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

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

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

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

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

VI: 1 The medicine and what it is used for

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

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

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

VI: 2 Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

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

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

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

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

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

VI: 2.1 List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Thrombocytopenia and coagulation abnormalities • Renal toxicity • Hydrocephalus
Missing information	• Safety profile in patients> 18 years of age • Safety profile in patients with severe and progressive scoliosis • Safety profile in patients receiving repetitive LPs • Safety profile in patients receiving long-term treatment with nusinersen • Safety profile in pregnant or breastfeeding women • Safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)

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

VI: 2.2 Summary of important risks

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

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

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

Important Potential Risk: ***Hydrocephalus***	
Evidence for linking the risk to the medicine	No events of hydrocephalus have been reported in the nusinersen clinical development programme or in nonclinical studies; however, based on the identification of 2 events of hydrocephalus in 2 patients in the post-marketing setting, a subsequent analysis of all available data (including published literature) was performed. Subsequently, whilst a causal association between the development of hydrocephalus and exposure to nusinersen treatment by lumbar puncture could not be established; on the basis of the intrathecal mode of administration (which has been attributed to transient drug-induced inflammation and associated with chemical meningitis) and the sparse information on post-marketing reports received to date, a causal association to nusinersen could not be completely excluded. Therefore, hydrocephalus is considered to be an important potential risk of nusinersen treatment until such time further meaningful data can be obtained.
Risk factors and risk groups	No specific risk factors for the development of hydrocephalus have been identified in patients receiving nusinersen.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4 and PL Section 2. ***Additional risk minimisation measures:*** • None ongoing; previously a Direct Healthcare Professional Communication (DHPC) relating to the important potential risks of hydrocephalus was sent. The dissemination of the DHPC was completed on 31 July 2018, and no further follow-up measures are deemed necessary at this time.
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.
Missing Information: ***Safety profile in patients >18 years of age***	
Risk minimisation measures	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

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

Missing Information: ***Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)***	
Risk minimisation measures	***Routine risk minimisation measures:*** • None ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	• MDA US Neuromuscular Disease Registry • ISMAC natural history study • TREAT-NMD Alliance registries See Section VI: 2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: DHPC, Direct Healthcare Professional Communication; ISMAC, International Spinal Muscular Atrophy Consortium; LP, lumbar puncture; MDA, Muscular Distrophy Association; PSUR, Periodic Safety Update Report; SMA, Spinal Muscular Atrophy; TREAT -NMD, Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases; US, United States.

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

- **Study ISIS 396443-CS11 (SHINE):** An open-label extension study for patients with SMA who previously participated in investigational studies of ISIS 396443 (nusinersen).
  - *Purpose of the study*: The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated 12 mg doses of nusinersen administered as intrathecal injections by lumbar puncture in subjects with SMA who previously participated in investigational studies of ISIS 396443.
- **Study 232SM201 (NURTURE):** An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and presymptomatic SMA.
  - *Purpose of the study:* The primary purpose of this study is to examine the efficacy of repeated doses of nusinersen administered as intrathecal injections in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA.

VI: 2.3.2 Other studies in post-authorisation development plan

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

- **Muscular Dystrophy Association (MDA) United States (US) Neuromuscular Disease Registry:** This is a prospective longitudinal registry designed to collect data

in four disease areas — amyotrophic lateral sclerosis, SMA, Duchenne muscular dystrophy and Becker muscular dystrophy.

  - *Purpose of the study:* To accelerate translational research to improve clinical care and patient outcomes by gaining a better understanding of the course of illness for specific neuromuscular diseases..

- **International SMA Consortium (ISMAC) natural history study:** This is a longitudinal natural history study of SMA patients with the 3 regional networks that comprise the ISMAC (led by: Dr. Francesco Muntoni at Great Ormond Street Hospital in the UK, Dr. Eugenio Mercuri at Universita Cattolica del Sacro Cuore in Italy, and Dr. Richard Finkel at Nemours Children's Health System in the US).
  - *Purpose of the study:* To allow researchers studying the biological basis of SMA and potential therapies in SMA access to individuals interested in participating in research and/or experimental therapies.
- **Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) Alliance registries:** This registry comprises data from multiple national longitudinal natural history studies combined under a research agreement with the TREAT-NMD Alliance.
  - *Purpose of the study:* To provide information on the natural history of SMA, provide context to understand the safety and effectiveness of new treatments, and support post-marketing surveillance for those new treatments.