenen 2018]. In the ISMAR registry, approximately 50% of the patients are female [Viscidi 2021].

Similar to other neuromuscular disorders, SMA has historically been considered a contraindication for pregnancy. However, with reports of successful pregnancies in those with SMA and the therapies that are currently available to treat SMA, individuals with SMA may reach childbearing age and consider pregnancy. A recent literature review identified 100 reported pregnancies in a total of 67 patients with SMA. Of these patients, 18 had Type II SMA, 44 had Type III SMA, 2 had Type IV SMA, and 3 did not have SMA type reported. This literature review concluded that prospective research on this topic is needed [Abati and Corti 2018].

Biogen recognizes the importance of disease registries in rare disease settings to capture data to further evaluate the safety and effectiveness of treatments like nusinersen in clinical practice. To that end, Biogen has established scientific collaborations with existing disease registries to support the continuation of data collection and analysis, and to build additional data collection and reporting capacity. The ISMAR-US, UK Adult SMA-REACH, and SMArtCARE SMA registries are established and well known within the SMA community and represent the largest known SMA disease registries globally [Mercuri 2019; Pechmann 2019]. They collect high-quality data that is harmonized with an internationally aligned core data set. Data from these registries have been published in peer-reviewed journals and presented at scientific meetings [Coratti 2020; Hagenacker 2020; Trucco 2021; Walter 2019].

Biogen believes that the likelihood of capturing reports of pregnant patients exposed to nusinersen will be increased by identifying patients within existing SMA registries. Furthermore, identifying pregnant patients from registries will allow for use of the existing data collected as part of the registries, in addition to using prospective data captured during pregnancy and after birth. Finally, SMA patients enrolled in existing registries may be more likely to participate in a pregnancy study because they have already consented to being enrolled in a disease registry.

In this pregnancy exposure registry-based study, eligible patients will be followed for pregnancy complications and outcomes until the end of their pregnancy and for up to 12 weeks after delivery, and infants will be followed for birth outcomes and adverse effects for approximately 2 years after birth.

The eligibility window for nusinersen exposure in this study was determined based on the half-life of nusinersen in plasma (63 to 87 days). Five times the upper range of this half-life yields a window of approximately 14.5 months (435 days). Therefore, any patient with SMA who receives a dose of nusinersen up to 14 months prior to the first day of their LMP before conception (14.5 months prior to conception) are eligible to enroll in this study.

Importantly, due to the expectation that SMA patients may also be taking risdiplam or may have recently switched from nusinersen to risdiplam, patients will be excluded from this study if they received risdiplam within a relevant exposure window prior to their

LMP before conception. This will reduce the impact of risdiplam as a confounder on any pregnancy or infant outcomes observed during the study. The apparent terminal elimination half-life of risdiplam in the SAD study BP29840 was 40.1 to 68.7 hours (from 2 to 18 mg), and the effective half-life of risdiplam based on population PK analyses was approximately 50 hours [EMA (EMEA/H/C/005145/0000) 2021]. The relevant exposure window for exclusion is 5 times the plasma half-life, or 10.4 days (using the effective half-life of 50 hours). To account for the upper range of the half-life, patients exposed to risdiplam no earlier than the first day of their LMP before conception will be excluded from this study.

Finally, given that SMA is an autosomal recessive disorder, there is a risk that a mother with SMA may transmit the disease to their children. This risk depends on the genetic status of the father. If the father does not carry the mutation, the children will be heterozygous carriers; if the father is a carrier, there is a 50% probability for the children to inherit the disease. Thus, it is possible that babies born to a mother with SMA will also have SMA. Genetic counseling should be offered to patients with SMA to discuss potential risks and screening opportunities; however, not all individuals with SMA will obtain genetic counseling and/or screening prior to pregnancy. The risk of SMA in the children of individuals with SMA, as compared with individuals in the general population, will be taken into consideration when analyzing the data on infants born to participants in this study.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

The research question of this study is to characterize how nusinersen may affect pregnancy outcomes and infants born to individuals with SMA who were exposed to nusinersen during a relevant window. For the purposes of this study, "relevant window" and "relevant exposure window" are defined as 14 months prior to the first day of the participant's LMP before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy.

8.2. Primary Objectives

The primary objectives of the study are:

- To prospectively evaluate pregnancy complications and outcomes in individuals with SMA who were exposed to nusinersen up to 14 months prior to the first day of their last menstrual period before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy.
- To prospectively evaluate birth outcomes and adverse effects in infants born to individuals with SMA who were exposed to nusinersen up to 14 months prior to the first day of their LMP before conception, 14.5 months before the date of conception, and/or at any time during their pregnancy.

The pregnancy and infant outcomes are described in Section 8.2.1 and further defined in Section 9.3.

8.2.1. Pregnancy and Infant Outcomes

Pregnancy outcomes include pregnancy loss (pregnancy termination, spontaneous abortion, and fetal death [stillbirth]) and live birth (premature birth and full-term birth). Within each of these categories, the fetus or infant will be evaluated as to the presence or absence of anomalies or other fetal effects.

Pregnancy Loss

- Pregnancy termination (any induced or voluntary fetal loss during pregnancy)
- Spontaneous abortion (< 20 weeks of gestation)
- Fetal death, including stillbirth (fetuses born dead at ≥ 20 weeks of gestation or fetuses born dead at ≥ 350 g if gestational age is unknown), which is further classified as follows:
  - Early fetal loss (fetal death occurring at ≥ 20 weeks but < 28 weeks of gestation)
  - Late fetal loss (occurring at ≥ 28 weeks of gestation)

Live Birth

- Premature birth (delivered < 37 weeks)

- Full term birth (delivered ≥ 37 weeks)

Infant deaths up to 52 weeks of age, as defined in Section 9.3, will be reported among live births.

Major Congenital Malformations

- Interchangeably referred to as congenital malformations, congenital anomalies, and birth defects.
- Abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired, as evaluated by independent advisors.

In addition, SGA births, abnormal postnatal growth and development (i.e., social/emotional, language/communication, neurocognitive, movement/physical development milestones) up to 2 years of age, ectopic pregnancies, and molar pregnancies will be reported for each pregnancy outcome (see Section 9.3). Given that SMA is a genetic condition, it is possible that babies born to an individual with SMA will also have SMA. Therefore, the diagnosis of SMA in infants will also be collected.

Maternal death during pregnancy, labor, delivery, or up to 12 weeks after delivery will be reported. Infant deaths occurring up to 52 weeks of age will also be reported.

8.3. Secondary Objectives

The secondary objective of the study is to evaluate pregnancy outcomes in individuals with SMA exposed to nusinersen as compared with individuals without SMA who were not exposed to nusinersen (e.g., individuals from external, general population comparators).

9. RESEARCH METHODS

9.1. Study Design

This is an observational cohort study utilizing data within existing SMA registries designed to evaluate pregnancy and birth outcomes in women with SMA who were exposed to nusinersen (see Section 9.3 for variables collected and reported during the study).

In an effort to ensure that this study collects, analyzes, and presents information that is accurate and useful to HCPs and others, the study will conform to the US FDA Guidance for Industry on Postapproval Pregnancy Safety Studies [FDA 2019].

9.2. Setting

Patients with SMA who are enrolled in the ISMAR-US, UK Adult SMA-REACH, and SMArtCARE SMA registries will be informed of the pregnancy study and encouraged to participate if they become pregnant within the relevant exposure window for nusinersen. The registries will collect information on the pregnancy and birth outcomes.

Reporting of pregnancy exposures to nusinersen is voluntary. Pregnancies should be reported as early as possible, ideally before prenatal testing beyond confirmatory pregnancy tests (e.g., alpha fetoprotein, sonography, amniocentesis) has been performed, but pregnancies that are reported after informative prenatal testing has been conducted will also be included in the study. Patients who test positive for a medical condition associated with negative pregnancy outcomes (e.g., syphilis) may also enroll in the study. Pregnancies with known outcomes at the time of the initial report (i.e., retrospective cases) will be included in this study but will be analyzed separately from cases in which the pregnancy outcome is unknown at the time of enrollment (i.e., prospective cases).

Pregnancies in partners of male patients who were exposed to nusinersen will not be included in the study but will be collected according to standard postmarketing pharmacovigilance practice.

The eligibility criteria and data captured in the study are intended to be uniform across all countries in which the study will be conducted. Any changes to eligibility criteria or data collection imposed by a local IRB or ethics committee will be noted in interim and final study reports.

Scientific oversight of the pregnancy study will be the responsibility of Biogen Epidemiology, while data collection and conduct of the ongoing registries will be managed by the registries.

9.2.1. Study Contact Schedule

There are no mandated physician visits for this study. Instead, it is expected that participants and HCPs will be contacted according to the recommended study contact schedule (Section 16). While contacts for this study are not mandated, registries will inform participants and HCPs of the expected contact schedule and make every effort to ensure data are entered for each expected contact. The registries will also utilize

electronic medical record review to collect data when contacting participants/HCPs is not feasible.

Pregnancy information will be collected by the registries from HCPs to determine eligibility. The registries will obtain informed consent for the pregnancy study (if not already adequately covered by the existing registry consent) prior to collecting data from the participant for the study.

After the participant enrolled in the registry provides consent for the pregnancy study, current demographic data, contact information, and pregnancy information, in addition to relevant medical history at the time the pregnancy is reported, will be collected. The contact information will be confidential and remain on site. Thereafter, it is expected that the participant will be contacted once per trimester to update contact information and ascertain the occurrence of a pregnancy outcome. It is expected that the participant's obstetric HCP will be contacted at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the EDD for the Pregnancy Outcome Follow-Up. At approximately 1, 2, 6, 12, 18, and 24 months after birth, it is expected that the pediatric HCP (or the participant) will be contacted for a Pediatric Follow-Up. All data collected will be entered into the registry. See Table 4 for a description of the expected contacts with participants and HCPs.

If the participant experiences an adverse pregnancy outcome or has a pregnancy termination or an abortion of unknown cause, the HCP is encouraged to report this outcome as soon as possible rather than to wait until the scheduled follow-up contact.

See Section 9.3.2 and Table 5 for the recommended information to be collected at different periods.

9.2.2. Study Population

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time the pregnancy is reported.

9.2.2.1. Inclusion Criteria

1. Individual who is currently pregnant (or was pregnant during the relevant exposure window; see inclusion criterion 4) and enrolled in the ISMAR-US, UK Adult SMA-REACH, or the Germany, Austria, or Switzerland network of the SMArtCARE registry.
2. Ability of the participant and/or their legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and where allowed by local regulations, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.
3. Genetic documentation of 5q SMA.
4. Documentation that the participant was exposed to nusinersen up to 14 months prior to the first day of their LMP before conception, 14.5 months before conception, and/or at any time during their pregnancy. If exact exposure dates are

unknown, the reporter must be able to estimate either the months of exposure during pregnancy or the trimester of exposure.

5. Agreement to release medical information, thereby permitting the registry to contact the participant's HCPs and the pediatric HCP for medical information.

9.2.2.2. Exclusion Criteria

1. Inability to comply with study requirements.
2. Other unspecified reasons that, in the opinion of the HCP, registry, or Biogen, make the patient unsuitable for enrollment.
3. Treatment with risdiplam at any time from the first day of their LMP, 2 weeks prior to the date of conception (approximately 5 half-lives), and/or plans to receive treatment with risdiplam during pregnancy.

9.2.3. Study Location

The study will be conducted in the US, UK, Germany, Austria, and Switzerland.

9.2.4. Study Duration

This study will be conducted for a minimum of 10 years from initiation of the first registry partnership for this study.

Each participant enrolled will be followed until the end of their pregnancy and for up to 12 weeks after delivery. Each infant will be followed for approximately 2 years after birth.

9.2.5. Lost to Follow-up

Enrolled pregnancies for which outcome information is unobtainable will be considered lost to follow-up. Before a case is considered lost to follow-up, the registry must make a minimum of monthly contact attempts over 6 months following the EDD to obtain pregnancy outcome information from the HCP. The registry will communicate with the HCP using the HCP's preferred contact method. If there is no response from the HCP, the registry will use other available contact methods based on past experience. Modes of communication with the HCP may include mail, fax, telephone, and email. The available modes of communication with the HCPs are intended to be uniform across countries in which the study will be conducted. Any changes to this imposed by a local IRB or ethics committee will be noted in interim and final study reports.

If the registry is unable to obtain the outcome of the pregnancy from the HCP, the registry may contact the participant or the secondary contact for outcome information, if consistent with local regulations.

9.2.6. Study Awareness and Outreach

Study awareness and retention initiatives will be conducted by the registries, as local regulations allow, and implemented under Biogen Epidemiology and Global Medical Safety guidance.

Steps to ensure recruitment and retention of participants will be implemented at the start of the study and may be modified as the study progresses and new enrollment information becomes available.

Active outreach will occur to increase awareness of the study and obtain reports of participants in the registries who were exposed to nusinersen during pregnancy or during the exposure window. Outreach efforts may include the following, as local regulations allow:

- Notification about the study to HCPs and patients currently participating in the registries. The following methods of communication may be used:
  - ISMAR-US, UK Adult SMA-REACH, and SMArtCARE registry websites
  - Newsletters to participants in the ISMAR-US, UK Adult SMA-REACH and SMArtCARE registries
  - FDA website listing pregnancy registries
  - National Institutes of Health ClinicalTrials.gov website
  - Patient advocacy groups
  - Scientific conferences
- Study and site engagement plan to help HCPs see the value of the study data

Apart from these potential methods of outreach, other methods will be explored, as needed. Potential recruitment efforts may also include digital and social media outreach, subject to internal compliance review and local regulations. All outreach methods will be approved by the appropriate review bodies. Awareness activities and content will be evaluated on a regular basis to ensure that target populations are being reached while minimizing burden on the recipients.

Retention will be optimized by monitoring the projected versus observed drop-out rates for the study and by modifying retention efforts for HCPs and participants as needed. In addition, a flexible follow-up schedule (e.g., telephone interviews) will be employed to allow for more convenient data collection and reduce the burden on participants and HCPs.

9.2.7. Withdrawal of Consent

Each participant or their legally authorized representative (where allowed per local regulations) has the right to withdraw consent from the study. Participation in the study will terminate immediately upon the participant's request. The registry will facilitate the withdrawal of consent process. The participant's medical data collected up until the time that consent is withdrawn will be retained and used in the study. If a participant is withdrawn from the study, Biogen's routine spontaneous postmarketing surveillance follow-up procedures will be followed (as required by local drug safety regulations) outside of this for any pregnancy outcomes and AEs.

9.2.8. Sponsor Termination of the Study

Biogen will continue the study until one or more of the following occurs:

- The feasibility of collecting sufficient information has diminished to unacceptable levels because of low exposure rates, poor enrollment, or loss to follow-up (see Section 9.2.5).
- Other methods of gathering appropriate information (e.g., electronic medical record databases) become achievable or are deemed preferable.

Early termination of the study would occur with the agreement of the appropriate regulatory authorities.

9.3. Variables

Each of the following variables will be collected and reported separately.

9.3.1. Variable Definitions

9.3.1.1. Pregnancy Loss

9.3.1.1.1. Pregnancy Termination

A pregnancy termination is defined as any induced or voluntary fetal loss during pregnancy. If possible, the reason for pregnancy termination (e.g., related to SMA, nusinersen, other) should be collected. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects.

9.3.1.1.2. Spontaneous Abortion

Spontaneous abortion is defined as any loss of a fetus due to natural causes at < 20 weeks of gestation [FDA 2002, 2019]. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects.

9.3.1.1.3. Fetal Death or Stillbirth

Fetal death or stillbirth refers to the death of a fetus prior to complete expulsion or extraction from the mother at ≥ 20 weeks of gestation [FDA 2019] (or at ≥ 350 g if gestational age is unknown). The death is indicated by the fact that, after separation from the mother, the fetus does not show any evidence of life (e.g., heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles). Fetal death occurring at ≥ 20 weeks but < 28 weeks of gestation is considered an early fetal loss. Fetal death occurring at ≥ 28 weeks is considered a late fetal loss.

In the event of a stillbirth or maternal death, full pathology details will be requested, if conducted. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects. The final classification between fetal death or stillbirth and spontaneous abortion will be made based on gestational age. If

these parameters are not available, the study will accept the classification indicated by the HCP.

9.3.1.2. Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate breathing or showing any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached. Death occurring after birth will be classified as described in Section 9.3.1.9, Section 9.3.1.10, and Section 9.3.1.11. Premature birth and full-term birth will be reported. Preterm birth will also be reported, defined as delivery at < 37 weeks gestation.

9.3.1.3. Birth Weight (Including Small for Gestational Age)

All live births will be classified as small, appropriate, or large for gestational age using the CDC definition of birth weight below the 10th percentile, between the 10th and 90th percentile, and above the 90th percentile, respectively. An infant's birth weight percentile and size for gestational age categorization will be based on World Health Organization growth charts or country-specific growth charts, as appropriate. Low birth weight (< 2500 g) will also be examined as an adverse pregnancy outcome.

9.3.1.4. Major Congenital Malformations

MCMs (interchangeably referred to as congenital malformations, congenital anomalies, and birth defects) are abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired, as evaluated by independent advisors (see Section 9.7.5).

All potential MCMs, including minor anomalies, from all countries in which the study will be conducted will be evaluated by a qualified independent teratologist or other appropriate MCM evaluator using all available medical records. The classification of all potential MCMs used in analyses will be based upon the teratologist's adjudication. The exact grouping of MCMs (e.g., major versus minor defects) will vary by analysis in order to mirror the classification systems used in the selected external comparator groups. Minor malformations, chromosomal abnormalities, genetic syndromes, positional defects, and prematurity-related defects will be excluded from major malformations in the primary analyses.

The major birth defect classification system used in this study will align with the choice of external comparator. For example, comparisons of the nusinersen-exposed participants to EUROCAT estimates will be consistent with the EUROCAT classification schema and the EMA pregnancy guidance. Similarly, the MACDP classification will be used when comparing to the MACDP external comparator. All cases will be reviewed based on earliest exposure to nusinersen.

9.3.1.5. Minor Congenital Malformation

Minor congenital malformation is defined as a structural abnormality present at birth that has a minimal effect on clinical function but may have a cosmetic effect.

9.3.1.6. Ectopic Pregnancies

Any reported ectopic pregnancy (defined as a pregnancy that occurs outside of the uterine cavity) will be subclassified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

9.3.1.7. Molar Pregnancies

Any reported molar pregnancy (defined as genetically abnormal conceptions characterized by abnormal chorionic villi, trophoblastic hyperplasia, poor fetal development, and an increased risk of malignant disease development) will be subclassified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

9.3.1.8. Maternal Death

The study defines maternal death as death of a pregnant individual during pregnancy, labor, or delivery. The study will also report maternal deaths that occur up to 12 weeks after delivery. In the event of maternal death, full pathology details will be requested.

9.3.1.9. Neonatal Death

The study defines a neonatal death as death occurring in a newborn prior to 28 days after birth. In the event of neonatal death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased newborn will be evaluated.

9.3.1.10. Perinatal Death

The study defines perinatal death as death occurring at or after 28 days and prior to 12 weeks after birth. In the event of perinatal death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased newborn will be evaluated.

9.3.1.11. Infant Death

The study defines infant death as death occurring between 12 and 52 weeks after birth, inclusive. In the event of infant death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased infant will be evaluated.

9.3.1.12. Abnormal Postnatal Growth and Development

Domains of developmental milestones (i.e., social/emotional, language/communication, neurocognitive, movement/physical development milestones) by age up to 52 weeks will be defined by guidelines provided by the CDC [CDC 2020]. As recommended by the

CDC, the World Health Organization Growth Charts (suitable for use in the US from birth to 24 months) will be applied for this study, where infant growth measurements will be used to estimate gender-specific weight-for-length, head circumference-for-age, length-for-age, and weight-for-age percentiles.

Postnatal growth deficiency or FTT will be defined as weight in the < 10th percentile for sex and chronological age using international growth reference standards from WHO for children aged 0 to 24 months. Postnatal growth deficiency will be evaluated at 1, 2, 6, 12, 18, and 24 months of age.

Infant developmental deficiency will be defined as failure to achieve developmental milestones for chronological age defined by CDC. Infant developmental deficiency will be evaluated at 1, 2, 6, 12, 18, and 24 months of age.

Developmental milestones will be collected as part of routine clinical practice with pediatrician-determined results of infant status (i.e., below, above, or at age-appropriate achievement) in each of the domains listed above. “Ages and Stages” or similar standardized assessments may be collected for this study if performed as part of routine clinical care. No additional information will be mandated for collection as part of this study.

9.3.1.13. Neurobehavioral Impairment

Neurobehavioral impairment will be assessed in infants at 2, 6, 12, 18, and 24 months based on evaluation by the pediatrician through examinations/assessments conducted in usual clinical practice.

9.3.1.14. Pregnancy Complications

The following pregnancy complications will also be monitored and reported during the study:

- Pre-eclampsia: Primary pre-eclampsia will be based on HCP-reported diagnosis. It is often defined as the presence of hypertension on 2 occasions at least 4 hours apart after 20 weeks of gestation (in an individual with a previously normal blood pressure) and proteinuria; or, in the absence of proteinuria, a new-onset hypertension accompanied by 1 of the following conditions: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms. Eclampsia is a severe, life-threatening complication of pre-eclampsia that results in seizures.
- Pregnancy-induced hypertension: High blood pressure (elevated: systolic between 120 and 129 and diastolic less than 80 mmHg; Stage 1 hypertension: systolic between 130 and 139 or diastolic between 80 and 89 mmHg; Stage 2 hypertension: systolic at least 140 or diastolic at least 90 mmHg) associated with pregnancy, as diagnosed by the treating HCP.
- Preterm labor: Preterm labor will be based on HCP-reported diagnosis. It is often characterized as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Any interventions or

treatments provided to the participant as a result of preterm labor will be collected.

- Gestational diabetes: Gestational diabetes will be based on HCP-reported diagnosis. It is often characterized by the development of carbohydrate intolerance with first onset or first recognition during pregnancy. A record of an oral glucose tolerance test during pregnancy will also be accepted for data collection, where available.
- Placenta previa: Placenta previa will be based on HCP diagnosis. It occurs when the placenta fully or partially covers the mother's cervix.

9.3.2. Information Collected at Each Timepoint

Refer to Table 5 for the recommended study contact schedule.

9.3.2.1. Enrollment

It is expected that information will be collected at the time consent is provided for the pregnancy study, as permitted by local regulations. The primary reporter of this information will be the participant and may be supplemented by information from the participant's HCP or electronic medical records. Data that have been collected as part of the core registry protocol will also be used, as applicable.

An example of the information that will be collected is as follows:

- Reporter
  - Medical specialty, if HCP
  - Telephone number and email address of the reporter
  - Date that pregnancy is reported to the registry
- Participant demographic and contact information
  - Birth year and race
  - Height
  - Weight
  - BMI will be calculated
  - Years of education
  - Occupation
  - Employment status
  - Complete name, address, telephone number, and email address*
  - Name, address, telephone number, and email address of a secondary contact outside of the participant's household in case the participant cannot be contacted*

*This information will be kept confidential and will remain on site. It will not be recorded in the data collection system or included in the study database.

- Medical history
  - Surgical and medical history
    - Relevant medical diagnoses/conditions, including but not limited to scoliosis, wheelchair use, and respiratory function
  - SMA history and genetic testing results
- Family medical history
  - Family history of adverse pregnancy outcomes, MCMs, and developmental delays
  - Family history of multiple births
- Pregnancy history
  - Previous pregnancies
    - Complications (e.g., pre-eclampsia, adverse reactions to medication)
    - Pregnancy outcome (e.g., live birth, spontaneous abortion, pregnancy termination)
    - MCMs or developmental delay
    - Birth length and birth weight of all previous live-birth infants
- Current pregnancy information
  - Date of LMP
  - EDD
  - Method of pregnancy confirmation
  - Health assessments
  - Prenatal testing
  - Outcome (if reported retrospectively)
- Pregnancy outcome risk factors
  - Smoking
  - Caffeine use (> 200 mg per day)
  - Alcohol use
  - Recreational drug use
- Nusinersen exposure history

  - The participant's complete prior and current nusinersen exposure will be captured, with dates for doses prior to and during pregnancy. If the exact dates are unavailable, the HCP or participant will provide the best approximation available (e.g., week).

- Other prior (up to 6 months before conception) and current medications (including folic acid and vitamins)

9.3.2.2. Each Trimester

It is expected that the registry will collect the following information from the participant (if consistent with local regulations) or HCP or electronic medical records at each trimester:

- Changes in participant contact information
- Changes in secondary contact information
- Pregnancy outcome risk factors
  - Smoking
  - Caffeine use (> 200 mg per day)
  - Alcohol use
  - Recreational drug use
- Changes in pregnancy status (if a pregnancy outcome has occurred, a pregnancy outcome assessment must be performed; see Section 9.3.2.4)
- Gestational age (in weeks)
- Weight gain during pregnancy
- Nusinersen exposure history and adherence
  - The participant's nusinersen exposure history will be captured, with dates for doses prior to and during pregnancy, if not already collected at an earlier timepoint. If the exact dates are unavailable, the HCP or participant will provide the best approximation available (e.g., week).
  - Delayed or missed doses (with reason) over the course of the pregnancy.
- Other current medications (including folic acid and vitamins)
- Complications during pregnancy (e.g., pre-eclampsia, adverse reaction to medication) with associated notable dates (e.g., onset, resolution)

9.3.2.3. Prenatal Follow-up

It is expected that the registry will collect changes in the following information from the participant's HCP at approximately 6 to 7 months of gestation for the Prenatal Follow-Up:

- Participant contact information
- Secondary contact information
- Medical history
- Pregnancy outcome risk factors
  - Smoking
  - Caffeine use (> 200 mg per day)
  - Alcohol use
  - Recreational drug use
- Prenatal testing
- Pregnancy status
- Gestational age (in weeks)
- Weight gain during pregnancy
- Nusinersen exposure history and adherence
  - The participant's nusinersen exposure history will be captured with dates for doses prior to and during pregnancy, if not already collected at an earlier timepoint. If the exact dates are unavailable, the HCP or participant will provide the best approximation available (e.g., week).
  - Delayed or missed doses (with reason) over the course of the pregnancy
- Other current medications (including folic acid and vitamins)
- Possible SMA symptoms as determined by the HCP (e.g., muscle weakness, change in gait, tremor, respiratory changes)
- Complications during pregnancy (e.g., pre-eclampsia, adverse reaction to medication) with associated notable dates (e.g., onset, resolution)

9.3.2.4. Pregnancy Outcome Follow-up

It is expected that the registry will collect the following information from the participant's HCP on record, from other practitioners, from electronic medical records, or from the participant, as needed, at approximately 4 weeks after the EDD:

- Pregnancy outcome risk factors
  - Smoking
  - Caffeine use (> 200 mg per day)
  - Alcohol use
  - Recreational drug use
- Weight gain during pregnancy

- Nusinersen exposure history and adherence
  - The participant's nusinersen exposure history will be captured with dates for doses prior to and during pregnancy, if not already captured at an earlier timepoint. If the exact dates are unavailable, the HCP or participant will provide the best approximation available (e.g., ± week).
  - Delayed or missed doses (with reason) over the course of the pregnancy
- Other current medications (including folic acid and vitamins)
- Possible SMA symptoms as determined by the HCP (e.g., muscle weakness, change in gait, tremor, respiratory changes) from the Prenatal Follow-Up assessment until the pregnancy outcome
- Pregnancy outcome (e.g., live birth, stillbirth, fetal loss, pregnancy termination [including reason, e.g., related to SMA, nusinersen, other], fetal anomaly)
- Type of delivery (e.g., vaginal, cesarean delivery [C-section]), including whether labor/delivery was induced early and, if applicable, the reason for induction
- Complications during pregnancy (e.g., pre-eclampsia, adverse reaction to medication) or birth (e.g., birth asphyxia) with associated notable dates (e.g., onset, resolution)
- Neonatal illnesses (e.g., prematurity, respiratory dysfunction, birth trauma) that resulted in hospitalization, including any treatments (e.g., drug therapies)
- Infant characteristics
  - Gestational age at birth (in weeks)
  - Sex
  - Weight and length
  - Head circumference
  - Birth order (for multiple births)
  - Apgar scores
  - Breastfeeding status (whether the infant is breastfeeding, bottle-fed, or both, as well as duration of breastfeeding, if applicable)
  - Genetic diagnoses, including SMA
  - Medications
  - Any MCM noted, including description and attribution
- Any untoward medical occurrence related to a pregnancy outcome, including neonatal illnesses, that could constitute an SAE as defined in Section 11 will also be reported.

The registry will contact the participant's HCP earlier in the pregnancy for outcome data if the participant reports an adverse pregnancy outcome or a pregnancy termination. Additional information and reports will be requested and collected for adverse pregnancy outcomes in the mother and infant as necessary, including autopsy and other pathology reports.

9.3.2.5. Pediatric Follow-up

It is expected that the following information will be collected from the pediatric HCP (or the participant, as necessary) when the infant is approximately 1, 2, 6, 12, 18, and 24 months of age:

- Pediatric illnesses (e.g., prematurity, respiratory dysfunction, birth trauma) that resulted in hospitalization, including any treatments (e.g., drug therapies)
- Infant characteristics
  - Head circumference
  - Feeding behavior
  - Weight and length
  - Developmental milestones (including postnatal growth deficiency or failure to thrive [FTT], infant development deficiency, and neurobehavioral impairment). Note: neurobehavioral impairment will be measured starting at 2 months of age.
  - Breastfeeding status (whether the infant is breastfeeding, bottle-fed, or both, as well as duration of breastfeeding, if applicable)
  - Genetic diagnoses, including SMA
  - Medications
- Evidence of any abnormality since last follow-up

Additional information and reports will be requested and collected for adverse pregnancy outcomes in the mother (i.e., death up to 12 weeks after delivery) and infant as necessary, including autopsy and other pathology reports.

9.4. Data Sources

Data will be participant- and clinician-reported. The registries will collect data from participants with SMA who are enrolled in the ISMAR-US, UK Adult SMA-REACH, and SMArtCARE SMA registries if they become pregnant within the relevant exposure window for nusinersen. Participants will be consented and enrolled through the registries (see information on informed consent in Section 10.2). The registries will also collect data from the participants' HCPs (e.g., obstetrician, pediatrician) and electronic medical records. In addition, previously collected data for the participant from the registry will be used. Biogen will receive data in the form of aggregate summary tables.

It is expected that participants and HCPs will be contacted according to the details outlined in Section 9.3.2 and the recommended study contact schedule (Section 16). While contacts for this study are not mandated, registries will inform participants and HCPs of the expected contact schedule and make every effort to ensure data are entered for each expected contact.

If the sample size allows for comparative analysis, reporting rates from the study will be compared with available background rates for pregnancy outcomes in women without SMA who were not exposed to nusinersen using the MACDP and EUROCAT general population databases, as appropriate (see Section 9.7.3.2).

9.5. Study Size

The goal of the research initiative is to enroll as many participants with SMA who receive nusinersen during pregnancy (or within the relevant exposure window) as possible. Based on the number of individuals of childbearing potential currently enrolled in the registries or who come of childbearing age over the duration of the study and the number of incident pregnancies observed in the registries to date, the estimated enrollment number over the 10-year study period is 20 pregnancies.

As of August 2024, the UK Adult SMA-REACH registry has approximately 285 genetically confirmed SMA patients with 72 using nusinersen [Walker 2024]. In the SMArtCARE registry, as of May 2021, there were 965 SMA patients enrolled. This includes 147 women of childbearing age, of whom 117 have been treated with nusinersen.

While enrollment may slow over time, some increase in new patients is expected in all of the registries. In addition to newly enrolled patients, younger patients are expected to reach childbearing age over the next few years. Together, these factors should lead to an increase in individuals of childbearing age in the registries, which will increase the likelihood of capturing incident pregnancies.

9.6. Data Management

Data management and statistical software to be used in the study, including procedures for data collection, retrieval, and preparation, are outlined in the statistical analysis plan. Data collection and management will be handled by the registries.

9.7. Data Analysis

9.7.1. General Discussion of the Analysis

All participants will be reviewed based on earliest exposure within the relevant nusinersen exposure window.

The registries and Biogen Epidemiology and Global Safety will carefully review each pregnancy outcome and the frequency of adverse pregnancy outcomes. For this study, gestational weeks are calculated beginning from the first day of the participant's LMP. If the date of LMP is not available, the EDD may be used. If the gestational week is

inconsistent with the exposure dates and/or the dates of outcomes (outside of 1 week for the first trimester, outside of 2 weeks for the second and third trimesters) and a corrected EDD (i.e., generally by ultrasound) is available, the corrected EDD is used for gestational week calculations.

Descriptive analyses will be performed to analyze the risks of MCMs, spontaneous abortions, SGA births, and abnormal postnatal growth and development.

Statistical analyses may be performed to examine potential increases in risks of MCMs, spontaneous abortions, SGA births, and abnormal postnatal growth and development as compared with the expected background prevalence. The prevalence and 95% CIs for study participants may be calculated to assess the presence of any excessive risk associated with nusinersen exposure.

All analyses will be conducted on an overall basis as well as grouped by the earliest trimester of exposure. For MCMs, analyses will be conducted only for participants who have exposure in the first trimester. In the absence of treatment initiation during the second and third trimester of pregnancy, the subgroups with small sample sizes may be collapsed as needed. Other adverse pregnancy outcomes will be examined similarly as the sample size permits.

A periodic review of the study will be performed by monitoring reports of adverse pregnancy outcomes for nusinersen (see Section 9.7.4).

9.7.2. Analysis Population

The primary population for analysis will be prospective reports of pregnancies exposed to nusinersen. Participants who enroll after the outcome of pregnancy is known will be enrolled as retrospective cases but will not be included in the primary analysis.

Analyses of MCMs, spontaneous abortions, SGA births, and abnormal postnatal growth and development may be conducted on the following subgroups:

- Participants who enroll prior to prenatal testing as well as participants who enroll after prenatal testing
- Participants who enroll after prenatal diagnosis showing any major structural defects
- Participants with similar characteristics to comparator data (e.g., MACDP, EUROCAT), if applicable

9.7.3. Methods of Analysis

Each pregnancy outcome will be classified into the categories described in Section 9.3 and will be collected and reported separately. Data will be presented in aggregate tables in the interim and final reports.

All analyses will be conducted on an overall basis, as well as stratified by earliest trimester of exposure. For MCMs, analyses will be conducted only for participants who have exposure in the first trimester. The prevalence and 95% CIs of spontaneous abortions, MCMs, SGA births, and abnormal postnatal growth and development will be

calculated. Other negative pregnancy outcomes will be similarly examined as the sample size permits. Infants with minor malformations, chromosomal abnormalities, genetic syndromes, positional defects, and prematurity-related defects will be excluded from the primary analyses related to MCM prevalence; these outcomes will be reported in the interim and final reports. Details of the analysis will be provided in the statistical analysis plan.

If sufficient enrollment numbers are obtained, analyses will also be stratified according to maternal age, gestational age at enrollment, medical condition at time of pregnancy that may affect pregnancy outcome (including but not limited to respiratory, neuropsychiatric, metabolic, cardiovascular, infectious, hematological disease or impairment), and other important risk factors (e.g., concurrent medications and substance use).

Demographic information, clinical characteristics, and other potential factors that may affect pregnancy outcome will be described.

The actual date of delivery (not the EDD) will be used in all analyses. EDD will only be used to schedule outreach to HCPs to ascertain the outcome of an expected birth.

For each interim analysis, pregnancy and infant outcomes will be analyzed cumulatively from the beginning of the study.

9.7.3.1. Pregnancy Reporting Rates

The denominator for calculating reporting rates of negative pregnancy outcomes will include prospective reports where prospective registration is defined as a report of a pregnancy exposed to nusinersen enrolled before the outcome of the pregnancy is known (see Section 9.9, which discusses potential biases).

9.7.3.1.1. Spontaneous Abortion

The prevalence of spontaneous abortion reported to the study will be calculated by dividing the number of fetal losses occurring at < 20 weeks of gestational age by the total number of pregnancies. If sufficient enrollment numbers are obtained, analysis of spontaneous abortions may be stratified by earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition that may result in negative pregnancy outcomes, and other maternal risk factors, as appropriate. Sensitivity analyses may be performed for spontaneous abortions and may be stratified by each trimester, along with these factors, when the sample size allows.

The 95% CIs for spontaneous abortion rates will be calculated based on the binomial distribution. If sufficient enrollment numbers are obtained, spontaneous abortion rates may also be presented in subgroups by the earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition, and other maternal risk factors at enrollment, as appropriate.

In addition, time to spontaneous abortion will be analyzed using the Kaplan-Meier method.

9.7.3.1.2. Major Congenital Malformations

The prevalence of MCMs (referred to as birth defects in EUROCAT) reported to the study will be calculated using EUROCAT conventions (http://www.eurocat-network.eu/accessprevalencedata/interpretationguide/calculationofprevalencerates). The prevalence of 1 or more MCMs in addition to the prevalence of specific MCMs will be calculated as follows:

Total Prevalence of Teratologist-Confirmed MCMs = Number of Teratologist-Confirmed Cases / Number of Births (Live and Still)

Other formulas for prevalence may be used to calculate estimates for comparisons to other background rates from other sources.

The analysis of MCM outcomes will be conducted only for participants who have exposure during the first trimester, adjusting for maternal age, medical condition, and other maternal risk factors at enrollment, as appropriate. Sensitivity analyses may be performed for MCMs and may be stratified by each trimester, along with the above factors, when the sample size allows.

The 95% CIs for MCM rates will be calculated based on the binomial distribution.

9.7.3.1.3. Small for Gestational Age Births

The prevalence of SGA births reported to the study will be calculated by dividing the number of SGA births by the total number of live births. If sufficient enrollment numbers are obtained, analysis of SGA births may be stratified by earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition, and other maternal risk factors, as appropriate. Sensitivity analyses may be performed for SGA births and may be stratified by each trimester, along with these factors, when the sample size allows.

The 95% CIs for SGA birth rates will be calculated based on the binomial distribution. If sufficient enrollment numbers are obtained, SGA birth rates may also be presented in subgroups by the earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition, and other maternal risk factors at enrollment, as appropriate.

9.7.3.1.4. Abnormal Postnatal Growth and Development

The prevalence of abnormal postnatal growth and development reported to the study will be calculated by dividing the number of events of abnormal postnatal growth and development by the total number of live births. If sufficient enrollment numbers are obtained, analysis of abnormal postnatal growth and development may be stratified by earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition, and other maternal risk factors, as appropriate. Sensitivity analyses may be performed for abnormal postnatal growth and development and may be stratified by each trimester, along with the above factors, when the sample size allows.

The 95% CIs for abnormal postnatal growth and development rates will be calculated based on the binomial distribution. If sufficient enrollment numbers are obtained, abnormal postnatal growth and development rates may also be presented in subgroups by

the earliest trimester of exposure, gestational age at enrollment, maternal age, medical condition, and other maternal risk factors at enrollment, as appropriate.

9.7.3.2. Comparative Analysis

As appropriate and where the sample size permits, MCM reporting rates, spontaneous abortion, SGA births, and abnormal postnatal growth and development rates from the study may be compared with their respective rates in the MACDP and EUROCAT general population databases, acknowledging the limitations of the databases. Robust SMA population-based reporting rates drawn from large SMA populations are unavailable, and rates from the general population remain the primary estimates with which comparisons can be made.

In order to minimize the differences between the comparison groups, subgroup analyses may be conducted, as appropriate, on subsets of the study defined by factors that better reflect the underlying population of the external data sources, such as age and nationality (e.g., within the EU, birth defect rates in the study compared to the general population via EUROCAT).

Comparative analyses will include only prospective reports (i.e., reports received before the outcome of the pregnancy is known). These comparisons will be based on examination of point estimates and 95% CIs. In addition to comparisons of infant outcomes (i.e., MCMs) based on events ascertained up to 52 weeks after birth, comparisons will be based on infant outcomes ascertained up to 12 weeks after birth in order to mirror the ascertainment period used in previous Biogen pregnancy registries.

9.7.4. Interim Analyses

Data from the study will be presented at least annually in descriptive summary reports. For each interim analysis, pregnancy and infant outcomes will be analyzed cumulatively from the beginning of the study.

9.7.5. Independent Advisors

A qualified independent teratologist or other appropriate MCM evaluator will be used throughout the study for evaluation of MCMs and other significant findings. An independent advisory board, consisting of the qualified independent teratologist and at least two other experts in pregnancy and/or maternal-infant health and/or reproductive epidemiology, will review and confirm the MCM evaluations as well as pregnancy outcome data on an annual basis. If deemed necessary by the external advisors, Biogen may also consult with other experts in relevant specialties. The advisory board will review all analyses prior to submission of interim reports.

9.8. Quality Control

9.8.1. Quality Assurance

The registries selected for this study will be evaluated to ensure they have demonstrated processes to ensure all data are reliable and processed correctly. Contractual agreements

with the registries will ensure such quality control is maintained through the life of the study.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform internal onsite audits or participation in external Agency inspections. The registries will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

9.8.2. Monitoring of the Study

Biogen may conduct onsite visits of the registry for the purpose of monitoring various aspects of the study. The registries must agree to provide marketing authorization holder (MAH)-authorized personnel with requested documentation for the purpose of verifying data provided for the study, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the registries or site staff.

9.8.3. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the HCP must notify Biogen and the corresponding registry in writing and receive written authorization from them to destroy study records. In addition, the HCP must notify Biogen of any changes in the archival arrangements, including but not limited to archival at an offsite facility or transfer of ownership if the HCP leaves the site.

9.9. Limitations of the Research Methods

Although measures will be taken to ensure that the study is methodologically robust, certain limitations should be acknowledged.

Estimating an accurate rate of early spontaneous pregnancy losses is difficult in voluntary pregnancy studies. Spontaneous abortions are likely to occur before the pregnancy is recognized. Even if the pregnancy is recognized, it may not be reported if the spontaneous abortion occurred prior to study enrollment. As such, there will likely be a reporting bias leading to an underestimation of the true early pregnancy loss rate. To address this bias, the study will evaluate pregnancy losses as a function of gestational age at enrollment into the study. Furthermore, inclusion of pregnancies whose outcome is known prior to registration may permit a fuller accounting of spontaneous abortions, though these pregnancies will not be included in the primary analyses to avoid the introduction of recall bias (e.g., participants with negative pregnancy outcomes may be more likely to report information about their pregnancies than participants with normal pregnancy outcomes) [Gliklich 2014]. Finally, pregnancy outcomes that occur outside the study will be collected as part of routine pharmacovigilance practice. These spontaneous reports will be analyzed outside of this study to determine whether there is a signal for an increased risk of adverse outcomes in early pregnancy, including spontaneous pregnancy loss.

Reporting pregnancy outcomes is voluntary, and it is possible that not all participants will complete all follow-up assessments. Enrolled pregnancies for which outcome information is unobtainable will be considered lost to follow-up. It is possible that outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with certainty what effect the potential biases of the loss to follow-up may have on the analysis. However, comparisons of the characteristics of each group will be conducted in an attempt to address this potential source of bias.

Background rates will be obtained from pregnancy outcome surveillance projects (e.g., MACDP and EUROCAT), but biases may be introduced by design differences across studies (e.g., small geographic region from which the data are drawn, differing eligibility criteria, duration of follow-up). MACDP and EUROCAT are general population cohorts that include individuals without extensive comorbidities and/or degenerative conditions such as SMA. Controlling for these differences in the analyses is thwarted by the lack of individual or aggregate data available on risk factors for pregnancy outcome. Given the limitations in available data sources for pregnancy outcome, Biogen and the independent advisory board will interpret the results using multiple external data sources, noting the strengths and limitations of each comparison. MCMs have already been adjudicated and classified according to the EUROCAT and MACDP criteria, thereby enabling robust comparisons of these outcomes as well as for spontaneous abortion and others.

Inclusion of participants with prenatal testing may introduce bias into the study. Therefore, some analyses may be stratified by prenatal testing status at enrollment. Because SMA is a genetic condition, preconception genetic counseling and genetic screening is recommended for patients with SMA who are pregnant or considering becoming pregnant; therefore, it is likely that many of the participants in this study will have prenatal testing [Abati and Corti 2018]. Similarly, individuals with conditions associated with negative pregnancy outcomes will be included and characterized in the study but will be adjusted for in the analysis, depending on the sample size and number of outcomes. This will ensure that etiologically ambiguous negative pregnancy outcomes (i.e., it would be unknown whether the condition or nusinersen exposure were the cause of the pregnancy outcome) do not lead to spurious associations.

Individuals with SMA who are exposed to nusinersen during pregnancy may have different outcomes than individuals in the general population who are pregnant due to SMA itself, as opposed to nusinersen. Due to the rarity of pregnancy in SMA patients, it is not possible to obtain a sufficiently large sample of individuals with SMA unexposed to nusinersen during pregnancy who could serve as a comparison group. Therefore, a limitation of this study is the inability to compare exposed and unexposed pregnancies. The study will address this limitation by evaluating pregnancy and birth outcomes in exposed participants in the context of their SMA diagnosis and, when possible, will compare observed events with those reported in SMA patients in the literature.

Given that SMA is a genetic disease, there is a risk that an affected mother may transmit the disease to their children. Therefore, infants in this study may themselves be diagnosed with SMA. Consequently, the risk of SMA in infants of individuals exposed to

nusinersen will be higher than in the general population of individuals without SMA. This will be taken into account in the interpretation of the study results.

Finally, while utilizing existing SMA registries for a pregnancy study allows for a captive population for whom some data have already been collected, as well as allowing an efficient study design, there are some limitations to the use of patient registries. Specifically, the data that can be collected is limited by local regulations and rules for each registry site, and Biogen must rely on the registries to conduct the study appropriately. These limitations will be addressed by providing resources and guidance for the registries on the study methodology to try to ensure complete data capture.

9.10. Other Aspects

9.10.1. Study Funding

Biogen is the MAH of the study and is funding the study. All financial details are provided in the separate contracts between the registries and Biogen.

9.10.2. Publications

Details on any restrictions on the publication of study data by registries are included in the clinical study agreement for this study.

10. PROTECTION OF HUMAN PARTICIPANTS

Biogen, the registries, any contracted third party, and the HCPs must comply with this protocol and applicable International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and Good Pharmacovigilance Practice (GVP) guidelines, and conduct the study according to local regulations.

The HCP may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH, GCP, and GVP guidelines. The HCP should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The HCP is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

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

10.1. Ethics Committee

Participating registries must obtain ethics committee approval of their protocol, ICF, and other required study documents prior to starting the study.

A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the HCPs to ensure that all aspects of institutional review are conducted in accordance with current government regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

10.2. Participant Information and Consent

Prior to any data collection under this protocol, informed consent with the approved ICF must be obtained either as part of the existing registry enrollment or specific to this study.

Participant consent (written or verbal per local regulations) must be obtained by the registry for the pregnancy study (if not already adequately covered by the existing registry consent). If the participant is a minor, written consent must be obtained from the parent or legal guardian as well as assent. A release of medical information will be obtained from the participant to permit the registry to contact HCPs related to the pregnancy (e.g., the participant's obstetric HCP) to follow up on the participant according to the schedule defined in Section 9.3.2. In addition, a release of medical information will be obtained from the parent or the infant's Personal Representative so that the registry can contact the pediatric HCP to follow up on the infant according to the schedule defined in Section 9.3.2.5.

Each ICF should contain an authorization allowing the registry to allow Biogen to use and disclose protected health information (i.e., participant-identifiable health information) in compliance with local law.

The original signed and dated ICF will be retained by the registries with the study records. The registries are responsible to ensure all local regulations are complied with in respect to the ICFs.

10.3. Changes to Final Study Protocol

The ethics committee and appropriate regulatory authorities will be contacted, as applicable, about changes to the protocol.

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 10.1 and 10.2).

10.4. Participant Data Protection

Prior to any data collection under this protocol, participants must also provide all authorizations required by local law.

During the study, the participant's race and year of birth will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). Because it is not known whether the effects of the nusinersen exposure are influenced by race, this information will be of value in the analysis of safety. Information on the participant's year of birth is necessary to confirm study eligibility, employ age-dependent stratification and outcome assessment, and conduct the planned statistical analysis. In addition, full date of birth will be collected for the infants (unless the collection is not permitted by applicable law or not approved by the governing ethics committee).

The participant will not be identified by name in the data collection system or in any study reports, and related publications, and these reports will be used for research purposes only. Biogen and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

10.5. Internal Safety Review

Biogen Epidemiology and Global Medical Safety and other applicable personnel at Biogen will review all SAEs on a regular basis.

10.6. Compensation for Injury

Not applicable.

10.7. Conflict of Interest

The registries should address any potential conflicts of interest (e.g., financial interest in Biogen) with the participant before the participant decides to participate in the study.

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

According to the Guideline on Good Pharmacovigilance Practices Module VI, noninterventional postauthorization studies with a design based on secondary use of data are not required to report suspected AEs:

> "The design of such studies is characterized by secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical record reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the submission of suspected adverse reactions in the form of ICSRs [Individual Case Safety Reports] is not required." [EMA (EMA/873138/2011) Rev 2 2017]

Therefore, no expedited reporting of AEs/adverse drug reactions is required, though the results of the final analysis will be reviewed to identify any safety signal(s).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data from the study will be presented at least annually in descriptive summary reports. Interim summaries of the study will be submitted as standalone documents at regular intervals.

12.1. Ethics Committee Notification of Study Completion or Termination

Where required, the health authorities and ethics committees must be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with necessary timelines.

12.2. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results (CSR synopsis), regardless of outcome, in the EU PAS register and on other publicly accessible websites in accordance with the applicable laws and regulations.

13. REFERENCES

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14. ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Table 3: List of Stand-Alone Documents for Protocol 232SM405

No.	Title or Content of Document
1	List of Registries and Responsible Parties

15. ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Study title: Spinraza (Nusinersen) SMA Pregnancy Exposure Study Within Existing SMA Registries

EU PAS Register® number: EUPAS104368
Study reference number (if applicable): 232SM405

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	Section 6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.2.3, 8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2.3, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2, 8.3
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2.1, 9.3
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.3
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.4
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	Annex 3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

For item 4.2.2, no age limits are specified in Section 9.2.2. For item 4.2.3, the countries of the registries are identified, but the country of origin of potential patients is not specified.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7, 7.2.3, 8
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.2, 8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.2.1, 9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.3
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.4 Are stratified analyses included?	☒	☐	☐	9.7.3
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.7.5

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.4

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 5 summarizes amendments to the protocol.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9.8.2, 12

Comments:

Name of the main author of the protocol: [redacted], ScD

Date:

Signature: _____

16. ANNEX 3: RECOMMENDED STUDY CONTACT SCHEDULE

Table 4: Expected Contacts With Participants and HCPs

Expected Contacts[1] with Participant	**Expected Contacts[1] with Participant's HCP (e.g., Obstetrician)**	**Expected Contacts[1] With Pediatric HCP (e.g., Pediatrician)[2]**
Enrollment First trimester[3]: for pregnancy status follow-up Second trimester[3]: for pregnancy status follow-up Third trimester[3]: for pregnancy status follow-up	Enrollment 6 to 7 months of gestation: for Prenatal Follow-Up 4 weeks after EDD[4]: for Pregnancy Outcome Follow-Up	1, 2, 6, 12, 18, and 24 months of age[5]: for Pediatric Follow-Up

[1] Contacts for this study are not mandated, but registries will inform participants and HCPs of the expected contact schedule and make every effort to ensure data are entered for each expected contact.
[2] Live births only.
[3] Follow up with the HCP, if needed.
[4] Follow up with other practitioners or the participant, if needed.
[5] Follow up with the participant, if needed.

Table 5: Recommended Study Contact Schedule

Data Collection	Enrollment	Prenatal Follow-Up		Pregnancy Outcome Follow-Up	Pediatric Follow-Up
	Initial Report/Registration by Participant and/or HCP[1]	Contact Participant or HCP at Each Trimester	Contact HCP at Approximately 6 to 7 Months of Gestation	Contact HCP(s) at Approximately 4 Weeks After EDD[2]	Contact Pediatric HCP at Approximately 1, 2, 6, 12, 18, and 24 Months of Age[3]
Informed Consent[4]	X				
Participant Demographics	X				
Participant Contact Information and Secondary Contact Information	X	X	X		
Medical History	X		X		
Pregnancy History and Current Pregnancy Information[5]	X				
Pregnancy Outcome Risk Factors[6]	X	X	X	X	
Prenatal Testing	X		X		
Current Pregnancy Status	X	X	X		
Gestational Age (in Weeks)		X	X	X	
Weight Gain During Pregnancy		X	X	X	
Nusinersen Exposure History and Adherence	X	X	X	X	

Data Collection	Enrollment	Prenatal Follow-Up		Pregnancy Outcome Follow-Up	Pediatric Follow-Up
	Initial Report/Registration by Participant and/or HCP[1]	**Contact Participant or HCP at Each Trimester**	**Contact HCP at Approximately 6 to 7 Months of Gestation**	**Contact HCP(s) at Approximately 4 Weeks After EDD**[2]	**Contact Pediatric HCP at Approximately 1, 2, 6, 12, 18, and 24 Months of Age**[3]
Prior and Current Medications Other Than Nusinersen	X[7]	X	X	X	
Possible SMA Symptoms[8]			X	X	
Pregnancy Outcome				X	
Type of Delivery				X[9]	
Complications During Pregnancy and/or Birth with Associated Notable Dates		X	X	X	
Neonatal or Pediatric Illness[10]				X	X
Infant Characteristics				X[11]	X[12]
Neurobehavioral Impairment					X[13]
Evidence of Any Abnormality Not Identified at Birth (if Applicable)					X
Pregnancy-related and Pregnancy Outcome Serious Adverse Events	----------Record throughout the final participant and infant contact----------				

[1] If the reporter is the participant, additional contact will be made with the participant's HCP to obtain medical information.

[2] If a participant experiences an adverse pregnancy outcome or has a pregnancy termination or an abortion of unknown cause, the HCP is encouraged to report this outcome as soon as possible.
[3] The registry will contact the pediatric HCP, designated either at enrollment or during one of the previous collection periods.
[4] Informed consent (written or verbal per local regulations or ethics committee requirements) must be obtained for the pregnancy study (if not already adequately covered by the existing registry consent). If the participant is a minor, written consent must be obtained from the parent or legal guardian. A release of medical information will also be obtained from the parent or the infant's Personal Representative so that the registry can contact the pediatric HCP for the 1, 2, 6, 12, 18, and 24 month follow-up visits.
[5] Details on previous pregnancies (if applicable) may include complications, outcomes, MCMs or developmental abnormalities, birth length, and birth weight. Current pregnancy information may include date of LMP, EDD, method of pregnancy confirmation, health assessments, prenatal testing, and outcome (if reported retrospectively).
[6] Risk factors include smoking, use of caffeine (> 200 mg per day), use of alcohol, and use of recreational drugs.
[7] Current medications and past medications up to 6 months prior to the first day of the participant's LMP before conception.
[8] As determined by the HCP (e.g., muscle weakness, change in gait, tremor, respiratory changes).
[9] For example, vaginal or cesarean delivery (C-section). Report should include whether labor/delivery was induced early and, if applicable, the reason for induction.
[10] Neonatal or pediatric illnesses (e.g., prematurity, respiratory dysfunction, birth trauma) that resulted in hospitalization, including any treatments (e.g., drug therapies).
[11] Gestational age at birth (in weeks), sex, weight, length, head circumference, birth order (for multiple births), Apgar scores, breastfeeding status, genetic diagnoses (including SMA) if applicable, medications, and any MCM noted, including description and attribution.
[12] Feeding behavior, head circumference, weight, length, developmental milestones, breastfeeding status, genetic diagnoses (including SMA) if applicable, and medications.
[13] Neurobehavioral impairment will be measured starting at 2 months of age.