Medicines Adverse Reactions Committee

Meeting date	**8 March 2018**	Agenda item	3.2.5
Title	**Risk Management Plan for nusinersen**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Nusinersen	**Medicines** Tbc likely Spinraza	**Sponsors** Biogen	
Funding	N/A		
Previous MARC meetings	N/A		
International action	Nusinersen received authorisation for marketing in the US 23 December 2016.		
Prescriber Update	N/A		
Schedule	Prescription medicine		
Usage data	N/A		
Advice sought	**The Committee is asked to advise whether:** – any changes are required to the RMP – any additional pharmacovigilance activities are required		

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1.0 PURPOSE

An application for consent to distribute nusinersen has been made to Medsafe by Biogen. This is a new category of medicine and therefore Medsafe is seeking the Committee's opinion on whether any additional post-market activities will be required, should this medicine be approved. The RMP provided to Medsafe is version 5.0, dated 24 April 2017.

2.0 RISK MANAGEMENT PLAN

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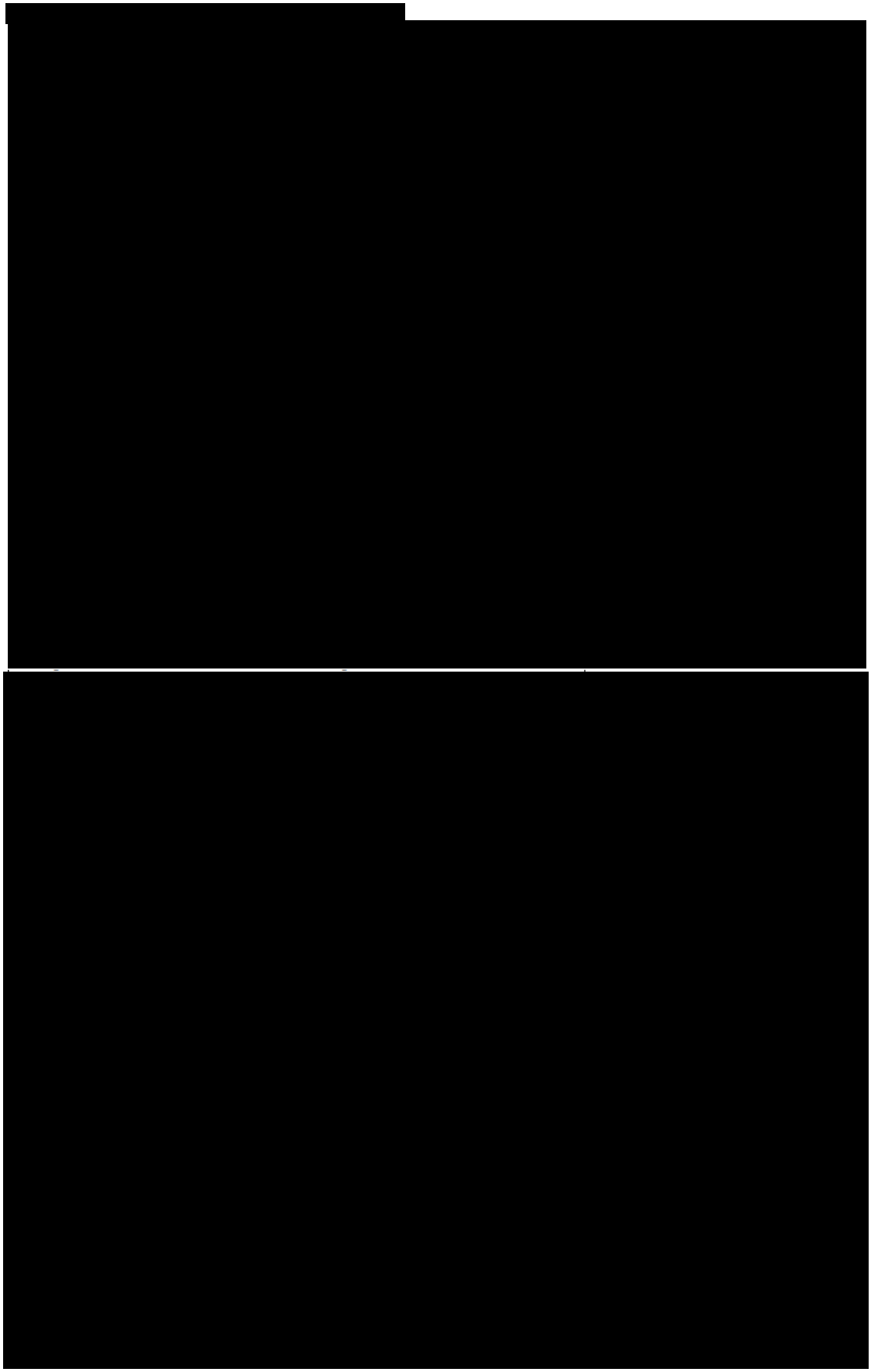

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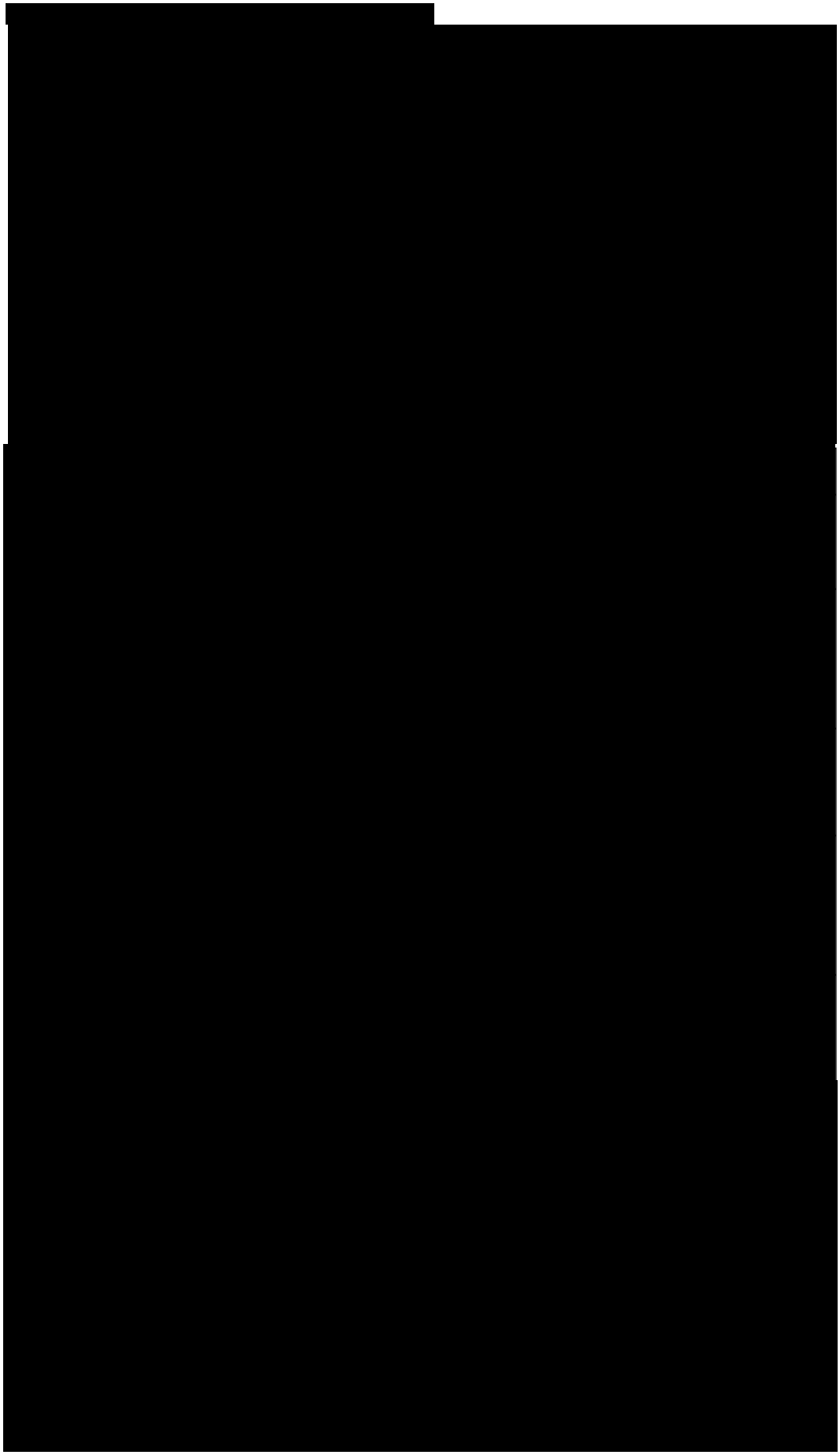

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2.5 Elements for the public summary

Spinal muscular atrophy (SMA) is a genetic disease caused by a shortage of a particular protein (called survival of motor neuron, or SMN). This results in the loss of nerve cells in the spine, leading to weakness of the muscles in the shoulders, hips, thighs, and upper back. SMA may also weaken the muscles used for breathing and swallowing. SMA is considered an orphan disease, which means that it affects fewer than 200,000 people in each country. SMA occurs in 8.5 to 10.3 per 100,000 live births.

Nusinersen works by helping the body to produce more of the SMN protein that people with SMA don't have enough of. This reduces the loss of nerve cells and so improves muscle strength.

Spinraza is used to treat a genetic disease called SMA. Spinraza is one of a group of medicines known as antisense oligonucleotides (ASO). It contains the active substance nusinersen.

Spinraza works by helping the body to produce more of the SMN protein that people with SMA are short of. This reduces the loss of nerve cells and so improves muscle strength.

It is unclear if there are additional unknown factors that might influence the response to nusinersen. It is uncertain what the appropriate amount of SMN protein is to remain symptom-free.

Table 9: Summary of the Risk Management Plan

Important identified risks

Risk	What is known	Preventability
None	Not applicable	Not applicable

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)	Preventability
Thrombocytopenia and coagulation abnormalities	Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides.	If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of Spinraza.
Renal toxicity	Renal toxicity has been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides.	If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.

Missing information

Risk	What is known
Safety profile in patients >18 years of age	There is currently limited data in patients over the age of 18 years. These data will accrue as children age to adult age with continued treatment and patients above 18 years old start new treatment. Nusinesen has not been studied in the elderly population. Therefore, the safety and efficacy in elderly patients have not been established.
Safety profile in patients with severe and progressive scoliosis	Scoliosis (curving of the back or spine) emerges in nearly 100% of nonambulatory patients with SMA with a severe progression, and it remains one of the major problems for orthopedic therapy [Haaker and Fujak 2013]. Scoliosis is frequently diagnosed at an early age [Haaker and Fujak 2013]. Scoliosis might newly appear in patients as part of the natural history of SMA and might complicate the lumbar puncture.
Safety profile in patients receiving repetitive LPs	Currently, the data are limited in patients with longer drug exposure who have received repetitive LPs. In the nusinersen clinical studies, no adverse trend or pattern was identified with multiple LPs, and no patients have discontinued due to AEs related to LPs. There were no AEs such as fibrosis (thickening and scarring of tissue) or arachnoiditis (pain disorder caused by inflammation of the membrane that surrounds the nerves and spinal cord) in patients with long-term exposure (>1081 days). The Applicant will try to follow patients with longer durations of treatment who have received repetitive LPs in the postmarketing setting through routine pharmacovigilance,which involves a review of new information on nusinersen that will be ongoing.
Safety profile in patients with long-term exposure to nusinersen	Eleven patients received 8 doses and 2 patients received 9 doses in the nusinersen clinical development programme. These data will continue to accrue as infants and children receive longer treatment durations of nusinersen. The Applicant will try to follow patients with longer durations of treatment in the postmarketing setting, in the clinical trial setting, and by collaborating with existing disease registries.
Safety profile in pregnant or breastfeeding women	There are no data on the use of nusinersen in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see SmPC section 4.6). It is unknown whether nusinersen/metabolites are excreted in human milk.
Safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	The mechanism of action of nusinersen is the same across all patients, regardless of the number of *SMN2* gene copies, age at onset of disease, or disease severity. Limited data are available in patients with a higher *SMN2* copy number (4 or 5 copies). No data are available in Type 0 and Type IV SMA patients. If Type 0 or Type IV patients would receive nusinersen, their safety profile would be further assessed in the postmarketing setting.

All medicines have a data sheet that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine and the risks and recommendations for minimising them. An abbreviated version of this in lay language is also provided for use by patients in the form of consumer medicine information. The measures in these documents are known as routine risk minimisation measures.

There are no additional risk minimisation measures.

The Applicant will conduct routine pharmacovigilance and will continue to monitor the safety profile and the longer-term efficacy in the ongoing clinical studies. In addition, the Applicant will collaborate with existing disease registries to understand the long-term benefit-risk safety profile of nusinersen.

Table 10: Summary of ongoing clinical studies

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of final results
Study SM202 (EMBRACE)	This is a Phase 2, randomized, double-blind, sham- procedure controlled study to assess the safety, tolerability, PK,	Long-term safety, tolerability, PK and efficacy data for patients with infantile and later onset SMA assessed for up to	Ongoing	2019
	and efficacy in patients who were not eligible to participate in studies CS3B or CS4. In light of emergent data, Part 1 of the study was terminated early and all subjects were rolled over into the open-label Part 2 of the study.	~43 months. Cardiac safety.		
MDA US Neuromuscular Disease Registry	Prospective longitudinal registry in a research agreement with the Muscular Dystrophy Association. As of January 2017, 28 participating clinics across the US, with 205 unique patients diagnosed across the spectrum of SMA. Data collection generally include patient demographics, SMN copy numbers, motor milestones, vital status, surgical history, hospitalisations, medications, mobility,	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Synopsis of available data and data fields in the MDA dataset: Within 1 month after EC decision
	scoliosis, other comorbidities, nutritional therapies, pulmonary function and devices, and cause of death.			

International SMA Consortium (ISMAC) natural history study	Longitudinal natural history study with the 3 regional centres that comprise the ISMAC (SMA Reach UK, Italian SMA Network, and Dr. Richard Finkel at Nemours Children's Health System). Outputs expected to include baseline characteristics of treated patients and longitudinal data on nusinersen treatment patterns, motor function, respiratory function, hospitalisations, and comorbidities.	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs
TREAT-NMD Alliance registries	Longitudinal natural history studies in a research agreement with the TREAT-NMD Alliance to expand current registries to include nusinersen treatment information. The Global SMA Patient Registry consists of 26 national patient registries representing 29 countries (20 countries in Europe), collecting data from genetically confirmed patients across the spectrum of SMA. Data are self-reported and/or provided by healthcare professionals. More than 5000 SMA patients worldwide have been enrolled in TREAT-NMD-associated registries.	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs

Study CS11 (SHINE) An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443	This is an open-label extension study in subjects with SMA who previously participated in investigational studies of ISIS 396443. The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of nusinersen (12 mg) administered as IT injections by lumbar puncture (LP) over an additional period of 5 years (totalling up to 8+ years with time in index study).	Long-term safety and efficacy	Ongoing	August 2023
Study CS5 (SM201/NURTURE) An Open-Label Study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and presymptomatic Spinal Muscular Atrophy	This is a Phase 2, open-label study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 in subjects with genetically diagnosed and presymptomatic SMA.	Long-term safety and efficacy	Ongoing	April 2023

3.0 DISCUSSION AND CONCLUSIONS

SMA is a rare disease associated with severe outcomes including death, depending on the number of copies of SMN2 the patient has. [redacted]

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4.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- any changes are required to the RMP
- any additional pharmacovigilance activities are required

5.0 ANNEXES

1. Risk Management Plan