



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for nusinersen (as heptadecasodium)

Proprietary Product Name: Spinraza

Sponsor: Biogen Australia Pty Ltd

**August 2018**

**TGA** Health Safety  
Regulation

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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## Common abbreviations

Abbreviation	Meaning
5q SMA	Spinal muscle atrophy, caused by mutations or homozygous deletions of the SMA1 gene on the q region of chromosome 5
6MWT	6 minute walk test
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
ACM	Advisory Committee on Medicines
aCSF	Artificial cerebrospinal fluid
ADA	Anti-drug antibodies
ALARP	As low as reasonably possible
ALP	Alkaline phosphatase
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
ASA	Australian Specific Annex
AUC	Area under the curve
BiPAP	Bi-level positive airway pressure
BP	British Pharmacopoeia
CHO	Chinese hamster ovary
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound Muscle Action Potential
C <sub>max</sub>	Maximum plasma concentration
CNS	Central nervous system
CYP	Cytochrome
DLP	Data lock point
ECG	Electrocardiograph
ED <sub>50</sub>	Median effective dose
EMA	European Medicines Agency

Abbreviation	Meaning
EU	European Union
FDA	Food and Drug Administration (United States)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HFMSE	Hammersmith Functional Motor Score Expanded
HINE	Hammersmith Infant Neurological Examination
hnRNP	Heterogeneous nuclear ribonucleoprotein
HR	Hazard ratio
ICH	International Conference on Harmonisation
ICV	Intra-cerebroventricular
ISO	International Organization for Standardization
ISS-N1	Intronic splicing silencer N1
IT	Intrathecal (injection)
mRNA	Messenger ribonucleic acid
NMT	Not more than
NNT	Number needed to treat
NOEL	No observable effect level
PedsQL	Pediatric Quality of Life Inventory
Ph Eur	European Pharmacopoeia
PI	Product Information
ppm	Parts per million
PSUR	Periodic safety update report
QTc	Corrected QT interval
RMP	Risk management plan
RNA	Ribonucleic acid
SC	Subcutaneous

Abbreviation	Meaning
SMA	Spinal muscular atrophy
SMN	Survival of motor neuron (protein)
SMN1	Survival of motor neuron 1 (gene)
SMN2	Survival of motor neuron 2 (gene)
TEAE	Treatment emergent adverse events
$t_{\max}$	Time of maximum plasma concentration
Type I SMA	Patients who have symptom onset < 6 months of age and never achieve independent sitting.
Type II SMA	Patients who have symptom onset > 6 months of age and sit independently , but never walks
Type III SMA	Patients who have symptom onset > 6 months or later and walks, but with difficulty
URTI	Upper respiratory tract infection
US	United States
USP	United States Pharmacopoeia
WFI	Water for injection

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	2 November 2017
<i>Date of entry onto ARTG</i>	3 November 2017
<i>Active ingredient:</i>	Nusinersen (as heptadecasodium) <sup>1</sup>
<i>Product name:</i>	Spinraza
<i>Sponsor's name and address:</i>	Biogen Australia Pty Ltd PO Box 360 North Ryde BC NSW 1670
<i>Dose form:</i>	Solution for injection
<i>Strength:</i>	12 mg/5 mL <sup>1</sup>
<i>Container:</i>	Type I glass vial
<i>Pack size:</i>	1 vial
<i>Approved therapeutic use:</i>	<i>Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).</i>
<i>Route of administration:</i>	Intrathecal injection
<i>Dosage:</i>	See the Product Information (PI), available as Attachment 1 for dosage information.
<i>ARTG number:</i>	282522

## Product background

This AusPAR describes the application by the sponsor to register Spinraza nusinersen (as heptadecasodium) for the following indication:

*'Spinraza is indicated for the treatment of Spinal Muscular Atrophy (SMA).'*

### Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a serious, debilitating, life threatening disease with a global incidence of 8.5 to 10.3 per 100,000 live births, approximately 1: 10,000 in Australia and a carrier frequency of 1 in 40 to 67.<sup>2</sup>

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<sup>1</sup> Nusinersen is supplied as nusinersen heptadecasodium. Each 5 mL vial contains 12.6 mg of nusinersen heptadecasodium, providing 12 mg of nusinersen as the active ingredient.

<sup>2</sup> Farrar M et al. Emerging therapies and Challenges in Spinal Muscular Atrophy. *Ann Neurol* 2017;81:355-368



### ***Aetiology***

SMA is an autosomal recessive neuromuscular disease characterised by the degeneration of motor neurons in the anterior horn of the spinal cord, and atrophy of the (voluntary) spinal muscles supplied by these neurons.

5q SMA results from mutations or homozygous deletions of the survival of motor 1 (SMN1) gene located on the q region of chromosome 5, normally responsible for encoding the survival of motor neuron (SMN) protein. This distinguishes the disorder from other motor disorders that bear a clinical resemblance.

The majority of cases of 5q SMA can be attributed to mutations in chromosomal region 5q11 to 5q13, leading to loss of function of the SMN1 gene. The lack of SMN protein causes dysfunction and eventual death of motor neurons. The SMN1 gene lies in a duplicated, inverted region of chromosome 5q that includes an almost identical copy of SMN1 called the survival of motor neuron 2 (SMN2) gene. SMN2 differs from SMN1 by 5 nucleotides. The reading frames for both genes encode proteins with identical amino acid sequences. The proteins produced by the genes undergo alternative splicing in which exons are either excluded or included from the mature protein coding sequences. The protein product of the SMN2 gene is spliced such that exon 7 is excluded from 90% of SMN2 gene transcripts whereas about 90% of SMN1 gene transcripts contain exon 7. Transcripts missing exon 7 produce a protein that is truncated, unstable and defective, resulting in about 10% as much fully functional SMN protein. SMN protein is important in the assembly transcription and biogenesis of small nuclear ribonucleic proteins, is implicated in axonal ribonucleic acid (RNA) transport and is expressed in all somatic cells. Although SMN protein appears in high levels in the central nervous system (CNS) it is also present in somatic cells but its role is unclear.

All patients have 2 copies of SMN1, one from each chromosome 5 but the number of copies of SMN2 is variable, from 0 to 8. SMN2 is an important disease modifier: the more copies of SMN2 in patients with 5q SMA, the less severe the disease. Increasing the amount of full length transcript from the SMN2 gene is predicted to result in an increase in SMN protein in patients with SMA.

### ***SMA type classification***

SMA has been categorised by age at disease onset and maximum motor function into Types 0 to IV that range in severity from a severe, immediately life threatening disease at birth (Type 0) to proximal muscle weakness in adulthood (Type IV). The most common variants (Type I to III) all present with an asymptomatic (pre-symptomatic) period followed by symptoms. Classification by age of symptom onset gives two main groups: infantile onset (closely resembling Type I) and later onset (Types II and III). The following classification table, (Table 1), is provided from the sponsor's submission.

**Table 1: SMA type and characteristics**

SMA Type	Typical Number of SMN2 Gene Copies	Age at Symptom Onset	Highest Function Achieved	Life Expectancy
Type 0	1	Fetal (born symptomatic)	Nil	~2 weeks
Type I <ul style="list-style-type: none"> <li>• Type Ia</li> <li>• Type Ib</li> <li>• Type Ic</li> </ul>	1-3	0 to 6 months  Fetal (symptom onset within 2 weeks of birth)  By 3 months  3 to 6 months	Never sits independently  Nil  Never rolls or sits independently  May gain neck support	<2 years
Type II	2-3	>6 months (later onset)	Sits independently, but never walks	25 years or longer with aggressive supportive care
Type III	3-5	>6 months (later onset)	Walks, but with difficulty	Normal
Type IV	4-6	≥18 years (later onset)	Increasing disabilities after onset	Normal

Infantile onset (Type I SMA) results in early death or permanent ventilation, generally before the age of 2 years in the absence of supportive care. The primary cause of morbidity and mortality in this group is pulmonary disease from bulbar and respiratory muscle weakness. Patients with Types II and III SMA also have bulbar and respiratory muscle weakness that causes morbidity and mortality. In addition, these children often develop scoliosis or kyphoscoliosis and contractures that impair mobility and respiratory function and may require spinal surgery to limit the respiratory impairment. Death from chronic respiratory muscle compromise usually occurs after the age of 20 in Type II SMA, although life expectancy approaches normal in patients with SMA Type III. SMA Type IV is adult onset, generally appearing after 18 years of age with proximal muscle weakness that can be progressive and lead to wheelchair dependency but with a normal life expectancy. The least common Type 0 or prenatal SMA is the most severe form, present at birth with severe hypotonia, weakness and sometimes congenital fracture, often with decreased fetal movements and polyhydramnios during the pregnancy. Most live less than 6 months.

#### **Current treatments**

There are no specific treatment options for SMA registered in Australia. Current medical care is supportive and depends on the severity of the disease and provided with a multidisciplinary approach. Treatments include nutritional support, respiratory care, physical and occupational therapy, pain management, orthotics and mobility aids, and for severe disease palliation rather than invasive or prolonged medical interventions. Overall, childhood SMA places a considerable burden on families and other carers to provide supportive care and to encourage as much independence as possible.

## Nusinersen

Nusinersen is a 2'-O - (2-methoxyethyl or 2'-MOE) antisense oligonucleotide, an 18 base residue (18-mer) phosphorothioate oligonucleotide, with a sequence complementary to an intronic splicing silencer (ISS-N1) at the 5' end of intron 7 of the SMN2 pre-messenger ribonucleic acid (mRNA), thus promoting the inclusion of exon 7 in the SMN2 mRNA transcript. This region of the SMN2 pre-mRNA is present in all patients with SMA. Nusinersen is expected to prevent the recruitment of splicing repressor proteins ribonucleoprotein A1 and A2 (intronic splicing silencer N1 (ISS-N1)). The sponsor has developed nusinersen as a solution for intrathecal (IT) injection.

### *Proposed formulation and dosage*

The proposed product Spinraza comprises of a vial contains 12.6 mg of nusinersen heptadecasodium, equivalent to 12 mg of nusinersen (or 2.4 mg/mL) in 5 mL of formulated artificial cerebrospinal fluid (aCSF) with each vial sufficient fill to deliver a 5.0 mL volume. The proposed administration is as an IT injection only by lumbar puncture for the treatment of SMA.

The proposed maximum daily dose is 12 mg/5 mL for a 24 month child. For infants younger than 24 months, the dosage is adjusted based on age.<sup>3</sup> Treatment is initiated with 4 loading doses one month apart, followed by maintenance dosing every 4 months.

## Regulatory status

Approval of nusinersen has not been previously considered for any indication in Australia. Nusinersen was granted orphan designation by the TGA in April 2016 for the treatment of SMA.

At the time the TGA considered this application, similar applications had been approved in the following countries or territories:

Nusinersen was approved in the United States (US) in December 2016 for the following indication:

*'Spinraza is a survival motor neurone-2 (SMN-2) directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients'.*

Nusinersen was authorised in the European Union (EU) for the following indication in May 2017:

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

Nusinersen was registered in Canada in June 2017 with the following indication:

*'Spinraza (nusinersen) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA)'*

## Orphan drug status

In Australia, nusinersen was granted orphan designation in April 2016 for the treatment of spinal muscular atrophy (SMA).

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<sup>3</sup> The approved dosage as per the Product Information is 12 mg/5 mL for all patients (regardless of age).

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Submission timeline

**Table 2: Timeline for Submission PM-2016-04042-1-3**

Description	Date
Submission dossier accepted and first round evaluation commenced	4 January 2017
First round evaluation completed	9 June 2017
Sponsor provides responses on questions raised in first round evaluation	6 July 2017
Second round evaluation completed	8 August 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	4 September 2017
Sponsor's pre-Advisory Committee meeting response	18 September 2017
Advisory Committee meeting	6 October 2017
Registration decision	2 November 2017
Entry onto ARTG	3 November 2017
Number of TGA working days from submission dossier acceptance to registration decision *	167

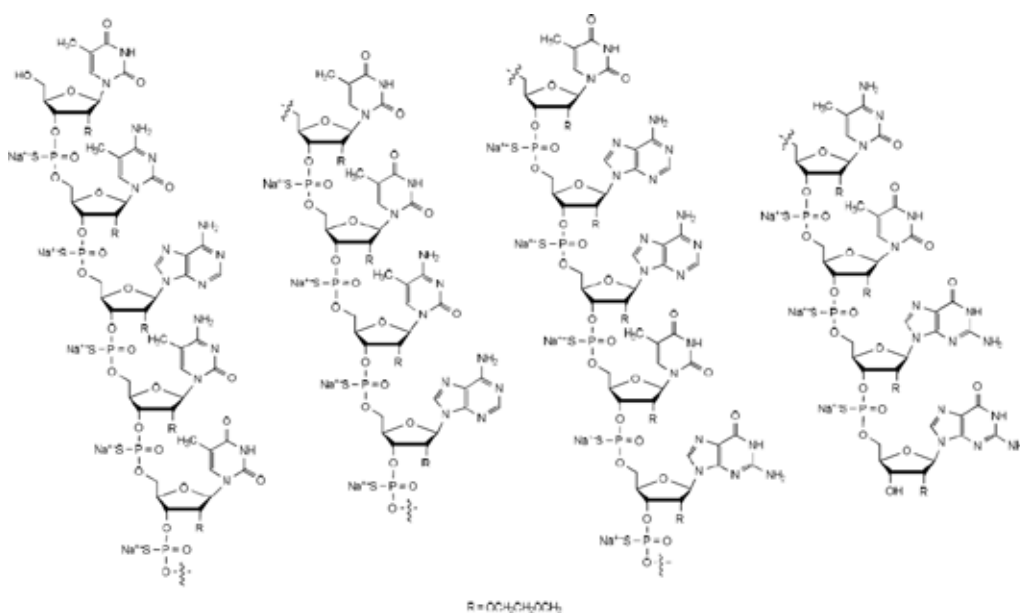
\* Statutory timeframe: 255 working days.

## III. Quality findings

### Drug substance (active ingredient)

Nusinersen is a white to yellow solid. It is freely soluble in water and aqueous sodium acetate buffer (pH 3), soluble in methanol, insoluble in acetone, ethanol, acetonitrile, isopropyl alcohol and chloroform.

Nusinersen heptadecasodium is synthetic substance made using computer-controlled solid phase synthesis. The absolute configuration of each 2'-O-(2-methoxyethyl)-D-ribose unit is (1R, 2R, 3R, 4R). The absolute configuration at each phosphorus atom is undefined and hence nusinersen is a mixture of 217 diastereoisomers or 131072 stereoisomers. The drug structure of nusinersen (as heptadecasodium) is shown in Figure 1, below.

**Figure 1: Drug structure of nusinersen as heptadecasodium**

The drug substance specifications include tests and limits for appearance, identity, purity, assay, specified impurities, residual solvents, elemental impurities, bacterial endotoxins and microbial limits. As an oligonucleotide, nusinersen is not covered by ICH Q3A, and impurities are required to be qualified.<sup>4</sup> Nusinersen is not subject to United States Pharmacopoeia (USP) or British Pharmacopoeia (BP)/European Pharmacopoeia (Ph Eur) monographs.

Due to the route of synthesis, the impurities listed in the specifications are not single impurities, but groups of impurities. For example, the impurities known as 'Full Length (P=O)<sub>1</sub>' have one of the P=S bonds oxidised to a P=O bond, but this could be any one of the 17 P=S bonds present in the molecule. Similarly, there is a set of impurities with one nucleotide missing 'Total (n - 1)' and a set where a double nucleotide has been added 'Total (n + 1)'.

In relation to the qualification of the proposed limits for related synthetic impurities and degradants, the toxicology section at the TGA has reviewed the data and arguments provided by the sponsor and (in short) concluded the related impurity limits can be considered qualified.

TGA engaged the sponsor in a detailed discussion about impurity specifications during the review. The principle of as low as reasonably possible (ALARP) had been followed in setting the original limits. However, only 3 commercial batches had been made and process capability could not be defined based on this small sample size. The TGA approved specification limits are aligned with those approved by the US FDA. The sponsor has given a commitment to review the limits again when the data from 10 commercial batches of drug substance are available. This approach is acceptable in terms of pharmaceutical chemistry to the TGA, with the evaluator stating that the related impurity limits can be considered qualified but should be tightened if the current process leads to related impurity levels significantly lower than the limits. The finalisation of the pharmaceutical chemistry evaluation was conditional on changes being made to the Risk management plan (RMP) and the Product Information (PI), and other post-approval commitments.

<sup>4</sup> ICH Q3A (R2): International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use harmonised tripartite guideline Q3A; Impurities in new drug substances, Current Step 4 version dated 25 October 2006.

Toxicological advice was also received that the proposed limits for elemental impurities that may be present are qualified, but again lower limits should be set if data on further batches indicate levels lower than the proposed limits are consistently met. For example, the proposed limit for [information redacted] is no more than (NMT) 10 parts per million (ppm), but the levels in all batches to date are < 1 ppm.

## Drug product

The proposed product is a single use, clear, colourless, sterile, isotonic solution for injection, practically free from visible particles, containing no preservatives for IT administration. It contains 12.6 mg of nusinersen heptadecasodium equivalent to 12 mg of nusinersen (or 2.4 mg/mL) in 5 mL of formulated aCSF.

The product is filled into clear, colourless Type I glass vials, with a bromobutyl rubber stopper and sealed with crimped aluminium seal and flip off plastic cap.

The manufacturing process used involves preparation of aCSF buffer by adding excipients and water for injection (WFI). The active pharmaceutical ingredient (API) is allowed to temperature equilibrate and is dissolved in aCSF in a bottle as a concentrate before compounding, dilution and mixing to ensure homogeneity. Solution homogeneity is measured across the batch.

The filters are flushed with water and bulk drug product to remove leachables and equilibrate the drug product concentration across the filter.

Bioburden reduction and sterilizing filtration steps are carried out and the compounded solution is aseptically filled into pre-sterilised vials. The vials are stoppered (with pre-sterilised stoppers), sealed and tested for leaks.

The finished product is controlled using the finished product specifications. The specifications include tests and limits for appearance, identity, assay, purity, specified related degradation products, extractable volume, pH, osmolality (isotonic with CSF), particulate matter, bacterial endotoxins and sterility.

The following sets of specified related degradation products are controlled in the drug product at the same level as they are controlled in the drug substance. As no increases in the degradants were observed during manufacture or storage of the product, this approach is acceptable.

Data was provided to support a shelf life of 36 months when stored between 2 to 8°C is assigned. The conditions 'Refrigerate. Do not freeze' and 'protect for light' also apply.

## Biopharmaceutics

3 drug product presentations were developed for clinical trials:

- A 5 mL vial containing 2.5 mL of a 20 mg/mL solution of nusinersen (as heptadecasodium) with a diluent of aCSF. The aCSF used in this 2 vial configuration was slightly different to the ready to use configurations.
- An International Organization for Standardization (ISO) 6R vial containing 5 mL of a ready to use 1.8 mg/mL nusinersen (as heptadecasodium) solution in aCSF.
- The proposed ISO 6R vial containing 5 mL of a ready to use 2.4 mg/mL nusinersen (as heptadecasodium) solution in aCSF.

The proposed ready to use formulation was used in the pivotal Phase III clinical studies.

## Quality summary and conclusions

### Quality Summary

- The proposed trade name Spinraza is acceptable from a pharmaceutical chemistry and clinical perspective.
- The proposed API specification for nusinersen (as heptadecasodium) is acceptable.
- The proposed finished product specifications for nusinersen solution for injection are acceptable.
- The Good Manufacturing Practice (GMP) clearances for all 8 overseas manufacturing sites are valid.
- A shelf life of 36 months when stored between 2 to 8°C is assigned. The conditions 'Refrigerate. Do not freeze' and 'protect for light' also apply.
- The proposed PI is acceptable from a pharmaceutical chemistry perspective.
- The final mock-up labels provided are acceptable.

### Quality conclusion and recommendation

Approval can be recommended with respect to chemistry and manufacturing control.

This recommendation depended on toxicology advice that concluded that the qualification of the related impurities and degradant product limits should be conditional on changes being made to the RMP and PI, and the post-approval provision of some empirical data.

Further, it is on the understanding that the sponsor will review these limits when more data is available.<sup>5</sup>

## IV. Nonclinical findings

### Pharmacology

#### Primary pharmacology

##### *Mechanism of action*

SMA is an autosomal recessive neuromuscular disease characterised by a loss of motor neurons. The loss of motor neurons leads to progressive and severe muscle weakness and atrophy of voluntary muscles of limbs and trunk with eventual paralysis as a result of degeneration of motor neurons in the anterior horn of the spinal cord.<sup>6</sup> The majority of cases of SMA can be attributed to mutations in chromosomal region 5q11-q13, leading to a loss of function of the SMN1 gene.<sup>7,8</sup> The SMN 1 gene lies in a duplicated region of chromosome 5. A nearly identical copy of the gene, SMN2, is expressed but fails to

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<sup>5</sup> Clarification : The sponsor agreed to re-evaluate specification limits for the impurities upon manufacture of 10 active pharmaceutical ingredient (API) batches.

<sup>6</sup> Crawford and Pardo (1996). The neurobiology of childhood spinal muscular atrophy. *Neurobiol. Dis.* 3: 97-110.

<sup>7</sup> Lefebvre et al., (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 80: 156-165.

<sup>8</sup> Ogino et al., (2002). Genetic risk assessment in carrier testing for spinal muscular atrophy. *Am. J. Med. Genet.* 110: 301-307.

compensate for the loss of SMN1 due to exon 7 skipping in the vast majority of mRNA transcripts producing an unstable truncated protein.<sup>9</sup>

Nusinersen, as an antisense oligonucleotide with a sequence complementary to an ISS-N1 site at the 5' end of intron 7 of the SMN2 gene, is expected to prevent the recruitment of splicing repressor proteins, heterogeneous ribonucleoprotein A1 and A2, leading to almost complete exon 7 inclusion in SMN2. The increased expression of full length SMN2 is anticipated to reduce disease severity in patients with SMA.

#### *In vitro*

*In vitro*, nusinersen bound to SMN2 pre-mRNA associated with chromatin and could displace or prevent binding of heterogeneous nuclear ribonucleoprotein (hnRNP) A1 and hnRNP A2/B1. Likely as a consequence of this, nusinersen treatment increased the inclusion of exon 7 in SMN2 transcripts in HeLa cells and increased SMN protein levels in SMA patient fibroblasts.

#### *In vivo*

In human subjects with SMA, disease severity is inversely correlated with genomic copy number of SMN2. Disease severity ranges from infant mortality, in the most severe cases, to minor motor impairment in the mildest cases.<sup>10</sup> The pharmacological action of nusinersen was examined in various murine SMA models with varying degrees of disease severity; mice containing 4 copies of the human SMN2 gene with a mild form of the disease and mice containing a single copy of the human SMN2 gene with a more severe disease phenotype. These models are considered appropriate models of the disease mimicking the varying degrees of disease severity.<sup>10</sup>

Intra-cerebroventricular (ICV) injection to adult mice with a mild form of the disease resulted in an increase in full length SMN2 transcript in the spinal cord and brain, increased the level of the SMN protein in the spinal cord, brain and CSF. SMN is primarily an intracellular protein; therefore, an increase in SMN protein in the CSF may not always correlate with an increase in tissue levels of the protein. The median effective dose (ED<sub>50</sub>) for a bolus ICV dose was 17 µg for the spinal cord and 35 µg for the brain. These doses are 6 to 12 times the maximum clinical dose (12 mg) based on comparative CSF volumes (36 µL in mice compared with 150 mL in adult human subjects), but the higher CSF turnover in mice (13 times per day compared with 4 times per day in humans) should also be considered in this dose comparison.<sup>11</sup> The effect was long lasting, correlating with the long half-life of the drug in CNS tissues.

In neonatal mice with a more severe form of the disease, ICV injection of nusinersen (approximately equivalent to the maximum clinical dose based on CSF volume) resulted in an increase in motor neuron cell counts in the cervical and thoracic regions of the spinal cord. There was also an increase in the size of myofibres and improved the architecture of the neuromuscular junction in the quadriceps and intercostal muscles (the muscle groups responsible for paralysis and respiratory deficits). Improved motor function (righting reflexes, grip strength and hind limb splay) was observed in treated animals. Furthermore, these animals survived longer than untreated SMA mice. The improvements in treated SMA mice did not fully restore the phenotype to that observed in wild-type mice, suggesting only partial abrogation of the disease.

<sup>9</sup> Cho, S. and Dreyfuss, G (2010). A degron created by SMN2 exon 7 skipping is a principal contributor to spinal muscular atrophy severity. *Genes Develop.* 24: 438-442.

<sup>10</sup> Bebee et al., (2012) Mouse models of SMA: tools for disease characterization and therapeutic development. *Hum Genet.* 131: 1277-1293.

<sup>11</sup> Smith et al., (2014) Characterization of individual mouse cerebrospinal fluid proteomes. *Proteomics* 14: 1102-1106.



In neonatal mice, subcutaneous (SC) injection of nusinersen appeared to be more efficacious (based on survival rates) than an ICV injection if the injection was administered early (for example post-natal Day 1). This may be attributable to restoration of peripheral effects associated with diminished SMN protein levels, which may not be effectively achieved with an ICV injection, combined with CNS exposure following systemic administration due to an incompletely formed blood-brain barrier in the neonatal mice. The combination of both SC and ICV injections was more efficacious than either ICV or SC injection alone.

The *in vivo* pharmacology studies support the proposed IT injection of nusinersen to increase SMN protein levels in the CNS and to ameliorate the effects on muscles responsible for paralysis and respiratory effects observed in patients with SMA. However, while it is noted that some systemic exposure occurs following intrathecal injection, it is uncertain if this is sufficient to improve any peripheral effects associated with the disease.

#### *Pharmacological action in animals*

The SMN2 gene (containing the C to T transition in exon 7 that results in exon 7 skipping compared with SMN1) is a human specific gene not found in non-human primates or rodents.<sup>12</sup> Therefore, nusinersen is not expected to be pharmacologically active in species typically used in toxicity studies.

#### **Secondary pharmacodynamics and safety pharmacology**

No receptor binding studies to assess potential off site targets were conducted. This is considered acceptable given that the mechanism of action of nusinersen does not involve protein binding.<sup>13</sup>

Nusinersen is not a substrate for RNase H, due to the 2'-MOE moiety, and, therefore, is not expected to be involved in any RNA silencing activity if off target hybridisation occurs. The sponsor assessed potential off target hybridisation sites using bioinformatics. Aside from SMN1 and SMN2, only one possible off target site with  $\geq 16$  contiguous nucleotide match was identified. This was a predicted non-coding RNA. 4 transcripts (pre-mRNA) with 15 contiguous nucleotide matches were identified. 2 were hypothetical genes; one the sponsor could show no evidence it was transcribed and another was predicted to be a non-coding RNA. The remaining two were intronic sequences of ZMAT4 and NAV4 and unlikely to affect splicing if hybridisation occurred. Possible effects due to binding to LOC105371082, LOC105373684, ZMAT4 and NAV4 would have been assessed in monkeys. It is inconclusive as to whether a possible effect on the hypothetical gene LOC643542 would have been assessed in monkeys due to a nucleotide mismatch in the middle of the sequence. These off target sites (in terms of nucleotide sequence) do not exist in mice or rabbits.

A dedicated safety pharmacology study assessed effects on respiratory and cardiovascular function in rats following intrathecal dosing ( $\leq 0.2$  mg/day). The study was Good Laboratory Practice (GLP) compliant and though the clinical route was used, estimated peak plasma levels are below those expected clinically (based on a comparison of mg/kg doses; 0.8 mg/kg compared with a maximum clinical dose of 3.2 mg/kg).<sup>14</sup> Furthermore, the rat is not considered an appropriate species to comprehensively assess effects on the

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<sup>12</sup> Rochette et al., (2001) SMN gene duplication and the emergence of the SMN2 gene occurred in distinct hominids: SMN2 is unique to *Homo sapiens*. *Hum Genet.* 108: 255-266.

<sup>13</sup> Berman, C et al., (2014) Recommendations for safety pharmacology evaluations of oligonucleotide-based therapeutics. *Nucleic Acid Ther.* 24: 291-301.

<sup>14</sup> Doses were compared on a mg/kg basis as effects are associated with C<sub>max</sub> (FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers); using a weight of 0.25 kg for rats and 3 kg for a human neonate and a clinical dose of 9.6 mg.

cardiovascular system (according to ICH S7B).<sup>15</sup> Therefore, no firm conclusions can be gained from the absence of findings in this study.

There were no clinical signs of respiratory effects in mice treated with  $\leq 50$  mg/kg SC nusinersen in a repeat-dose toxicity study. Peak plasma levels are estimated to exceed the clinical maximum plasma concentration ( $C_{max}$ ), therefore, no significant effects on respiratory function are predicted during clinical use. A lack of an effect on respiratory function is similar to that reported for other 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotides (2'MOE ASOs).<sup>16</sup>

There was no effect on electrocardiograph (ECG) parameters in Cynomolgus monkeys treated with repeated intrathecal doses of  $\leq 4$  mg nusinersen. Unfortunately, ECG parameters were not assessed at the time of maximum plasma concentration ( $t_{max}$ ) (24 h post-dose in the 53 week study and 7 days post dose in the 14 week study) and plasma levels of drug related material at these time points were below the clinical  $C_{max}$  (62 ng/mL and 9.8 ng/mL compared with a clinical  $C_{max}$  of 199 ng/mL). Therefore, no conclusions can be drawn from the absence of findings in these studies. The effect of nusinersen on the cardiovascular system has not been adequately assessed by the submitted studies.

Acute transient deficits in lower spinal reflexes were observed in cynomolgus monkeys following intrathecal lumbar doses of  $\geq 3$  mg (resulting in an estimated CSF  $C_{max}$  14 times the clinical CSF  $C_{max}$ ;<sup>17</sup> or 2.5 times the clinical dose when correcting for CSF volume). These neurological effects were not associated with any microscopic or long term changes in the CNS or spinal cord tissues. The underlying cause for these effects is unknown. However, these neurological deficits were observed in all cynomolgus monkey studies, with deficits becoming evident 1 h post-dose and lasting up to 8 h post-dose (on occasion, generally reversed by 24 to 48 h post-dose) confirming an association with nusinersen treatment and suggesting a correlation with peak CSF concentrations, possibly associated with the site of injection. The peak CSF concentration at the no observable effect level (NOEL) (1 mg) is estimated to be around 3 times the clinical CSF  $C_{max}$ .<sup>18</sup> The margin at the NOEL indicates acute transient neurological deficits may be seen in some patients.

## Pharmacokinetics

Following IT dosing to monkeys, peak CSF concentrations were observed within the first 30 minutes of dosing. The CSF concentration time profile consisted of 2 phases; a relatively fast decline phase (up to 24 to 48 h) followed by a slower decline phase (over  $> 70$  days). The mean residence time over the first 48 h was 4.4 to 7.7 h and the CSF clearance of nusinersen related material over the first 24 h was 2.0 mL/h, a value similar to the CSF turnover rate (1.8 mL/h) indicating this as the primary mode of clearance from the CNS.<sup>19</sup> Consistent with this, peak plasma levels of nusinersen related material were observed at 2 to 5 h. Similar to the pharmacokinetic profile in the CSF, a biphasic profile was seen in the plasma concentration time curve, with a relatively rapid decline phase and a slower terminal phase. The rapid decline phase likely represents distribution into peripheral tissues. The slow terminal phase in both the plasma and CSF concentration versus time profiles represents an equilibrium with tissue, combined with clearance from

<sup>15</sup> ICH S7B; ICH harmonised tripartite guideline S7B: The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. Current Step 4 version dated 12 May 2005

<sup>16</sup> Kim, T et al., (2014) Antisense oligonucleotides on neurobehavior, respiratory, and cardiovascular function, and hERG channel current studies. *J. Pharmacol. Toxicol. Methods* 69: 49-60.

<sup>17</sup> Based on CSF pharmacokinetic data contained in Study 396443-AS01.

<sup>18</sup> Based on CSF pharmacokinetic data contained in Study 396443-Apharmacokinetic01.

<sup>19</sup> Sung, C et al. (1994) A pharmacokinetic model of topotecan clearance from plasma and cerebrospinal fluid. *Cancer Res.* 54: 5118-5122.

the body and CNS compartments, respectively.<sup>20</sup> Longer half-lives were observed in CNS tissues (> 30 days) than the liver (around 12 days), likely a result of slower degradation in these tissues.

In human subjects, the volume of distribution in the CSF was greater than the CSF volume, suggesting significant distribution into CNS tissues. Consistent with this, there was extensive distribution into CNS tissues following IT dosing to Cynomolgus monkeys. Tissues closer to the injection site (for example, thoracic and lumbar spinal cords) had higher levels of nusinersen related material than more distal sites (for example, cervical spinal cord and brain tissues). No specific studies investigated the extent of systemic distribution, though high levels were shown in the kidney and, to a lesser extent, the liver of Cynomolgus monkeys following IT dosing. Systemic distribution of antisense oligonucleotides is largely sequence-independent. Therefore, biodistribution studies with other 2'-MOE phosphorothioate oligonucleotides may be used to predict the systemic biodistribution of nusinersen related material. Published data indicate significant distribution of this type of oligonucleotide to the liver, kidney, spleen, bone marrow, muscle, intestine and adipose tissue.<sup>20,21</sup>

Metabolism of nusinersen involved 3' and 5' exonuclease action in mice, monkeys and humans. Digestion from the 3' end was more extensive in monkeys and humans (not determined in mice), consistent with that observed for other antisense oligonucleotides.<sup>22</sup> Nusinersen metabolites were evident in the brain and lumbar spinal cord as well as the plasma, liver and kidney of monkeys following IT dosing, suggesting some metabolism occurs in the CNS. The kidney and liver are known to be sites of metabolism of 2'-MOE phosphorothioate oligonucleotides.<sup>22</sup>

No specific excretion studies were submitted. Based on CSF and plasma pharmacokinetic data, clearance from the CNS (into the systemic circulation) occurred primarily via CSF turnover. Excretion from the body is likely to be primarily via the urinary route as metabolites, based on the chemical nature of the oligonucleotide.<sup>22</sup>

As the systemic pharmacokinetic profile of antisense oligonucleotides is generally consistent across species, the mouse and monkey are considered appropriate animal models, from a pharmacokinetic perspective, to assess the systemic toxicity of nusinersen. The CSF turnover rate is similar in monkeys and human subjects (4 times a day).<sup>23</sup> Therefore, monkeys are considered an appropriate species from a pharmacokinetic perspective to assess local toxicity following IT dosing.

### Pharmacokinetic drug interactions

Nusinersen is not a substrate for cytochrome (CYP) 450 enzymes.<sup>24</sup> No clinically relevant inhibition of CYP1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 activity was observed in in vitro

<sup>20</sup> Geary et al. (2008) Pharmacokinetic/Pharmacodynamic Properties of Phosphorothioate 2'-O-(2-Methoxyethyl)-Modified Antisense Oligonucleotides in Animals and Man. In: Crooke ST, editor. Antisense Drug Technology: Principles, Strategies and Applications. Boca Raton: Taylor and Francis; p. 305-26.

<sup>21</sup> Butler et al. (1997) Cellular distribution of phosphorothioate oligodeoxynucleotides in normal rodent tissues. *Lab Invest.* 77: 379-388.

<sup>22</sup> Dirin, M. and Winkler, J. (2013) Influence of diverse chemical modifications on the ADME characteristics and toxicology of antisense oligonucleotides. *Expert Opin. Biol. Ther.* 13: 875-888.

<sup>23</sup> Bergman I et al., (1998) Pharmacokinetics of IgG and IgM anti-ganglioside antibodies in rats and monkeys after intrathecal administration. *J. Pharmacol. Experiment. Ther.* 284: 111-115.

<sup>24</sup> The following assumptions were made:

- molecular weight, 7501; dose, 12 mg; C<sub>max</sub>, 26.5 nM (total); free fraction, 6%
- for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, BCRP, BSEP and P-glycoprotein): if the IC<sub>50</sub> is ≤ 50 fold the unbound clinical C<sub>max</sub>, an in vivo interaction is considered possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC<sub>50</sub> is ≤ 25 fold the unbound hepatic inlet concentration, an in vivo interaction is considered possible.

assays. Nusinersen did not induce CYP1A2, 2B6 or 3A4 in human hepatocyte cultures. Nusinersen was neither a substrate nor an inhibitor of BCRP, P-glycoprotein, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. Pharmacokinetic drug interactions involving CYP450 enzymes or transporters are not predicted from in vitro data.

## Toxicology

### Acute toxicity

Single dose toxicity of nusinersen was assessed in Cynomolgus monkeys following IT dosing. The maximum non-lethal dose was the highest tested dose, 7 mg. Transient neurological deficits and very slight to minimal cellular infiltrates in the meninges covering the brain were seen in treated animals. No systemic effects were evident. Similar findings were seen in the repeat dose toxicity studies in this species.

### Repeat dose toxicity

Repeat dose toxicity studies were conducted in mice (3 months, SC route) and cynomolgus monkeys (up to 53 weeks, IT route). The duration of treatment in the pivotal monkey study is considered sufficient. However, the duration of treatment in the mouse study is shorter than would normally be expected given the intended duration of treatment (6 months for a drug that is intended to be used for > 3 months).<sup>25</sup> As most of the toxicity findings in mice were consistent with the oligonucleotide class of nusinersen, it might be doubtful that additional findings would have been revealed in a longer term study. However, it is recommended that such a study be conducted to confirm this (see also Carcinogenicity, below).

Juvenile animals were used in all studies (mice, 4 days old and monkeys, 8 to 11 months old at the start of dosing) consistent with the proposed paediatric indication (see also Paediatric use, below). The choice of the SC route for mice is considered acceptable to assess systemic toxicity. The clinical route (IT) was used for the studies in monkeys. Also, the monkey is considered an appropriate species based on CSF dynamics and pharmacokinetic profile (the CSF turnover rate in both monkeys and humans is 4 times a day). Both monkeys and mice are considered acceptable species from a systemic pharmacokinetic perspective. While nusinersen is not pharmacologically active in either species, nusinersen is intended to normalise SMN protein levels in patients and therefore adverse effects associated with the primary pharmacological activity of nusinersen are not expected. It is unknown whether off-target hybridisation effects were evaluated in these studies.

The dosing regimen in the animal studies, like the proposed clinical dosing regimen, consisted of a loading dose phase followed by a maintenance dose phase. For each of these phases, dosing was more frequent in animals than that anticipated clinically; loading dose regimen once weekly in animals compared with fortnightly in human subjects; maintenance dose regimen fortnightly or every 6 weeks in animals compared with every 4 months in human subjects. This is considered appropriate.

### Relative exposure

Adequate plasma area under the curve data were not available from mice and humans, therefore animal to human comparisons for systemic effects were determined on a mg/kg basis. Interspecies comparisons on a mg/kg basis is considered more appropriate than on

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<sup>25</sup> ICH M3(R2): Non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

a mg/m<sup>2</sup> basis for this type of drug.<sup>26,27</sup> As nusinersen related material is primarily cleared from the CSF via CSF turnover into the systemic circulation, a direct comparison of SC doses in mice with an IT dose in humans is considered acceptable and would be conservative. Doses were directly compared, irrespective of dosing regimen. As dosing in animals was more frequent than that anticipated clinically, the actual dose ratios are expected to be higher than those shown in Table 3, below. Dose/bodyweight values were determined for monkeys and humans assuming body weights (3 kg for monkeys and 3 kg for humans (neonate, most conservative estimate)).

Animal to human local exposures were determined based on dose to CSF volume (15 mL in monkeys and 120 mL in humans, irrespective of dosing regimen).<sup>28,29</sup> As with systemic dose comparisons, due to the more frequent dosing in animals, actual dose ratios would be expected to be higher than the values shown in Table 3. The dose ratios shown in Table 3 should be taken as a guide only (rather than absolute numbers) and are considered conservative. Therefore, the doses used in the repeat dose toxicity study in mice are considered adequate to have assessed the systemic toxicity profile and doses used in the monkey studies are considered adequate to have assessed the local toxicity of nusinersen.

**Table 3: Relative exposure in repeat dose toxicity studies**

Species	Study duration (Study ID)	Dose (mg)	Route	Systemic exposures		Local exposures	
				Dose by body weight (mg/kg)	Dose ratio	Dose by CSF volume (µg/mL)	Dose ratio
<b>Mouse</b> CD-1	13 weeks (Study-AS07)	-	SC	1	0.25	-	-
		-		10	2.5	-	-
		-		50	13	-	-
<b>Monkey</b> Cynomolgus	14 weeks (Study AS03)	0.3	IT	0.1	0.03	20	0.2
		1		0.33	0.08	67	0.67
		3		1	0.25	200	2
	53 weeks (Study AS06)	0.3		0.1	0.03	20	0.2
		1		0.33	0.08	67	0.67
		4		1.3	0.3	267	2.7
<b>Human</b>		12		4		100	

<sup>26</sup> FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005.

<sup>27</sup> Mahmood, I. (2011) Pharmacokinetic allometric scaling of oligonucleotides. *Nucl. Acid Therap.* 21: 315-321.

<sup>28</sup> Value provided by the sponsor in the dossier.

<sup>29</sup> Miller, M. et al. (2013) An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a Phase I, randomized, first-in-man study. *Lancet Neurol.* 12: 435-442.

### *Major toxicities*

The majority of findings for nusinersen were associated with a pro-inflammatory response or with accumulation of the oligonucleotide. Additional findings were also noted in the CNS.

#### *Effects associated with accumulation of the oligonucleotide in tissue*

Basophilic granules were observed in the kidney of mice treated with  $\geq 10$  mg/kg SC nusinersen. Antisense oligonucleotides accumulate to high concentrations in the kidney and this accumulation appears microscopically as basophilic granules.<sup>30</sup> Therefore, in the absence of any degenerative changes (at  $\leq 50$  mg/kg), this finding is not considered adverse.<sup>31</sup> Consistent with this, there was no evidence of an effect on kidney function based on serum chemistry parameters (urinalysis parameters were not assessed). There were no microscopic changes in the kidney in cynomolgus monkeys treated with  $\leq 4$  mg nusinersen intrathecally for 53 weeks. No renal effects are anticipated during clinical use.

In mice treated with  $\geq 10$  mg/kg SC nusinersen, increased liver weights and Kupffer cell hypertrophy were seen. There was no evidence of hepatic degenerative lesions.

Hippocampal vacuolation was evident in cynomolgus monkeys treated intrathecally with  $\geq 1$  mg nusinersen for 53 weeks. This is likely associated with oligonucleotide accumulation in these tissues. A mechanistic study demonstrated that the vacuolation was an artefact that occurs during fixation (as has been observed during the fixation process of kidney samples containing oligonucleotide stores) and is not considered adverse.<sup>31</sup>

As there were no obvious adverse effects associated with accumulation in these tissues, these findings are not considered a clinical concern.

#### *Effects associated with a pro-inflammatory response*

Vacuolated macrophages in the lymph nodes (at  $\geq 10$  mg/kg SC nusinersen) at the SC injection site (at  $\geq 1$  mg/kg SC nusinersen) were observed in mice treated for 13 weeks. A predominance of myeloid cells was observed in the bone marrow of male mice treated with  $\geq 1$  mg/kg and female mice treated with  $\geq 10$  mg/kg SC nusinersen. These effects were not considered adverse. Given the high doses used in mice, a systemic inflammatory response is not expected during clinical use.

#### *Additional findings in the CNS*

Hippocampal neuronal/glial cell necrosis was seen in a number of monkeys treated with 3 mg IT nusinersen for 14 weeks. While an associated effect on neuro behaviour was not evident, it is unlikely that the neurological effects were comprehensively examined. These effects were considered adverse, with a NOEL of 1 mg IT nusinersen. According to the estimated local dose ratio in Table 3 above, the NOEL is below the clinical dose (on a mg/CSF volume basis). However, IT dosing in the 14 week study was quite frequent (every 1 to 2 weeks) in contrast to the proposed clinical maintenance dosing regimen (every 4 months) and no such neuronal/glial cell degenerative effects were seen in monkeys in the pivotal 53 week study, where the maximum dose level was higher (around 3 times the clinical dose based on CSF volume) but dosing was less frequent (once every 6 weeks in the maintenance phase). Given the dose and dosing frequency proposed clinically, these neuronal/glial cell degenerative effects are not expected to be a concern in patients.

While necrotic cells/cellular debris were noted in monkeys in the longer term study (at  $\geq 1$  mg IT nusinersen), these have an unknown origin but were not neurons. There

<sup>30</sup> Henry S et al., (2008) Toxicologic Properties of 2'-O-Methoxyethyl Chimeric Antisense Inhibitors in Animals and Man, pp. 327-362. In: Antisense Drug Technology (Second Edition), Ed: Stanley T. Crooke, CRC Press, New York, New York.

<sup>31</sup> Engelhardt J. (2016) Comparative renal toxicopathology of antisense oligonucleotides. *Nucleic Acid Therapeutics* 26: 199-209.

were no obvious neuro behavioural effects associated with these findings, but group sizes were small (n = 5/sex) and a full neurological assessment is unlikely to have been performed. The NOEL for this effect was below the clinical dose on a direct dose (based on CSF volume) comparison (given in Table 3). It is not known if neurological effects associated with this necrotic debris may manifest during clinical use.

As mentioned in the safety pharmacology section, acute transient deficits were seen in the lower spinal reflexes in monkeys following IT dosing. These deficits were not associated with any of the aforementioned histopathology findings.

Perivascular macrophage infiltrates were seen in the brain and spinal cord of monkeys treated with  $\geq 1$  mg IT nusinersen for 14 weeks. There did not appear to be any evidence of an inflammatory or microglial response. There were no obvious neuro behavioural effects or CNS tissue degenerative lesions associated with these infiltrates. No such effects were observed in the longer term monkey study at a higher maximum dose (around 3 times the clinical dose on a CSF volume basis) and less frequent dosing. These findings are unlikely to be a clinical concern.

### **Genotoxicity**

The genotoxic potential of nusinersen was tested in a bacterial mutagenicity assay, in vitro clastogenicity assay in Chinese hamster ovary (CHO) cells and a mouse micronucleus test. The conduct of the studies was generally acceptable, though higher doses could have been used in the mouse micronucleus test as limited toxicity was observed; the highest tested dose was 750 mg/kg SC, in contrast with the limit dose of 2000 mg/kg recommended in ICH S(R1).<sup>32</sup> Negative results were returned in all assays.

Two issues with in vitro genotoxicity testing of antisense oligonucleotides is the demonstration of cellular uptake of the oligonucleotide and whether appreciable levels of the monomer are available to assess the effects of these on mutation and chromosomal aberration rates.<sup>33</sup> No studies with nusinersen were provided by the sponsor to assess this. A phosphorothioate oligodeoxynucleotide (as opposed to nusinersen, a 2'-MOE phosphorothioate oligonucleotide) has been shown to be taken up by CHO and bacterial cells used in the standard genotoxicity studies.<sup>34</sup> With the different chemistries between nusinersen and the model oligonucleotide, similar uptake rates cannot necessarily be assumed. While no data were provided by the sponsor to demonstrate uptake of 2'-MOE phosphorothioate oligonucleotides into CHO and bacterial cells, some data have shown uptake of oligonucleotides with this chemistry into other cell types (for example, hepatocytes) without transfection.<sup>35</sup> Therefore, nusinersen may have been taken up by cells used in the in vitro genotoxicity studies.

The sponsor stated that nusinersen is unlikely to be metabolised (to monomers) by the S9 fraction used in the assays but the monomers may be formed intracellularly by nuclease action.<sup>36</sup> Intracellular formation of monomers in bacterial cells (*S. typhimurium* TA98) and CHO cells was demonstrated for a model phosphorothioate deoxyoligonucleotide (not 2'-MOE modified) with 18% and 32%, respectively, of the total intracellular (applied) oligonucleotide present as metabolites. However, 2'-MOE modified oligonucleotides are

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<sup>32</sup> ICH S(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.

<sup>33</sup> Berman et al., (2016) OSWG recommendations for genotoxicity testing of novel oligonucleotide-based therapeutics. *Nucl. Acid Therapeut.* 26: 73-86.

<sup>34</sup> Henry S et al., (2002) Assessment of the genotoxic potential of ISIS 2302: a phosphorothioate oligodeoxynucleotide. *Mutagen.* 17: 201-209.

<sup>35</sup> Koller E et al., (2011) Mechanisms of single-stranded phosphorothioate modified antisense oligonucleotide accumulation in hepatocytes. *Nucleic Acids Res.* 39: 4795-4807.

<sup>36</sup> The S9 fraction is the supernatant fraction obtained from an organ (typically liver) homogenate by centrifuging at 9000 g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes and is most frequently used in assays measuring the metabolism of drugs and other xenobiotics.

much more resistant to nuclease action than the model phosphorothioate deoxyoligonucleotide.<sup>37,38</sup> Therefore, based on the level of metabolism of the model oligonucleotide and given the differences in the rate of degradation between the model oligonucleotide and nusinersen;<sup>39</sup> the oligonucleotide monomers are unlikely to have been present at a sufficient level in the in vitro genotoxicity studies to have adequately assessed the genotoxic potential of these breakdown products.

The sponsor stated that 2'-MOE nucleotide monomers are poor substrates for nucleotide/nucleoside kinases and DNA polymerases, citing personal communication but providing no actual data. This information is critical to assess if the nucleotide monomers from nusinersen have the potential to cause DNA mutations or chromosomal aberrations. Data have been published to indicate that 2'-O-methyl nucleotides are poor substrates for human DNA polymerase, whereas 2'-fluoro nucleotides could serve as substrates for this enzyme.<sup>40</sup> The difference was considered to be related to the size of the substituent, with the 2'-O-methyl group being larger than the 2'-fluoro group. By this rationale, 2'-MOE nucleotide monomers may also be poor substrates for human DNA polymerase, though empirical data to demonstrate this should have been provided by the sponsor. It is recommended that these data be provided as a condition of registration.

A theoretical risk with oligonucleotides is the formation of triple helices with DNA.<sup>41</sup> This scenario is unlikely as nusinersen does not contain the signature sequences suggested to be necessary for triple helix formation.

In conclusion, the genotoxic potential of nusinersen has not been fully assessed, but is likely to be low.

### ***Carcinogenicity***

No carcinogenicity studies were submitted. The following reasons were provided by the sponsor: it is impractical to perform repeated ICV/IT dosing in rodents, the low systemic exposure following IT dosing, the absence of pre-neoplastic lesions in repeat-dose toxicity studies and the negative genotoxicity results. However, given the uncertainty regarding genotoxicity and the positive carcinogenicity findings with a related compound (which was considered to be a class effect), the potential for carcinogenic effects with nusinersen should be examined.<sup>42</sup> The systemic doses at which tumours were observed with the related compound were relatively high compared with the expected systemic exposure due to nusinersen.<sup>42</sup> Therefore, the absence of a carcinogenicity study should not preclude registration with the following caveat. It is noted that the US FDA has requested that the sponsor conduct a carcinogenicity study as a post-marketing commitment in that country. This should also be a condition of registration by the TGA.

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<sup>37</sup> Geary et al., (2008) Pharmacokinetic/Pharmacodynamic Properties of Phosphorothioate 2'-O-(2-Methoxyethyl)-Modified Antisense Oligonucleotides in Animals and Man. In: Crooke ST, editor. Antisense Drug Technology: Principles, Strategies and Applications. BocaRaton: Taylor and Francis; p. 305-26.

<sup>38</sup> Dirin M and Winkler J. (2013) Influence of diverse chemical modifications on the ADME characteristics and toxicology of antisense oligonucleotides. *Expert Opin. Biol. Ther.* 13: 875-888.

<sup>39</sup> The plasma half-life of the model oligonucleotide in human subjects is 53 to 54 min (or around 0.04 days) in contrast to a plasma half-life of 86.5 days for nusinersen in human subjects (2163 times longer. Glover, J et al., (1997) Phase I Safety and Pharmacokinetic Profile of an Intercellular Adhesion Molecule-1 Antisense Oligodeoxynucleotide (ISIS 2302). *J. Pharmacol. Exp. Therapeutics* 282: 1173-1180).

<sup>40</sup> Richardson, F et al., (2000) Polymerization of 2'-fluoro and 2'-O-methyl-dNTPs by human DNA polymerase  $\alpha$ , polymerase  $\gamma$  and primase. *Biochem. Pharmacol.* 59: 1045-1052.

<sup>41</sup> Berman, C.L. et al. (2016) OSWG recommendations for genotoxicity testing of novel oligonucleotide-based therapeutics. *Nucleic Acid Ther.* 26: 73-86.

<sup>42</sup> US FDA Pharmacology review of mipomersen: there was an increased incidence of hepatocellular adenomas & combined hepatocellular adenomas/carcinomas, fibrosarcomas of skin/subcutis, haemangiosarcomas in mice treated with 60 mg/kg/week SC mipomersen. The NOEL was 20 mg/kg/week mipomersen (or 320 mg/kg/4 months). This is high in contrast to a clinical maintenance dose of 12 mg in a human subject of 50 kg every 4 months (0.24 mg/kg/4 months).



### Reproductive toxicity

Reproductive toxicity studies assessed effects on fertility (mouse), embryofetal development (rabbit) and pre/postnatal development (mouse). Pivotal studies were GLP compliant. While nusinersen is not pharmacologically active in these species, the choice of species is considered appropriate. Dosing of nusinersen was systemic (via the SC route) in all studies, with the dosing interval more frequent than the clinical dosing regimen; every 2 days to assess effects on fertility and effects associated with gestational exposure and once per week to assess effects following lactational exposure. As a consequence, systemic exposures are estimated to far exceed the systemic exposure in patients, as shown below in Table 4. The conduct of the studies (including animal numbers, dosing periods and analyses) were considered appropriate.

**Table 4: Relative exposure in reproductive toxicity studies**

Species	Study (Study ID)	Dose (mg/kg/week SC)	Dose ratio
<b>Mouse</b> (CD-1)	Fertility and embryofetal development (Study AS08)	10.5	44
		35	146
		87.5	365
	Pre/postnatal development (Study AS12)	5	21
		20	83
		60	250
<b>Rabbit</b> (NZW)	Embryofetal development (Study AS09)	21	88
		44.1	184
		87.5	365
<b>Human</b> <sup>a</sup>		0.24	

a) Assuming a 12 mg dose for a 50 kg individual; no effects on fertility were seen in male and female mice treated with  $\leq 25$  mg/kg/2 days SC nusinersen.

Minimal placental transfer of drug related material was seen in mice and rabbits (placental levels were 2.3to 8.2% of maternal liver levels) but there was no evidence of fetal exposure. No adverse fetal effects were seen in mice and rabbits treated with  $\leq 87.5$  mg/kg/week SC. As most human subjects have multiple copies of the SMN1 and SMN2 genes (and likely varying levels of SMN protein), if any fetal exposure of nusinersen occurred, adverse effects associated with pharmacological activity are not predicted.

Excretion of nusinersen related material was limited in lactating mice (levels in milk were 2% of maternal liver levels). This, combined with the poor oral absorption of oligonucleotides, would suggest exposure in breast fed infants is expected to be low to negligible.<sup>22</sup> No adverse effects were seen in breast fed pups following maternal exposure during the gestational and lactational period.

Overall, no adverse effects on reproductive parameters are expected during clinical use.

### *Pregnancy classification*

The sponsor has proposed Pregnancy Category A.<sup>43</sup> This category is for products for which there is sufficient data in pregnant women to allay concerns regarding embryofetal effects. This is not considered an appropriate category for this product. Category B1 is considered more appropriate.<sup>44</sup> This category is for products for which there are adequate animal data that demonstrated an absence of embryofetal effects during pregnancy.

### *Local tolerance*

See the repeat dose toxicity section, above.

### *Immunogenicity/immunotoxicity*

Complement activation has been reported to occur in non-human primate studies with antisense oligonucleotides, though less so with 2'-MOE phosphorothioate oligonucleotides.<sup>45</sup> A slight increase (1.3 to 1.4 times) in the levels of the complement split product Bb in the plasma of cynomolgus monkeys receiving a single IT dose of nusinersen ( $\geq 3$  mg), but this was not considered biologically significant.<sup>46</sup> There was no evidence of complement activation in either the plasma or CSF of cynomolgus monkeys following repeated IT dosing of  $\leq 4$  mg nusinersen. Overall, complement activation is not expected to be a concern in patients.

Anti-drug antibodies were detected in a number of cynomolgus monkeys receiving  $\geq 1$  mg IT nusinersen. Anti-drug antibodies may be seen in patients receiving nusinersen. The effects on long term efficacy are unknown.

There was no effect on T cell dependent antibody responses in cynomolgus monkeys treated with  $\leq 4$  mg IT nusinersen.

### *Paediatric use*

The draft PI document states that treatment with Spinraza should be initiated as early as possible after diagnosis and proposes a dose and dosing regimen for infants of 0 to 3 months of age. The age of monkeys used in the studies (approximately 8 to 11 months old at initiation) corresponds approximately to a 2.5 to 3.5 year old human;<sup>47</sup> however, this does not necessarily take into account any species differences in the timing of organ development.

No species provides a direct correlation to human neurological development.<sup>47</sup> No precise information equates various stages of pre-partum and post-partum brain development in humans and animals.<sup>48</sup> However, the timing of landmarks of postnatal morphological and functional CNS development is known for both monkeys and humans.<sup>48,49</sup> Given the age of monkeys in the toxicity studies, the full effects on postnatal neurogenesis and CNS

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<sup>43</sup> Australian Pregnancy Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

<sup>44</sup> Australian Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

<sup>45</sup> Dobrovolskaia M, and McNeil S. (2015) Immunological and hematological toxicities challenging clinical translation of nucleic acid-based therapeutics. *Expert Opin. Biol. Ther.* 15: 1023-1048.

<sup>46</sup> Complement Bb is a split product of complement B. It can be used as a marker of complement cascade activation.

<sup>47</sup> Baldrick P. (2010) Juvenile animal testing in drug development - Is it useful? *Reg. Toxicol. Pharmacol.* 57: 291-299.

<sup>48</sup> Wood S et al. (2003) Species comparison of postnatal CNS development: functional measures. *Birth Defects Res (B)* 68: 391-407.

<sup>49</sup> Watson R et al. (2006) Postnatal growth and morphological development of the brain: a species comparison. *Birth Defects Res (B)* 77: 471-484.

functional development would not have been assessed. However, the use of younger animals may not have been practical due to restrictions in the age they can be shipped (because of welfare regulations and practicalities of animal husbandry) and the quarantine and acclimation periods.<sup>50</sup> Therefore, the safety of nusinersen, in particular to CNS development and function, in infants < 2.5 years cannot be addressed from the nonclinical data submitted by the sponsor.

The kidney is an organ that accumulates antisense oligonucleotides. Nephrogenesis is complete by birth in mice, monkeys and humans. Therefore, the anatomical development of the kidney is not expected to be affected by nusinersen treatment. Effects on kidney functional development would have been assessed in the combined mouse (where dosing commenced on postnatal Day 4) and monkey studies. No adverse functional effects were evident.

In monkeys, a number of treated animals demonstrated delays in learning ability. However, there was no clear dose response and a clear association with treatment was not apparent.

## Nonclinical summary and conclusions

The scope of the submitted nonclinical dossier was mostly acceptable, though there are still some outstanding issues regarding off target hybridisation effects, genotoxicity, carcinogenicity and impurities. All pivotal safety related studies were GLP compliant.

In vitro, nusinersen bound to SMN2 pre-mRNA and increased the inclusion of exon 7 in SMN2 transcripts in human cells. In mouse models of SMA, ICV injection of nusinersen resulted in an increase in full length SMN2 transcript in the spinal cord and brain, increased the level of the SMN protein in the spinal cord, brain and CSF. In neonatal mice with a more severe form of the disease, ICV injection of nusinersen resulted in an increase in motor neuron cell counts in the cervical and thoracic regions of the spinal cord, increased the size of myofibres, improved the architecture of the neuromuscular junction in the quadriceps and intercostal muscles, improved motor function and increased survival. The improvements in treated SMA mice did not fully restore the phenotype to that observed in wild-type mice, suggesting only partial abrogation of the disease. In neonatal mice, SC injection of nusinersen appeared to be more efficacious (based on survival rates) than an ICV injection if the injection was administered early (for example, on postnatal Day 1).

Nusinersen is not expected to be involved in any RNA silencing activity if off target hybridisation occurs. A number of potential off target effects were identified. These off target effects would have been assessed in monkeys, though systemic doses were low.

No overt respiratory effects were observed in mice. Potential cardiovascular effects have not been adequately assessed. Acute transient deficits in lower spinal reflexes were observed in cynomolgus monkeys immediately following IT lumbar doses of  $\geq 3$  mg.

Following IT dosing to monkeys, much of the nusinersen related material was cleared from the CSF via CSF turnover. Distribution into CNS tissues was demonstrated. The half-life of drug related material in CNS tissues was very long, thus supporting a long duration between doses. Metabolism of nusinersen involved 3' and 5' exonuclease action in mice, monkeys and humans. No specific excretion studies were submitted. Excretion from the body is likely to be primarily via the urinary route as metabolites.

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<sup>50</sup> Morford L et al. (2011) Preclinical safety evaluations supporting pediatric drug development with biopharmaceuticals: strategy, challenges, current practices. Birth Defects Res. (B) 92: 359-380.

Pharmacokinetic drug interactions involving CYP450 enzymes or transporters are not predicted from *in vitro* data.

Single dose toxicity of nusinersen was assessed in cynomolgus monkeys following IT dosing. The maximum non-lethal dose was the highest tested dose, 7 mg.

Repeat-dose toxicity studies were conducted in mice (3 months, SC route) and Cynomolgus monkeys (up to 53 weeks, IT route). Juvenile animals were used in all studies. The majority of findings for nusinersen were associated with a pro-inflammatory response or with accumulation of the oligonucleotide. These are not considered of clinical concern. Additional findings in the CNS included hippocampal neuronal/glial cell necrosis (not considered a concern in patients), necrotic cells/cellular debris (not of neuronal origin; uncertain effect on neurological function; potentially clinically relevant) and perivascular macrophage infiltrates were seen in the brain and spinal cord (not considered a concern in patients).

Nusinersen was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in CHO cells) or *in vivo* (in the mouse micronucleus test). However, uptake of nusinersen into bacterial and mammalian cells was not demonstrated. Carcinogenicity studies have not been conducted.

No effects on fertility were seen in treated male and female mice. Minimal placental transfer of drug related material was seen in mice and rabbits. No adverse fetal effects were seen in mice and rabbits. Excretion of nusinersen related material was limited in lactating mice. No adverse effects were seen in breast-fed pups following maternal exposure during the gestational and lactational period. No adverse effects on reproductive parameters are expected during clinical use.

Anti-drug antibodies were detected in a number of treated cynomolgus monkeys.

Given the age of monkeys in the toxicity studies, the full effects on postnatal neurogenesis and CNS functional development would not have been assessed.

There was considerable written discussion between the sponsor and the TGA's toxicology area concerning the proposed limits and qualification of the related substance impurities and elemental impurities in the drug substance and drug product. The sponsor has committed to reviewing these limits when more commercial batch data are available.

## Conclusions

The *in vivo* pharmacology studies support the proposed intrathecal injection of nusinersen to increase SMN protein levels in the CNS and ameliorate the effects on muscles responsible for paralysis and respiratory effects observed in patients with SMA. However, while it is noted that some systemic exposure occurs following intrathecal injection, it is uncertain if this is sufficient to improve any peripheral effects associated with the disease.

Based on the combined safety studies, the following have been identified as potential effects during clinical use:

- Acute transient deficits in lower spinal reflexes following injection.
- Anti-drug antibodies may be seen in patients receiving nusinersen. The effects on long term efficacy are unknown.

The following safety parameters have not been adequately assessed:

- Effects on the cardiovascular system.
- Source and neurological effect of necrotic cells and cellular debris in the CNS of treated monkeys.
- Carcinogenic potential.

- Genotoxic potential (no demonstration of cellular uptake).
- The safety of nusinersen, in particular to CNS development and function, in infants < 2.5 years cannot be addressed from the submitted nonclinical dossier.

### **Recommendation and proposed conditions of registration for the delegate**

There are no objections to the registration of Spinraza, with the following conditions of registration:

- The sponsor should provide empirical data showing that 2'-MOE nucleotide monomers are poor substrates for human DNA polymerase.
- The carcinogenicity of nusinersen should be assessed.
- Post marketing monitoring of acute, adverse CNS effects following nusinersen administration should be a priority.

## **V. Clinical findings**

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### **Introduction**

#### **Clinical rationale**

##### ***Current disease management options***

A consensus statement for the standard of care in SMA is intended as a guideline for the care of patients with SMA.<sup>51</sup> For infants with Type I SMA, current medical care is supportive and is focused on respiratory and nutritional support. Chronic respiratory management includes providing methods for airway clearance, including mechanical insufflation/exsufflation or manual cough assist and non-invasive ventilator support such as bi-level positive airway pressure (BiPAP). Acute respiratory infections are often life threatening for these patients and require these same methods of increased airway clearance and increased ventilation support. Nonetheless, despite best supportive efforts, the progression of respiratory deficits, continuous progression of weakness, and consequent premature death are unavoidable.

The standard of care for later onset SMA is dependent on the severity of the disease but may include physical and occupational therapy, nutritional support, pain management, orthotics, environmental controls and home modifications to facilitate safe mobility, and spinal surgery.

Supportive measures for patients with SMA may prolong survival and improve a patient's quality of life; however, there are currently no therapies to maintain motor function, improve motor function, or reduce permanent ventilation or death in patients with SMA.

##### ***Unmet need***

Patients with SMA and the families who care for them describe a significant need for therapies that improve motor function and increase survival.<sup>52</sup> Improvements in motor

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<sup>51</sup> Wang C et al., (2007) Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* 2007; 22: 1027-49.

<sup>52</sup> Qian Y et al., (2015) Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurol.* 2015; 15: 217.

function would ease the significant burden of supportive care, offer greater independence, and improve the patient's quality of life as well as that of their caregivers.

In all cases, there exists a high unmet need for a therapy that will prevent the development or reverse the course of neuromuscular weakness among all patients and prolong survival in the most affected patients.

### **Guidance**

The evaluator was supplied with the following European Medicines Agency (EMA) Guidelines which were applied in the evaluation of this dossier:

- EMA Guideline: Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population.
- EMA Guideline: Investigation of Medicinal Products in the Paediatric Population.
- EMA Guideline: Investigation of Medicinal Products in Term and Preterm neonates.

### **Contents of the clinical dossier**

The submitted clinical studies were divided into groups based upon SMA characteristics as follows:

#### **Infantile onset SMA:**

- Study CS3B: A pivotal, multicentre, randomised, Phase III, sham controlled study in symptomatic subjects with infantile onset SMA.
- Study CS3A: A supportive, multicentre, Phase II, open-label (uncontrolled) study in symptomatic subjects with infantile onset SMA.

#### **Later onset SMA:**

- Study CS4: A pivotal, Phase III, sham controlled study in subjects with later onset SMA.
- Study CS1: A completed, Phase I, first in human, single dose, open label dose escalation study.
- Study CS10: A completed, multicentre, Phase I, single dose, open label extension study for subjects who participated in Study CS1.
- Study CS2: A completed, multicentre, Phase I/IIa, open label, dose escalation study, could include subjects who participated in Study CS1.
- Study CS12: A multicentre, Phase I, open label extension study in subjects who completed Studies CS2 or CS10.

#### **Infantile or later onset SMA:**

- Study SM202: An ongoing, Phase II, sham controlled study with an open-label phase in subjects with SMA not eligible to participate in Studies CS3B or CS4.
- Study CS11: An ongoing, open label extension study for subjects with SMA who previously participated in investigational studies of nusinersen, including Studies CS12, CS3B, and CS4.

#### **Pre-symptomatic SMA:**

- Study SM201: A supportive, multicentre, Phase II, open label study in subjects with genetically diagnosed, pre-symptomatic SMA.

In addition the dossier contained the Clinical Overview, Summaries of Clinical Pharmacology, Clinical Efficacy and Clinical Safety and literature references.

Following the first round evaluation, in response to TGA questions, supplementary data (clinical study reports for Studies CS3B, CS4, and SM201) were supplied by the sponsor. The final study report for Study CS4 is not included in the dossier. This is expected to be submitted by June 2017.<sup>53</sup>

### Paediatric data

As children are the primary group affected by SMA, they were included in the clinical data.

### Good clinical practice

The clinical study reports in the submission indicated that the studies complied with Good Clinical Practice.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Studies providing pharmacokinetic data are summarised in Table 5, below.

**Table 5: Submitted pharmacokinetic studies**

Pharmacokinetic topic	Subtopic	Study ID
<b>Pharmacokinetics in healthy adults</b>	No pharmacokinetic studies in healthy adults were conducted	
<b>Pharmacokinetics in special populations</b>	Target population <sup>3</sup> Single dose	Study CS1 (completed) <sup>1</sup>
	Multi-dose	Study CS2 (completed) <sup>1</sup> Study CS10 (completed) Study CS12 (ongoing) Study CS4 (ongoing) Study CS3A (ongoing) Study CS3B (completed) Studies SM201/CS5 (ongoing)
	Hepatic impairment	No studies were conducted
	Renal impairment	No studies were conducted
	Neonates/infants/children/ adolescents	See Target Population studies
	Elderly	No studies were conducted
	Other special populations	No studies were conducted

<sup>53</sup> The sponsor provided the final study report for CS4 during the time of the evaluation by the TGA.

Pharmacokinetic topic	Subtopic	Study ID
Pharmacokinetic interactions	No pharmacokinetic interaction studies were conducted	
Population pharmacokinetic analyses	Other	Report IS11 Report CPP-017

1) Indicates the primary pharmacokinetic aim of the study; 2) bioequivalence of different formulations; 3) Subjects who would be eligible to receive the drug if approved for the proposed indication.

### Evaluator's conclusions on pharmacokinetics

There were two pharmacokinetic studies submitted which investigated the intrathecal dosing of nusinersen. The administered doses were between 1 mg and 12 mg. Initially doses up to 9 mg were investigated. The dosing was then extended to 12 mg. There were no dose limiting adverse effects at 12 mg, however higher doses were not investigated. This has not been specifically addressed by the sponsor. Both studies were conducted in children diagnosed with SMA and were aged less than 18 years. Further pharmacokinetic data in children less than 18 years of age with a diagnosis of SMA was provided from the pivotal and supportive efficacy studies.

Serum levels of nusinersen were an order of magnitude lower than CSF concentrations. Because of the intermittent nature of the CSF sampling, the data were insufficient to predict the actual half-life in CSF. However, there are 2 population pharmacokinetic analyses. These analyses well conducted and they clarify the pharmacokinetic profile of nusinersen in both CSF and plasma.

There are deficiencies in the presented pharmacokinetic data that need to be addressed:

- Clarify the development of the dosing schedule. Specifically, the sponsor should explain why doses higher than 12 mg were not explored.
- There are no data in adults older than 18 years of age. There may be age-related changes in CSF composition and circulation that impact upon the pharmacokinetics of nusinersen. Therefore, the sponsor should obtain data in adults treated with SMA as surviving adult patients are treated with nusinersen.

## Pharmacodynamics

### Studies providing pharmacodynamic data

No specific pharmacodynamic studies were provided in the dossier; however, all of the submitted studies contained some pharmacodynamic data. The pharmacokinetic studies (Study CS1 and Study CS2, as listed in Table 6 below) did contain some specific pharmacodynamic endpoints which were SMN protein concentration in CSF and immunogenicity.



**Table 6: Submitted pharmacodynamic studies**

Pharmacodynamic topic	Subtopic	Study ID
Primary Pharmacology	Effect on SMN protein concentration in cerebrospinal fluid	Study CS1 Study CS2
	Effect on immunogenicity	Study CS1 Study CS2

**Evaluator's conclusions on pharmacodynamics**

No specific pharmacodynamic studies were conducted. The sponsor was unable to demonstrate a clear dose response relationship between the CSF concentrations of nusinersen and SMN protein concentrations in CSF. This does not necessarily mean that intracellular concentrations of SMN protein were not elevated in a dose dependent manner.

**Dosage selection for the pivotal studies****Rationale for dosage selection**

No formal dose finding studies were conducted that demonstrated that the proposed dosage regimen was the optimal one. The final recommended dosing regimen was based upon the pharmacokinetic studies, which investigated doses up to 12 mg. The subsequent efficacy in the clinical studies was demonstrated at this dose.

**Evaluator's conclusions on dose finding for the pivotal studies**

The basis of the final recommended dosing is not entirely clear. It may be that alternative dosing regimens are more effective but equally safe.

The sponsor should further clarify the exact basis on which the proposed dosing regimen was based. The sponsor should also discuss whether an increased dose may be of benefit to poor responders.

**Efficacy****Studies providing efficacy data**

Studies providing efficacy data are outlined under 'contents of the clinical dossier', above.

**Evaluator's conclusions on efficacy**

The randomised controlled trials support the efficacy of nusinersen in the treatment of SMA Type II and Type III when compared to sham treated controls.

In Study CS3b (severely affected patients), 51% of subjects in the nusinersen group achieved a motor milestone response compared to 0% in the control group ( $p < 0.0001$ ). There was a significantly prolonged overall survival time observed in the treated group with 13 deaths (16%) in the treatment group compared with 16 deaths (39%) in the control group ( $p = 0.0041$ ).

In Study CS4 (less severely affected patients), the change from Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) score at 15 months was compared between the 2 treatment groups.<sup>54</sup> The treatment group showed an improvement of 4 while the control group had a worsening of 1.9. The difference between the groups was 5.9 (treatment group compared to controls) ( $p = 0.0000002$ ). There were no deaths in either group.

The efficacy is supported by the supplementary studies, which also demonstrated efficacy in both ambulant and non-ambulant patients. The pivotal studies were well conducted and included sham treated controls. The primary endpoints were appropriate for assessing neuromuscular development in patients with SMA at different stages of development. The appropriate patient groups, those with SMA Types II and III were studied. There was evidence of prevention of regression or improvements in motor development that would not be expected in patients with SMA. While patients did not have motor development at the level of their unaffected peers, this was a clinically significant advance on what is available currently. The main missing information is whether the improvements will be sustained over a longer period of years and this will require longitudinal follow-up studies in the post-marketing period. While detailed quality of life studies were not conducted, the outcomes demonstrated will be of significant interest to patients and their families.

The sponsor should provide updates on outcomes of the ongoing supportive studies as these become available.

## Safety

### Studies providing safety data

All completed and ongoing studies provided data for the assessment of safety. See 'contents of the clinical dossier' above, for further details.

### Patient exposure

A total of 260 subjects have received nusinersen by IT injection:

- For subjects with infantile onset SMA, a total of 100 subjects were exposed to nusinersen for 91.21 subject years. The sham controlled experience in infantile onset SMA consisted of data from 80 subjects who received nusinersen and 41 subjects who received sham with an overall mean duration of exposure of 251.8 days.
- For subjects with pre-symptomatic SMA, a total of 20 subjects were exposed to nusinersen for 16.48 subject years.
- For subjects with later onset SMA, a total of 140 subjects were exposed to nusinersen for 247.63 subject years.
- Additionally, 21 infants and children with SMA are participating in ongoing, blinded clinical studies of nusinersen.

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<sup>54</sup> The HFMSE is a validated and since revised functional motor scale devised for use in children with SMA, in particular those with limited mobility, to give objective information on motor ability and clinical progression. The scale based upon scoring of discrete activities, was designed to be self-explanatory, quick, easy to use, reproducible and reliable. Maim, M et al., (2003) The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *Eur J Paediatr Neurol.* 2003;7:155-15.

**Safety issues with the potential for major regulatory impact**

Specific safety issues raised in the dossier and examined by the evaluator are listed under the evaluator's conclusions below. For further discussion, see Attachment 2.

**Post marketing data**

As a new chemical entity, no post marketing data exists.

**Evaluator's conclusions on safety**

Overall the safety profile of nusinersen is favourable compared to other antisense molecules. This may be, in part, due to the fact that it is largely confined to the CSF and systemic exposure is limited. Many of the adverse events documented were related to the progress of the underlying disease including the deaths and the requirement for ventilator support.

The specific safety issues raised in the dossier are listed below.

- There is a risk of complications of the lumbar puncture associated with administration of nusinersen, especially if there is concurrent thrombocytopenia. The lower platelet count observed in itself would most likely not be clinically significant. However, if there were a small risk of an extradural bleed with a lumbar puncture, this may be unacceptable because of the potential for a severe outcome with paraplegia. There may also be the risk associated with sedation if this is required for the performance of the lumbar puncture.
- The risk of prolonged QTc has not been completely tested.<sup>55</sup> The assessment of the QTc interval is not fully described. This is important as there were reports of ventricular tachycardia in treated patients that are otherwise unexplained.
- There is a potential renal risk of proteinuria given the nature of nusinersen as an antisense oligonucleotide. There is no signal for this in the clinical trials. However, as the systemic exposure of nusinersen is lower than if an oligonucleotide were administered directly into the systemic circulation, renal risks may require a prolonged exposure to be identified.
- Hyponatraemia has been reported in some patients treated with nusinersen. This did not result in any observable acute clinical deterioration in the studies. Prolonged or severe hyponatraemia can result in clinical consequences if unrecognised or untreated.
- Some patients treated with nusinersen had increases in alanine transaminase (ALT) levels. It is uncertain whether these changes may represent an increased risk of liver damage due to nusinersen.
- There is an ongoing risk of immunological reactions in patients treated with nusinersen. The extent and implications of such reactions are, at present, unknown. The development of antibodies with other biological agents can result in either a decrease in efficacy of the treatment or a severe allergic reaction which can be life-threatening. Neither of these was observed in the clinical studies.
- There is an unanswered question about the risk of vasculitis in patients treated with nusinersen. There is a single case report (Study CS3B) which may have been a case of vasculitis.

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<sup>55</sup> The QTc, is the QT interval (the time taken from the Q wave to the T wave of a cardiac cycle) corrected for heart rate.

- In the sponsor's submission to the FDA, 3 cases of vasculitis were identified which were not clearly apparent in the dossier submitted to the TGA. These cases should be identified in the dossier and described in detail.
- In Study CS3B, there was relatively poor growth in some patients treated with nusinersen when compared to sham treated patients. This is unexpected given the clinical motor improvement and the overall improvement in survival.
- Hippocampal damage identified in pre-clinical studies has not been identified in the clinical studies but remains a potential risk with prolonged exposure to nusinersen.
- There is currently a lack of long term data in the use of nusinersen. It is uncertain whether the clinical benefits observed in the studies will persist over years
- There is a lack of safety data in adults over the age of 18 years of age treated with nusinersen. It is uncertain whether adults will have a higher rate of particular adverse effects; for example, immunological reactions or organ dysfunction.

## First round benefit-risk assessment

### First round assessment of benefits

The evaluator's first round assessment of the benefits of Spinraza nusinersen for the proposed indication are outlined in Table 7 below.

**Table 7: First round assessment of benefits**

Indication	
Benefits	Strengths and Uncertainties
<p>Spinal muscular atrophy (SMA), is a severe neuromuscular disease. Spinraza, nusinersen is the first novel treatment to offer improvement in outcome for both symptomatic and pre-symptomatic patients with SMA Types I, II and III. The main benefits of Spinraza are the improvement in muscle function and improved survival in treated patients as demonstrated in the pivotal studies.</p> <p>In severely affected individuals with infantile onset SMA Type (Study CS3b)<sup>56</sup>, there were significant clinical improvements in treated patients.</p> <p>51% of subjects in the treatment group achieved a response compared to 0% in the control group (<math>p &lt; 0.0001</math>).</p> <p>16 subjects (22%) achieved full head control, 6 subjects (8%) achieved independent sitting, and 1 subject (1%) achieved standing.</p>	<p>The strength of the application is the strong treatment effect of nusinersen in terms of motor function and potential survival in an otherwise untreatable disease.</p> <p>There is significant uncertainty about the long term effectiveness of nusinersen in all patients with SMA. There is also a lack of data in the treatment of milder disease in adults greater than 18 years of age.</p> <p>Furthermore, there are no data on the use of nusinersen in the most severe form of the disease (SMA 0) or the mildest adult form (SMA IV). However, it is likely that that a Type 0 SMA patient would survive long enough to benefit from treatment.</p> <p>Another uncertainty is whether the proposed dose of nusinersen (12 mg intrathecally administered once every 4 months after an initial loading regimen) is optimal or whether higher or more</p>

<sup>56</sup> The selection criteria for Study CS3b was infantile onset SMA,  $\leq 6$  months of age at symptom onset,  $\leq 7$  months of age at screening (which includes patients most likely to develop Type I and potentially some early onset Type II SMA). Please see Table 1 for classification of SMA types.

Indication	
Benefits	Strengths and Uncertainties
<p>Survival was improved in treated patients with 13 deaths (16%) in the treated groups compared to 16 subjects (39%) the control group (p = 0.0041).</p> <p>In less severely affected individuals with later onset SMA Type (Study CS4)<sup>57</sup>, the interim efficacy analysis demonstrated that significant clinical improvements at 15 months of treatment. The HFMSE scores from Baseline to Month 15 improved by 4 in the treatment group while there was a decline of 1.9. The total difference of 5.9 was highly statistically significant (p = 0.0000002). There were no deaths in this study.</p> <p>The supporting uncontrolled studies are consistent with the pivotal controlled studies. They do demonstrate improvement in motor function where inevitable motor decline or severe delay is the usual outcome in SMA.</p> <p>The safety profile of Spinraza is acceptable given the severity of the disease that is being treated. There are few drug-related adverse events and there were no severe outcomes (such as death or increased rate of ventilation) attributable to the treatment. This is in a disease where premature death or ventilator dependency is common and inevitable in Type I SMA.</p>	<p>frequent dosing may further improve outcomes.</p>

### First round assessment of risks

The evaluator's first round assessment of risks of Spinraza nusinersen for the proposed indication are outlined in Table 8, below.

**Table 8: First round assessment of risks**

Risks	Strengths and Uncertainties
<p>Given the rarity of SMA and the difficulty of performing placebo-controlled clinical trials in such a severe disease, the dossier presents a comprehensive review of the risks associated with nusinersen. Overall, for a treatment of such a severe disease the treatment has quite a low risk of adverse events. The main risk is associated with the</p>	<p>The incorporation of long-term post-marketing monitoring of both efficacy and safety as proposed in the EU registration will potentially clarify the long term outcomes of the treatment of patients with SMA with nusinersen.</p> <p>This monitoring of the patient cohort (more</p>

<sup>57</sup> The selection criteria for Study CS4 was for later onset SMA, > 6 months of age at symptom onset, which includes patients most likely to develop Type II or Type III SMA. Please see Table 1 for classification of SMA types

Risks	Strengths and Uncertainties
<p>intrathecal administration and the complications of recurrent lumbar punctures (especially as nusinersen may be associated with thrombocytopaenia in some cases).</p> <p>There are also the potential risks of organ dysfunction, immunoreactivity and CNS damage as described in the animal models.</p> <p>There is also the risk that the short-term gains in motor function may not persist or continue long term.</p> <p>The specific safety issues are included below this table.</p>	<p>than just routine postmarket surveillance) of these patients will determine the rate of immunoreactivity, whether there is a significant risk from the recurrent lumbar punctures and identify and whether the hippocampal changes in animals appear to translate into clinically significant sequelae in patients.</p> <p>There is still significant uncertainty as to whether 12 mg is the optimal dose or further benefits could be gained by increasing the dose. There is no current plan to address this.</p>

The specific safety issues raised in the dossier are outlined as follows:

- There is a risk of complications of the lumbar puncture associated with administration of nusinersen, especially if there is concurrent thrombocytopenia. The lower platelet count observed in itself would most likely not be clinically significant. However, if there were a small risk of an extradural bleed with a lumbar puncture, this may be unacceptable because of the potential for a severe outcome with paraplegia. There may also be the risk associated with sedation if this is required for the performance of the lumbar puncture.
- The risk of prolonged QTc has not been completely tested. The assessment of the QTc interval is not fully described. This is important as there were reports of ventricular tachycardia in treated patients that are otherwise unexplained.
- There is a potential renal risk of proteinuria given the nature of nusinersen as an antisense oligonucleotide. There is no signal for this in the clinical trials. However, as the systemic exposure of nusinersen is lower than if an oligonucleotide were administered directly into the systemic circulation, renal risks may require a prolonged exposure to be identified.
- Hyponatraemia has been reported in some patients treated with nusinersen. This did not result in any observable acute clinical deterioration in the studies. Prolonged or severe hyponatraemia can result in clinical consequences if unrecognised or untreated.
- Some patients treated with nusinersen had increases in ALT levels. It is uncertain whether these changes may represent an increased risk of liver damage due to nusinersen.
- There is an ongoing risk of immunological reactions in patients treated with nusinersen. The extent and implications of such reactions are, at present, unknown. The development of antibodies with other biological agents can result in either a decrease in efficacy of the treatment or a severe allergic reaction which can be life-threatening. Neither of these was observed in the clinical studies.
- There is an unanswered question about the risk of vasculitis in patients treated with nusinersen. There is a single case report (Study CS3B) which may have been a case of vasculitis.
- In the sponsor's submission to the FDA, 3 cases of vasculitis were identified which were not clearly apparent in the dossier submitted to the TGA. These cases should be identified in the dossier and described in detail.

- In Study CS3B, there was relatively poor growth in some patients treated with nusinersen when compared to sham treated patients. This is unexpected given the clinical motor improvement and the overall improvement in survival.
- Hippocampal damage identified in pre-clinical studies has not been identified in the clinical studies but remains a potential risk with prolonged exposure to nusinersen.
- There is currently a lack of long-term data in the use of nusinersen. It is uncertain whether the clinical benefits observed in the studies will persist over years
- There is a lack of safety data in adults over the age of 18 years of age treated with nusinersen. It is uncertain whether adults will have a higher rate of particular adverse effects; for example, immunological reactions or organ dysfunction.

### **First round assessment of benefit-risk balance**

The benefits of the use of Spinraza in patients with SMA are significant. Spinraza addresses an unmet need in this groups of severely affected individuals. There are improvements in motor function and survival in treated patients when compared with sham treated controls. These changes are clinically and statistically highly significant. In infantile onset Type SMA, there is an improvement in motor function and survival following treatment compared to controls. In later onset SMA Type there is a highly significant improvement in motor function compared to controls.

This is pivotal as, up until now, there has been no effective therapy for SMA. Up until now, supportive therapies such as physiotherapy and occupational therapy do not alter the progress of the disease with progressive muscle weakness. As the SMA worsens, poor lung function may result in recurrent respiratory infections and the consequences of muscle weakness. These are addressed by specific therapies including antibiotics, alimantal supplementation and ventilatory support. However, none of these therapies address the fundamental problem of the inevitable physical decline associated. Spinraza is the first treatment to address the underlying cause of SMA and result in an improved outcome.

SMA Type 0 and Type IV were not addressed in the dossier. Type 0 SMA is a severe disease and patients do not live long enough to potentially benefit from therapy. Also, as patients with Type 0 only have a single copy of the SMA2 gene, there is limited potential for Spinraza to be effective. Type IV SMA is a relatively mild disease with near normal motor function and a normal life expectancy; the risk to benefit ratio of treatment with Spinraza in these patients may be unfavourable. Type IV SMA was not addressed in the dossier and is not specifically excluded in the proposed indication. The 'Precautions' section of the PI should include the statement that Type IV SMA is a mild disease with normal lifespan and Spinraza has not been investigated in this group of patients.

The risks of the use of Spinraza are related to the uncertainty as to whether the dosing is optimal, the long term efficacy, use in adults over 18 years of age. Otherwise there are few drug-related adverse events and there were no severe outcomes (such as death or increased rate of ventilation) that were attributable to the treatment. Most of the treatment related adverse effects related to the lumbar puncture procedure such as nausea post-sedation or post-lumbar puncture syndrome. In Study CS3B no adverse events were considered by the study investigators as being related to Spinraza. There are some unresolved safety concerns including potential QT changes, the risk of recurrent lumbar punctures and central nervous system effects. There is also a risk associated with sedation if this is required as part of performing the lumbar puncture. The QT changes are inadequately investigated and this is a specific deficiency in the studies. The other risks, including those associated with the lumbar puncture and the administration of a medicine in to the CNS, are inherent to the management of the SMA with Spinraza. These risks can

be addressed by the sponsor in their follow-up responses to the questions and the implementation of a comprehensive post-marketing program.

Spinraza is an effective treatment in a severe disease (SMA) with no effective treatment. It addresses an unmet need and the safety profile is acceptable given the severity of the illness. Furthermore, the outstanding risks can be addressed by the sponsor. The benefits of Spinraza outweigh the outstanding risks and it can be recommended for approval for marketing in Australia.

### **First round recommendation regarding authorisation**

The evaluator recommends the authorisation of Spinraza '*for the treatment of spinal muscular atrophy (SMA)*'. This is because of the significant improvement in motor function and improved survival in patients with SMA treated with Spinraza. There are some outstanding issues regarding whether 12 mg is the optimal dosing and some safety concerns around the risk of lumbar puncture if a patient develops thrombocytopenia. However, these can be addressed with the suggested changes to the product information and ongoing post marketing surveillance.

### **Clinical questions and second round evaluation of clinical data submitted in response to questions**

For details of the clinical questions, sponsor's responses and the evaluation of these responses please see Attachment 2.

### **Second round benefit-risk assessment**

#### **Second round assessment of benefits**

After consideration of the responses to clinical questions, the benefits of Spinraza (nusinersen) in the proposed usage are similar to those identified in the first round assessment above:

- Nusinersen is the first novel treatment to offer improvement in outcome for both symptomatic and pre-symptomatic patients with SMA Types I, II and III. The main benefits are the improvement in muscle function and improved survival in treated patients as demonstrated in the pivotal studies. It is uncertain whether these benefits will be maintained long term across the various SMA types, whether SMA types not included in the clinical trial program will experience benefit from treatment and whether any benefit will be demonstrated for the adult patient population.
- In severely affected individuals with infantile onset SMA ( Study CS3B), there were significant clinical improvements in treated patients:
  - 51% of subjects in the treatment group achieved a response compared to 0% in the control group ( $p < 0.0001$ ). This translates to a number needed to treat (NNT) of 2 for this endpoint. Two patients would need to receive treatment over 10 months for one patient to meet the definition of a responder.
  - Time to death or permanent ventilation was prolonged in subjects treated with nusinersen; there was a 47% reduction in the risk of death or permanent ventilation compared with subjects who received the sham procedure (hazard ratio (HR) 0.530 (95% CI 0.3156, 0.8902  $p = 0.0164$ ). The NNT for this endpoint



was 4, as in four patients would need to received treatment for 10 months to prevent one event of death or permanent ventilation.

- Study CS4 in individuals with later onset SMA type, the final efficacy analysis demonstrated significant improvements in HFSME scores at 15 months of treatment. The HFMSE scores from Baseline to Month 15 improved by 3.9 in the treatment group while there was and a decline of 1.0 in the control group. The total difference of 4.9 was statistically significant ( $p = 0.0000001$ ).
- The safety profile of nusinersen is acceptable given the severity of SMA. There were few drug-related adverse events and there were no severe outcomes attributed to treatment. However, overall clinical trial exposure is relatively low given the rarity of SMA and there are ongoing clinical trials to further characterise the safety and efficacy of long term treatment.

## Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Spinraza (nusinersen) in the proposed usage are:

- The proposed indication includes all SMA types. Nusinersen has not been evaluated for safety or efficacy in SMA Types 0 and IV and non-5q SMA. It is unclear whether treatment with nusinersen would confer any benefit in these patient subgroups. Type IV SMA (adult onset SMA) is the mildest form of SMA and patients are ambulatory with a normal life expectancy. The benefit-risk profile may not positive in this patient population given the risks associated with antisense oligonucleotides and with intrathecal administration. The clinical studies submitted included patients with subjects with infantile onset and genetically diagnosed (Type I) SMA, pre-symptomatic SMA (Type I or Type II) and subjects with later onset (Type II and Type III) SMA.
- As SMA is a rare condition and clinical trial exposure has been limited with respect to patient numbers and length of treatment exposure. There is a lack of long-term data for nusinersen treatment and it is not known whether the clinical benefits observed in the studies will be maintained. As outlined above, the sponsor has committed to long-term post-marketing monitoring of both efficacy and safety as proposed in the EU registration that may clarify the long-term outcomes of the treatment.
- Only a small number of patients over the age of 18 have been included in nusinersen clinical trials to date and there is also a lack of data regarding the safety and efficacy of nusinersen treatment in this patients group. It is uncertain whether adults will experience similar clinical benefit or have higher rates of adverse events.
- There is still significant uncertainty regarding the optimal dose and dosing schedule. The same dose and dosing schedule has been requested for all patients (loading doses on Days 0, 14, 28 and 63, followed by 4 monthly maintenance doses). For patients with later onset SMA the clinical trials have had a 6 monthly maintenance dosage regimen except for Study SM202, the results of which are not yet available and the study has only exploratory efficacy endpoints.
- Nusinersen requires intrathecal administration which carries procedure related risks. The important potential risk of thrombocytopaenia is of particular relevance to the management of risks associated with intrathecal administration. The sponsor intends to monitor thrombocytopaenia and coagulation abnormalities as an important potential risk as part of the RMP. The communication of this risk has been partially addressed in proposed changes to the Australian PI but further information is warranted.

- There is a risk of complications with the lumbar puncture associated with administration of nusinersen, especially if there is concurrent thrombocytopenia. There are also risks associated with sedation that may be required for the lumbar puncture procedure.
- As outlined in first round, there is an ongoing risk of immunological reactions in patients treated with nusinersen. Decreases in efficacy and severe allergic reactions have not been observed in clinical studies to date but the extent and implications of such reactions are, at present, unknown. 6% of clinical trial subjects developed anti-nusinersen antibodies post-baseline but the clinical significance of this is unclear. The uncertainty regarding the clinical significance of anti-drug antibodies and should be communicated to prescribers.
- Hippocampal damage identified in pre-clinical studies has not been identified in the clinical studies but remains a potential risk with prolonged exposure to nusinersen. The sponsor has not described their approach to detecting necrotic CNS changes in treated patients in the sponsor's second round response. This issue is considered unresolved.
- The risk of prolonged QTc has not been completely tested. This is important as there were reports of ventricular tachycardia in treated patients that are otherwise unexplained.
- There is a potential renal risk of proteinuria given the nature of nusinersen as an antisense oligonucleotide. There is no signal for this in the clinical trials. However, as the systemic exposure of nusinersen is lower than if an oligonucleotide were administered directly into the systemic circulation, renal risks may require a prolonged exposure to be identified.
- Hyponatraemia has been reported in some patients treated with nusinersen. This did not result in any observable acute clinical deterioration in the studies. Prolonged or severe hyponatraemia can result in clinical consequences if unrecognised or untreated.
- Some patients treated with nusinersen had increases in ALT levels. It is uncertain whether these changes may represent an increased risk of liver damage due to nusinersen.
- The sponsor has addressed the issue of vasculitis in patients treated with nusinersen but the broader adverse event of rash needs to be communicated to prescribers.
- In Study CS3B, there was relatively poor growth in some patients treated with nusinersen when compared to sham treated patients. This is unexpected given the clinical motor improvement and the overall improvement in survival.

## Second round assessment of benefit-risk balance

The benefit-risk balance of Spinraza (nusinersen) remains favourable but the proposed indication should be refined to exclude the non-5q SMA population. As outlined in the first round, the drug addresses an unmet need in a population of patients with severe disease. Clinically and statistically significant improvements in motor function and survival have been demonstrated. In infantile onset SMA, Study CS3B demonstrated an improvement in motor function and survival following treatment compared to controls. In later onset SMA, there is a highly significant improvement in motor function compared to controls.

5q SMA Types 0 and IV were not addressed in the dossier. As stated above, the indication should be refined to exclude non-5q SMA patients. As outlined in the first round there is limited potential for nusinersen to be effective in Type 0 SMA and the risk to benefit ratio

of treatment in Type IV SMA has not been characterised and may be unfavourable. However, specific exclusion of Type 0 and Type IV SMA from the proposed indication is not recommended as these subtypes have the same underlying basic biology of SMA and in certain cases a trial of nusinersen therapy may be warranted. Instead, the 'Precautions' section of the PI should include the statement that nusinersen has not been investigated in these patient groups. In addition, the initiation of treatment should be limited to healthcare professionals experienced in the treatment of SMA.

The risks of the use of nusinersen are related to the uncertainty as to whether the dosing is optimal, the long-term efficacy, use in adults over 18 years of age. There were few drug-related adverse events and there were no severe outcomes attributable to the treatment. There are some unresolved safety concerns including potential QT changes, the risk of recurrent lumbar punctures and central nervous system effects. As outlined in the first round evaluation, the QT changes are inadequately investigated and this should be addressed in the PI. The serious potential risk of CNS effects has not been addressed in the sponsor's post-first round response. The risks of renal toxicity, thrombocytopenia, hyponatraemia and rash need to be addressed in the PI. Advice should be provided to clinicians regarding testing for thrombocytopenia and coagulation abnormalities and urinary protein.

As outlined in the first round the benefit-risk balance is favourable but several outstanding risks need to be addressed by the sponsor through ongoing clinical studies, post-market monitoring of safety and efficacy and changes to the PI to better communicate the outstanding risks and uncertainties.

The evaluator recommends the authorisation of Spinraza (nusinersen) for the treatment of 5q spinal muscular atrophy (SMA). The proposed changes to the indication are discussed above. This recommendation is based on the improvements in motor function and improved survival in patients with SMA treated with nusinersen. There are some outstanding issues regarding optimal dosing and some safety concerns relating to QT changes, CNS effects, the risks of recurrent lumbar puncture, renal toxicity and thrombocytopenia. However, these can be addressed with the suggested changes to the PI and ongoing post-marketing surveillance.

## VI. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP), version 1.0; 26 September 2016; data lock point (DLP) 15 July 2016 and an Australian Specific Annex (ASA) version 1.0; dated November 2016 which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 9, below.

**Table 9: Summary of safety concerns**

Summary of safety concerns	
<b>Important identified risks</b>	None

Summary of safety concerns	
<b>Important potential risks</b>	Serious infection in the context of lumbar puncture*
<b>Missing information</b>	Safety profile of patients > 18 years
	Safety profile in Patients with severe and progressive scoliosis
	Safety profile in Patients receiving repetitive lumbar punctures
	Safety profile in Patients with long-term exposure
	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 (for example Type 0, and Type IV SMA)

\*The EMA has recommended the removal of this safety concern, in response to EMA Day 90 Questions.<sup>58</sup>

The sponsor has proposed that there are no identified risks associated with nusinersen. The summary of safety concerns is considered incomplete.

### Pharmacovigilance plan

Routine pharmacovigilance activities will be conducted in Australia to monitor all the safety concerns.<sup>59</sup> Structured follow up forms are not proposed for characterisation of any of the safety concerns. The sponsor should propose the use of structured follow up forms to enhance the collection of routine pharmacovigilance for the important potential risks recommended to be included in this report.

There are no additional studies referenced in the pharmacovigilance plan in the ASA or the EU-RMP, but the sponsor will continue to monitor safety in ongoing trials which include:

- Study CS11: A Phase III, multicentre, open label extension study to Studies CS3B, CS4, and CS12 to collect long term safety data, with a blinded loading period and an open label maintenance period. Planned completion in January 2020.
- Study SM202: A Phase II, worldwide, double blind, sham procedure controlled study. Planned completion November 2019.

No studies in special populations (renal, hepatic impairment) are proposed due to the small sample size in this rare disease. This is acceptable.

Long term safety data are not available. The sponsor has not proposed any patient registry based post market surveillance studies in the RMP. However, in response to questions from EMA, the sponsor has agreed to add a pharmacovigilance activity: 'gathering of additional safety data by collaborating with existing disease registries to the RMP'.<sup>60</sup> The

<sup>58</sup> Response to EMA Day 90 questions.

<sup>59</sup> Routine pharmacovigilance practices involve the following activities: All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; Reporting to regulatory authorities; Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; Submission of PSURs; Meeting other local regulatory agency requirements.

<sup>60</sup> Response to the EMA Q127

sponsor has plans to utilise existing SMA patient registries overseas (USMDA, TREAT NMD, ISMASC: a proposed collaboration between investigators in the US, Italy, and UK), to develop post market surveillance studies of long term safety.

The RMP should be updated if these studies are confirmed, and it is considered appropriate to extrapolate the results of these overseas studies to Australian patients. The sponsor should consider the need for adequate pharmacovigilance of long term safety in Australia if the overseas registries are not confirmed.

Table 10 outlines the ongoing or proposed studies in the revised version of the RMP.

**Table 10: Ongoing and proposed pharmacovigilance related studies**

Study/activity	Objectives	Safety concerns addressed	Status	Final reports/ Milestones
Study SM202	This is a Phase II, randomised, double blind, sham procedure controlled study to assess the safety, tolerability, pharmacokinetic, 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.	Long term safety, tolerability, pharmacokinetic and efficacy data for patients with infantile and later onset SMA assessed for up to around 43 months. Cardiac.	Ongoing	2019
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, scoliosis, other comorbidities, nutritional therapies, pulmonary function and devices, and cause of death.	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 (for example, Type 0 and Type IV SMA); safety profile of patients > 18 years	Planned	Preliminary study synopsis 1 month after EC.

Study/activity	Objectives	Safety concerns addressed	Status	Final reports/ Milestones
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 (for example Type 0 and Type IV SMA); safety profile of patients > 18 years.	Ongoing	Updates to be provided in PSURs
TREAT-NMD	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 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 Type IV SMA); safety profile of patients > 18 years	Ongoing	Updates to be provided in PSURs.

**Table 11: Long term safety and efficacy studies**

Study short name and title	Rationale and study objectives/study design	Milestone(s)	Due Date(s)
Study CS11 (SHINE) An open label extension study for patients with spinal muscular atrophy who	This is an open label extension study in subjects with SMA who previously participated in investigational	First patient dosed	17 November 2015
		Last patient dosed	Q3 2017

Study short name and title	Rationale and study objectives/study design	Milestone(s)	Due Date(s)
previously participated in investigational studies of ISIS 396443 (nusinersen).	studies of nusinersen. 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 over an additional period of 5 years (totalling up to 8+ years with time in index study).	Last patient completed	Q3 2022
		Final study report	August 2023
Study CS5 (SM201/NURTURE) An open label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 (nusinersen) delivered intrathecally to subjects with genetically diagnosed and presymptomatic spinal muscular atrophy.	This is a Phase II, open label study to assess the efficacy, safety, tolerability, and pharmacokinetic of multiple doses of nusinersen in subjects with genetically diagnosed and pre-symptomatic SMA.	First patient dosed	20 May 2015
		Last patient dosed	1 February 2017
		Last patient completed	Q1 2022
		Final study report	April 2023

### Risk minimisation activities

Routine risk minimisation only is proposed. There are no identified risks to be mitigated. No additional risk minimisation is considered necessary by the sponsor, and routine pharmacovigilance is considered sufficient to evaluate the effectiveness of the RMP.

### Reconciliation of issues outlined in the RMP report

Table 12 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

**Table 12: Reconciliation of issues outlined in the RMP report**

Reconciliation of issues outlined in the RMP report
<b>Recommendation 1.</b> The sponsor should address the nonclinical and clinical evaluator's recommendations for the safety specification, in the summary of safety concerns in the ASA.
<i>Sponsor's response:</i> The sponsor has provided a revised RMP that aligns with the

### Reconciliation of issues outlined in the RMP report

latest agreed EU-RMP safety specification. The sponsor also refers TGA to the responses submitted for the first 8 safety based questions raised in the clinical evaluation report [see Attachment 2].

*RMP evaluator comment:* The toxicology area of the TGA evaluated the nonclinical aspects of the safety specification and the nonclinical evaluator provided the following safety related conclusions and recommendations:

*'Results and conclusions drawn from the nonclinical program for nusinersen detailed in the sponsor's draft RMP are in general concordance with those of the Nonclinical Evaluator, with the following exceptions:*

- *Details regarding the pre/postnatal study in mice should be included*
- *There are still outstanding questions regarding the adequacy of the genotoxicity studies*
- *With respect to carcinogenicity, it should be stated that the carcinogenic risk is not known at this stage.*
- *Acute, transient neurological deficits may be seen in some patients and would be considered an unwanted effect. This should be identified as an Important potential risk'.*

*'Based on the combined safety studies, the following have been identified as potential effects during clinical use:*

- *Acute transient deficits in lower spinal reflexes following injection.*
- *Anti-drug antibodies may be seen in patients receiving nusinersen. The effects on long term efficacy are unknown.*

*The following safety parameters have not been adequately assessed:*

- *Effects of potential off-target hybridisation*
- *Effects on the cardiovascular system*
- *Source and neurological effect of necrotic cells and cellular debris in the CNS of treated monkeys.*
- *Genotoxic potential*
- *Carcinogenic potential*
- *The safety of nusinersen, in particular to CNS development and function, in infants < 2.5 years cannot be addressed from the submitted nonclinical dossier'.*

There are outstanding safety concerns identified by the clinical evaluator and associated recommendations for the risk management plan and activities.

Second round clinical evaluator comments on the draft RMP:

*'The Summary of Safety Concerns in the draft Risk Management Plan (Version 5.0) is not entirely satisfactory and should be revised, having regard to the following comments. Several potential risks are not described in the Summary of Safety Concerns such as QT prolongation. There are outstanding concerns regarding the risk of CNS effects that have not been addressed by the sponsor and this potential risk is not described in the summary of safety concerns'.*

[In addition, see the second round overall conclusions on safety, assessment of



Reconciliation of issues outlined in the RMP report
risks and assessment of overall benefit-risk balance, above].
<p><b>Recommendation 2.</b> The following changes to the list of safety concerns should be made:</p> <ol style="list-style-type: none"> <li>1. Add Important potential risk: Neurologic toxicity</li> <li>2. Add important potential risk: Hyponatremia</li> <li>3. Add important potential risk: Hepatotoxicity</li> <li>4. Changes agreed to in the Day 120 response to EMA questions: <ol style="list-style-type: none"> <li>a. Add important potential risk: ‘thrombocytopenia/coagulation abnormalities’</li> <li>b. Add important potential risk: ‘renal toxicity’</li> <li>c. Remove important potential risk: ‘serious infection in the context of lumbar puncture’.</li> </ol> </li> </ol>
<i>Sponsor’s response:</i> The sponsor does not agree to Changes 1 to 3, above. The sponsor has updated the RMP as agreed in the Day 120 Response to EMA.
<i>RMP evaluator comment:</i> See RMP evaluator comment to Recommendation 1, above.
<p><b>Recommendation 3.</b> The following safety concerns should be discussed in the safety specification, and included in the list of safety concerns or missing information. If not, the sponsor should justify their omission:</p> <ol style="list-style-type: none"> <li>1. Rash and Vasculitis</li> <li>2. Effects of nusinersen on growth / effects on development of infants &lt; 2.5 years of age</li> <li>3. Genotoxicity/Carcinogenicity</li> <li>4. Immunogenicity</li> <li>5. Effects on cardiac conduction (QT prolongation)</li> </ol>
<i>Sponsor’s response:</i> The sponsor does not agree to any change.
<i>RMP evaluator comment:</i> See RMP evaluator comment to Recommendation 1, above.
<p><b>Recommendation 4.</b> The sponsor should provide a revised ASA that aligns with the latest agreed EU-RMP safety specification.</p>
<i>Sponsor’s response:</i> ‘The sponsor has provided a revised ASA that aligns with the latest agreed EU-RMP safety specification’.
<p><i>RMP evaluator comment:</i> Outstanding recommendation: The ASA does not align with the EU-RMP safety specification. The following two important potential risks have been omitted:</p> <ol style="list-style-type: none"> <li>1. ‘Renal toxicity’</li> </ol>

Reconciliation of issues outlined in the RMP report
2. 'Thrombocytopaenia and coagulation abnormalities'.
<b>Recommendation 5.</b> The sponsor should propose the use of follow-up forms to enhance the collection of routine pharmacovigilance for the important potential risks recommended.
<i>Sponsor's response:</i> The sponsor 'uses data collection tools when specific events are reported, such as thrombocytopenia and coagulation abnormalities or events suggestive of renal toxicity. Please refer to the responses submitted for the safety based clinical questions 1 through 8'. [See Attachment 2].
<p><i>RMP evaluator comment:</i> Outstanding recommendation: The sponsor has not provided follow-up forms for evaluation. Annex 7 to the EU-RMP where they should be located is empty; no Australian adapted targeted follow-up forms have been submitted with the ASA. The ASA does not include the important potential risks; the EU-RMP pharmacovigilance plan does not describe the use of Specific adverse event follow-up forms for these important potential risks.</p> <p>The sponsor must list the targeted follow-up forms as part of routine pharmacovigilance activities in the ASA, assigned against the relevant safety concerns (renal toxicity, thrombocytopaenia).</p> <p>The sponsor must submit Australian adapted targeted follow-up forms for evaluation. It is recommended that appropriate patient ethnicity demographic categories are used on the form. Specifically, the patients' Australian Indigenous identity status (Aboriginal and Torres Strait Islander, ATSI) <i>must</i> be recorded as one of the following options: 'Aboriginal', 'Aboriginal and Torres Strait Islander', 'Torres Strait Islander', or 'neither'.</p>
<b>Recommendation 6.</b> The sponsor should update the pharmacovigilance plan to include details of the overseas patient registries based safety surveillance studies if these are confirmed.
<i>Sponsor's response:</i> 'In conclusion, the sponsor is proposing a multi-pronged approach for the collection of long-term safety data for nusinersen. We will continue to monitor patient safety in the ongoing clinical studies and in the post-marketing setting, and we will gather additional data by leveraging and building upon existing SMA disease registries. The sponsor believes that this approach is the most prudent and efficient approach in understanding the long-term safety of [nusinersen], given the rarity of the disease and the relatively small number of specialists who treat it. The RMP has been updated to reflect this multipronged approach. Updates on these efforts will be provided in conjunction with the nusinersen PSURs' [excerpt].
<i>RMP evaluator comment:</i> Outstanding recommendation: The sponsor has provided a progress update on the post-market safety follow up activities using key investigators and existing registries. Further updates will be provided in periodic safety update reports (PSUR). Acknowledging the difficulties in study design for a rare disease, the response is acceptable; however, the pharmacovigilance plan must be updated to address the outstanding clinical and nonclinical recommendations for the safety specification. The ASA should be updated with Australian details of the additional pharmacovigilance activities (Australian patient involvement, reporting milestones for submission to TGA).

### Reconciliation of issues outlined in the RMP report

**Recommendation 7.** The risk minimisation plan should be updated to address the new safety concerns.

*Sponsor's response:* The risk minimisation plan has been updated to reflect the important potential risks of thrombocytopenia and coagulation abnormalities, and renal toxicity. Please refer to the enclosed RMP and to the responses of Questions 1 through 8 in [Attachment 2].

*RMP evaluator comment:* The changes are noted. The sponsor should include additional safety concerns as recommended.

### Summary of recommendations

There are outstanding recommendations.

The proposed safety specification does not address all of the important potential risks and missing information identified in the advice from the nonclinical and clinical evaluators.

All these additional concerns must be addressed in the Australian-specific annex (ASA) safety specification; the pharmacovigilance and risk minimisation activities should also be updated to monitor, investigate, characterise, and mitigate these concerns in Australia.

- **Recommendation 8:** (outstanding, Recommendation 1) The sponsor should address the nonclinical and clinical evaluator's outstanding recommendations for the safety specification, in the summary of safety concerns in the ASA.
- **Recommendation 9:** (outstanding, Recommendation 4) The following two important potential risks must be included in the summary of safety concerns in the ASA so that it aligns with the EU-RMP: 'thrombocytopenia and coagulation abnormalities', 'renal toxicity'.

### Pharmacovigilance

- **Recommendation 10:** Provide, in the ASA, the requested details of Australian involvement and expected reporting milestones for the pharmacovigilance activities proposed in the EU-RMP.
- **Recommendation 11:** Implement targeted follow-up questionnaires as part of routine pharmacovigilance activities in Australia, for the relevant safety concerns (renal toxicity, thrombocytopenia), and provide Australian adapted targeted follow-up forms for evaluation. These must collect the patients' Australian Indigenous identity status (Aboriginal and Torres Strait Islander, ATSI) which *must* be recorded as one of the following options: 'Aboriginal', 'Aboriginal and Torres Strait Islander', 'Torres Strait Islander', or 'neither'.

### Other advice to the delegate

No suggested RMP condition of registration can be provided until the outstanding recommendations are addressed.

- **Recommendation 12:** (outstanding) The Delegate is asked to consider amending the indication to specify '5q Spinal Muscular Atrophy' or 'SMN1 related Spinal Muscular Atrophy'. This should reinforce the need for a correct diagnosis and therefore prevent off label use in non-5q SMA patients.
- **Recommendation 13:** The use of nusinersen (initiation of therapy) should be limited to healthcare professionals with experience in the management of SMA.

## VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

Impurity limits were discussed extensively as part of the evaluation.<sup>61</sup> The sponsor provided additional justification of the proposed limits which allowed the chemistry evaluator to recommend approval with respect to the chemistry and manufacturing control for nusinersen. The evaluator noted the recommendation of the nonclinical evaluator and the sponsor's commitments internationally to review the impurity limits when more data are available.

Nusinersen is a synthetic substance made using computer controlled solid phase synthesis. The oligonucleotide sequence can be depicted as 5' MeU<sup>Me</sup>CA<sup>Me</sup>C<sup>Me</sup>U<sup>Me</sup>U<sup>Me</sup>U<sup>Me</sup>CA<sup>Me</sup>UAA<sup>Me</sup>UG<sup>Me</sup>C<sup>Me</sup>UGG-3'. Nusinersen exhibits stereoisomerism because of the chiral centres in the phosphorotioate backbone.

The absolute configuration of each 2'-O-(-methoxyethyl)-D-ribose unit is (1R, 2R, 3R, 4R). It has a molecular weight of 7127.19 g/mol (free base). The absolute configuration at each phosphorus atom is undefined and nusinersen is a mixture of diastereoisomers and stereoisomers.

The active substance is a white to yellow hygroscopic amorphous solid, freely soluble in water, soluble in methanol and insoluble in acetone, ethanol, acetonitrile, isopropyl alcohol and chloroform.

The drug substance is manufactured in a series of steps that follow solid phase phosphoramidite oligonucleotide synthesis. The API is synthesised one residue at a time from its 3' to 5' end by sequential coupling of phosphoramidite starting materials. Subsequent steps include purification, detritylation and freeze drying. The drug substance specifications include tests and limits for appearance, identity, purity, assay specified impurities, residual solvents, elemental impurities, bacterial endotoxins and microbial limits.

The drug product manufacturing process involves preparation of the aCSF buffer, diluted and mixed to ensure homogeneity, filtered and aseptically filled into pre-sterilised vials that are stoppered and sealed. The finished product specifications include tests and limits for appearance, identity, assays, purity, specified related degradation products, extractable volume, pH, osmolality (isotonic with CSF), particulate matter, bacterial endotoxins and sterility. No increases in the degradants were observed during manufacture or storage of the product.

The drug product is a single use, clear, colourless, sterile, isotonic solution for injection, practically free from visible particles, preservative-free, for IT administration. It contains 12.6 mg of nusinersen heptadecanatrium equivalent to 12 mg nusinersen in 5 mL of aCSF. The aCSF consists of phosphate buffers and electrolytes to match the pH, osmolality and electrolyte composition of human CSF. The presentation is a single use, clear, colourless Type I glass vial with a bromobutyl rubber stopper and sealed with crimped aluminium seal and flip off plastic cap.

3 drug product presentations were developed for clinical trials a 5 mL vial containing 2.5 mL of a 20 mg/mL solution with a diluent of aCSF in 2 vials, a 5 mL of a ready to use

<sup>61</sup> Clarification: three rounds of quality evaluation were undertaken by the TGA with the assessment of this submission.

1.8 mg/mL nusinersen solution in aCSF and a 5 mL of a ready to use 2.4 mg/mL nusinersen solution in aCSF. The proposed ready to use formulation was used in the pivotal Phase III studies.

The evaluator noted that as an oligonucleotide, nusinersen is -not covered by ICH Q3A and impurities are required to be qualified.<sup>4</sup> Impurities were analysed and discussed in depth;<sup>62</sup> and some are reported in groups of impurities rather than single impurities.<sup>4</sup> The evaluator noted that the limits to the impurities had been revised for the product based on the FDA evaluation, and that from the first 3 commercial batches the drug product was well within these specified limits. The evaluator has recommended a condition of registration to provide revised limits based on data from ten commercial batches to the TGA when available. A similar post-market commitment has been agreed by the sponsor with the EU.

## Nonclinical

After 2 rounds of evaluation the nonclinical evaluator could not recommend approval of nusinersen. After the evaluation of additional justification and data analysis provided by the sponsor, at the third round of evaluation the nonclinical evaluator had no objections to the registration of Spinraza conditional on the following:

- The sponsor should provide empirical data showing that 2'-MOE nucleotide monomers are poor substrates for human DNA polymerase.
- The carcinogenicity of nusinersen should be assessed.
- Post marketing monitoring of acute, adverse CNS effects following nusinersen administration should be a priority.
- The draft PI should be amended as directed in the report.

Humans are the only species to have SMN2 so genetically modified animal models were studied. *In vitro*, nusinersen bound to SMN2 pre-mRNA and increased the inclusion of exon 7 in SMN2 transcripts in human cells. In mouse SMA models ICV injection of nusinersen resulted in full length SMN2 transcript in the spinal cord and brain, and increased the level of the SMN protein in the spinal cord, brain and CSF. In more severely affected neonatal mice it increased motor neuron cell numbers in the cervical and thoracic spine, increased the size of myofibres, improved the architecture of the neuromuscular junction in the quadriceps and intercostal muscles, improved motor function and improved survival. Although improved, the affected mice did not return to the wild type (unaffected) phenotype. Based on survival, early treatment appeared more efficacious.

Due to the 2'-MOE moiety nusinersen is not expected to be involved in any RNA silencing activity if off target hybridisation occurs. The evaluator considered off target hybridisation effects to be an unresolved uncertainty with the submission. No receptor binding studies to assess potential off-site targets were conducted, but this was considered acceptable considering the mechanism of action does not involve protein binding.

In monkeys, peak CSF concentrations after IT dosing occurred in 30 minutes. The concentration time-profile showed a relatively fast initial decline of 24 to 48 hours then a slower decline phase over > 70 days. Nusinersen was cleared from the CSF via CSF turnover. It was distributed to CNS tissues with a long terminal elimination half-life from these tissues. In plasma, a rapid decline phase and long terminal phase was also seen; the long decline phase representing equilibrium with tissues and clearance from the relevant compartment. Metabolism was via 3' and 5' exonuclease in mice, monkeys and humans.

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<sup>62</sup> The impurities included both oligonucleotide and elemental impurities.

Metabolites were found in brain, lumbar spinal cord, plasma, liver and kidneys of monkeys after IT dosing indicating some metabolism in the CNS.

In mice given  $\geq 10$  mg/kg SC nusinersen accumulation of the oligonucleotide (basophilic granules) found in kidney tissue was not associated with organ dysfunction based on serum chemistry but urinalysis was not assessed. Monkeys given  $\geq 1$  mg IT nusinersen for 53 weeks had hippocampal vacuolation. This is considered by the evaluator likely to be associated with oligonucleotide accumulation in these tissues but may have been due to fixing processes and is not considered of clinical concern.

Acute transient deficits in low spinal reflexes were observed in cynomolgus monkeys at 1 hour and lasting up to 8 hours following IT lumbar doses of  $\geq 3$  mg (CSF  $C_{max}$  14 times the clinical CSF  $C_{max}$ ), suggesting a correlation with peak CSF concentrations. Hippocampal neuronal/glial cell necrosis was seen in a number of monkeys treated with 3 mg nusinersen IT every 1 to 2 weeks for 14 weeks but not in the pivotal 53 week monkey study with 6 weekly dosing (in the maintenance phase). Perivascular infiltrates were also seen in the CNS of the monkeys in the high dose study. In general observations no neuro-behavioural effects were seen.

Complement activation related to nusinersen in the CSF or plasma was not seen. In monkeys, anti-drug antibodies formed in a number of subjects but were of unclear significance and there was no effect on T cell dependent antibody responses.

Genotoxicity was tested in a bacterial mutagenicity assay, in vitro clastogenicity assay in CHO cells and a mouse micronucleus test. The assays were negative but the studies did not demonstrate uptake of the nusinersen into the cells, making the outcome difficult to interpret. The evaluator recommended changes to the genotoxicity statement in the PI to address this missing data, unless the sponsor made an undertaking to address the uncertainty in the studies. In the assessment of the potential for nucleotide monomers from nusinersen to cause DNA mutations or chromosomal aberrations the sponsor provided a justification based on oligonucleotides other than those with a 2'-MOE moiety. The evaluator considered empirical data should be provided and recommended provision of such data as a condition of registration.

No carcinogenicity studies were provided. The evaluator has considered a carcinogenicity study should also be provided to the TGA as a condition of registration.

Minimal placental transfer of drug related material was seen in mice and rabbits (placental levels were 2.3 to 8.2% of maternal liver) but there was no evidence of fetal exposure. Levels in breast milk of lactating mice were 2% of maternal liver levels. The evaluator determined a pregnancy Category B1 reflective of the evidence presented and this has been agreed by the sponsor.<sup>44</sup> Given the poor oral absorption of oligonucleotides the evaluator considered the exposure in breast-fed infants to be low to negligible.

Impurities in the formulation were of concern in the nonclinical evaluation. As noted in the chemistry evaluation the specifications of the impurities are not set out in an accepted monograph for nusinersen, and needed to be qualified. The nonclinical evaluation report contains a detailed description of the impurities and the reasons these were not considered qualified. For the majority a lack of data on the off target hybridisation effect was of concern. The sponsor provided additional justification at the end of the second round evaluation, reviewed by the evaluator who resolved that the proposed limits for the specified impurities are unlikely to cause off target hybridisation effects with a safety impact in patients. Chronic systemic toxicity based on a less than lifetime acceptable intake calculation using 20  $\mu$ g/day for a 50 year lifetime was 2.1% and 1.8% for a 70 year lifetime. The evaluator accepted these calculations 'in this case due to the intended patient group'. The sponsor considered the CNS toxicity unlikely due to the absence of acute CNS toxicities to date, that the monkey toxicities were inconsistent with the time course of the

antisense mechanism of nusinersen and because of the dose were likely due to administration of high doses of a charged polymer.

The evaluator noted the proposed limits for elemental impurities are set approximately 10 fold greater than the observed amounts in the commercial batches to date but are lower than the ICH Q3D guidance. At the proposed limits there would be acute increases of particular confidential elemental impurities in the CSF, the clinical consequences of which are uncertain. These exposures are considered unlikely to result in acute or chronic systemic toxicity and ensure that patients, including neonates, are exposed to non-toxic levels of [Information redacted]. A confidential elemental impurity remains unqualified at the proposed limit, although it is noted that current exposures from the commercial batches are actually  $\leq 1$  ppm.

## Clinical

The clinical dossier was submitted as a rolling submission and comprised:

- 8 studies containing pharmacokinetic data: Study CS1 (later onset SMA), Study CS2 (later onset SMA), Study CS10 (later onset SMA), Study CS12 (open label extension from Studies CS2 or CS10, later onset SMA)
- 2 population pharmacokinetic analyses (IS11, CPP-017)
- Clinical efficacy and safety studies with evaluable data
  - Pivotal Phase III Studies CS3b (ENDEAR trial, infantile onset SMA), CS4 (CHERISH trial, later onset SMA)
  - Phase II Studies CS3a (infantile onset SMA), M201/CS5 (NURTURE trial, pre-symptomatic, ongoing))
  - Phase I Studies CS1 (later onset SMA), CS10 (later onset SMA), CS2 (later onset SMA), CS12 (later onset SMA)
- 1 Integrated Summary of Safety, 1 Immunogenicity study in humans and monkeys
- Literature references.

## Pharmacology

### *Pharmacokinetics*

The pharmacokinetics of nusinersen in later onset SMA has been characterised from later onset SMA patients (Studies CS1, CS2, CS10 and the ongoing CS12), infantile onset SMA (Studies CS3A and CS3B) and in pre-symptomatic infants (Study SM201). Data from these studies were pooled and modelled in population pharmacokinetic studies.

Pharmacokinetic in CSF:

- No bioavailability data were provided.
- Nusinersen is widely distributed throughout the CNS
- CSF concentrations increased proportionally from 1 mg to 12 mg and dose proportionally from 6 mg to 12 mg. Trough CSF concentrations accumulated approximately 1.4 to 3 fold and reached steady state after multiple 12 mg doses at about 22.5 months in later onset SMA.
- CSF steady state level for 12 mg dosing in Study CS3a was achieved after Day 631.

Plasma:

- 12 mg IT nusinersen rapidly transferred from the CSF to the systemic circulation. Peak levels in a few hours (around 4 hours in later onset SMA and 1.7 to 2.25 hours in infantile onset SMA after 12 mg dosing, with weight-based equivalent dosing a 6 mg equivalent dose had a plasma  $t_{max}$  of 6 hours).
- $C_{max}$  was greater in infantile onset: 829 to 1026 ng/mL compared to later onset SMA (189 to 350 ng/mL).
- A direct comparison of systemic exposure is limited by different time points of analysis but the area under the curve (AUC) from 0 to 4 h in infantile onset was 2181 to 2657 ng\*hr/mL whereas in later onset SMA, AUC from 0 to 20 h was 3523 ng\*hr/mL and AUC from 0 to 6 h was 1783 ng\*hr/mL.
- Nusinersen had  $\geq 94\%$  plasma protein binding to whole plasma proteins in an in vitro study of human plasma but  $\leq 25\%$  CSF protein bound at 5  $\mu\text{g/mL}$  concentration, and 0% at 150 ng/mL (15 to 24.9%) depending on the method used.
- There was a relatively rapid decline in plasma to  $< 1\%$  peak concentration at 7 days post dose, then slow decline (biphasic disposition in plasma, redistribution to tissues). The terminal elimination half-life in plasma was estimated to be 63 to 87 days in later onset SMA but there were too few samples to estimate this parameter in infantile onset SMA.
- Metabolism is thought to be by exonuclease (3'-5')-mediated hydrolysis which is not liver dependent. Four hours post dose 98% nusinersen was intact in plasma and 2% was a 17-mer oligonucleotide (N-1 from the 3' end).
- Less than 0.5% of the administered dose was excreted in urine in the first 24 hours; however urine was not collected for the entire half-life of the product. The sponsor considers renal elimination is the likely primary route of elimination of nusinersen and its metabolites. Intact nusinersen was the most abundant oligonucleotide in the urine (63%). Another 28% and 8%, respectively, of the total nucleotides were N-1 and N-2 from the 3' end.
- No interaction studies were conducted but interactions were not expected after in vitro testing of transporters and CYP3A4 in primary human hepatocyte culture.
- No specific studies were conducted in patients with hepatic or renal impairment or in the elderly.

#### Population pharmacokinetics:

- Pharmacokinetic data from Studies CS1, CS2, CS10, CS3a and CS12 were used in the population pharmacokinetic analysis.
- The final model was a 4 compartment model with 2 compartments representing the CSF and CNS tissue and 2 representing the plasma and a peripheral compartment. Nusinersen was widely distributed in the CNS with an apparent  $V_d$  in CNS 600 fold greater than the  $V_d$  in CSF. The only significant covariate was body weight.
- The model was updated to allow additional predictions to inform the final fixed-dose dosage regimen.
- Based on single dose simulations the terminal half-life in CSF in later onset SMA was 160 to 163 days and 159 to 172 days for infantile onset SMA.
- Single dose simulations compared the fixed dose regimen with the age adjusted dose regimen and found high variability across the age ranges for  $C_{max}$  and AUC although there did not appear to be clinically meaningful differences between single fixed dose and age adjusted dosing. While AUC was similar across the age groups there was a higher  $C_{max}$  in the 0 to 3 month age group with the 12 mg fixed dose.



- Dose linearity was shown between 3 and 12 mg doses.

### ***Pharmacodynamics***

The following is a summary of the pharmacodynamics data:

- There is no available biomarker for nusinersen.
- No specific pharmacodynamic studies were conducted and the data were insufficient to document a timeline of the pharmacodynamic effects.
- There was no clear association between CSF SMN proteins and nusinersen levels although dose dependent increase in SMN protein concentration in CSF was suggested in Study CS2. The optimal time for measurement is unknown.
- Autopsy samples from nusinersen treated patients had an overall 2.0 to 3.2 fold higher level of SMN2 transcripts containing exon 7 than untreated SMA controls. Higher levels of SMN2 with exon 7 were found in spinal cord and CSF tissues including glial, Purkinje and endothelial tissue than with the untreated controls. The findings were not consistent across all reports although differences in tissue integrity and staining techniques may have contributed.
- No apparent gender or race differences in pharmacodynamic effects were seen.
- Younger children tended to have higher SMN2 protein with exon 7 than older children
- CSF exposure was simulated and linked to pharmacodynamic data from Study CS3A for the exposure-response analysis. The pharmacokinetic-pharmacodynamics model was an indirect response model with a central compartment (CSF) three peripheral compartments (CNS tissues, plasma and peripheral tissues).

### **Efficacy**

Dose for the pivotal studies. No formal dose finding studies were conducted, although dose escalation was a feature of Studies CS1 and CS2, and Study CS2 was used for dose range finding. Based on studies in transgenic mice the estimated target tissue concentration needed to produce 50 to 90% SMN2 exon 7 inclusion was between 1 and 10 µg/g in spinal cord tissue. The 12 mg dose was predicted to achieve 10 µg/g in lumbar and 3 µg/g in the cervical spinal cord levels, and the loading dose was predicted to achieve levels of 24 µg/g and 8 µg/g in lumbar and cervical spinal tissue. The maintenance dose interval was based in estimated spinal tissue and CSF half-life. Scaled equivalent dosing according to CSF volume was used in Study CS3b and in the early dosing of Study CS4.

#### ***Study CS3B (the ENDEAR trial)***

Study CS3B (the ENDEAR trial) was a Phase III, randomised, double blind multiple dose, sham procedure controlled study to investigate the efficacy, safety, tolerability and pharmacokinetic of 12 mg scaled equivalent IT nusinersen using a loading dose regimen at Days 1, 15, 29, 64 and maintenance doses at Days 183 and 302 (conducted over 10 months) in 122 patients with documented 5q SMA homozygous deletion or mutation, 2 copies of SMN2, and clinical onset of signs and symptoms of SMA at age ≤ 6 months. Other inclusion criteria were ≤ 7 months of age at screening, receiving adequate hydration and nutrition and body weight ≥ third percentile, gestational age of 37 to 42 weeks. Exclusion criteria included hypoxaemia or active infection at screening, a history of brain or spinal cord disease that would interfere with lumbar puncture procedures or CSF circulation (including a CNS catheter or shunt for CSF drainage) and clinically significantly abnormal haematology or clinical chemistry that would render the patient unsuitable for inclusion. Patients were randomised 2:1 to active treatment and stratified by disease duration (≤ 12 weeks or > 12 weeks). The dose scaling resulted in children 0 to 3 months receiving 9.6 mg, 3 to 6 months 10.3 mg, 6 to 12 months 10.8 mg, 12 to 24 months 11.3 mg

and thereafter 12 mg. For the primary endpoint of motor milestone response, the study had 78% power to differentiate a response rate of 38.5% for the nusinersen group versus 11.5% response rate for the control group, and 80% power to detect a doubling in median time to death or permanent ventilation in the nusinersen versus the control group at an overall 2 sided 5% significance level.

Patients were aged 30 to 262 days (median 175 days), 86% were White and 55% were female. The groups were balanced for disease duration (43% ≤ 12 weeks, median 13.1 weeks), and 99% had 2 copies of the SMN2 gene (one patient with 3 copies was in the control group). 90% of the nusinersen and 78% of the control groups had symptoms within the first 12 weeks of life (median age of onset 6.5 weeks and 8 weeks for the nusinersen and control groups, respectively) and a greater proportion had paradoxical breathing (89% versus 66%), respiratory symptoms or pneumonia (35% versus 22%) and swallowing/feeding difficulties (51% versus 29%). Premature withdrawals occurred in 1 patient prior to treatment, 17/41 of the control group and 15/80 of the nusinersen group withdrew after treatment (mostly due to adverse events).

The 2 primary efficacy endpoints were:

- The proportion of motor milestone responders (measured according to Section 2 of the Hammersmith Infant Neurological Examination (HINE)) was 51% in the nusinersen group (n = 80) and 0% in the control group (n = 41) (p < 0.0001). In the nusinersen group 22% gained full head control, 8% independent sitting, and 1% standing. The effect was seen in (pre-specified) subgroups of disease duration, age at onset of SMA symptoms, and geographic region, and supported by sensitivity analyses.
- The time to death or time to permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy): HR for nusinersen was 0.53 (95% CI: 0.316, 0.890). The difference was most apparent after day 91 of treatment. The HR adjusted for disease duration for nusinersen 0.372 (95% CI 0.179, 0.775)).

Secondary endpoints:

- The CHOP INTEND response;<sup>63</sup> (change in score of ≥ 4 points above baseline) measured at Day 183, Day 302 or Day 394 study visits was seen in 71% in the nusinersen group and 3% in the control group (1 patient only).
- A trend for improvement was seen in nusinersen patients needing permanent ventilation; 23% nusinersen versus 32% control (p = 0.13).
- The proportion of compound muscle action potential (CMAP) responders was 36% in the nusinersen group and 5% in the control group.
- The time to death or permanent ventilation (patients with disease duration at screening ≤ median) HR nusinersen versus control = 0.24 (95% CI: 0.1 to 0.58).
- The time to death or permanent ventilation (patients with disease duration > median) HR nusinersen versus control 0.84 (95% CI: 0.43 to 1.67).

Tertiary endpoints were growth, number of serious respiratory events (2.57 versus 4.03 serious respiratory events per year; nusinersen versus control), number of hours of ventilation support (% time on ventilatory support was 29.8% nusinersen and 37.2% control), number and length of hospitalisations (number of hospitalisations HR 0.75 (95% CI: 0.54, 1.05) for nusinersen versus control).

<sup>63</sup> CHOP INTEND is an acronym for the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, developed to quantify the motor abilities of patients with SMA. Glanzman A et al (2010). The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord.* 2010; 20:155-161.

Patients in this study were eligible to transition to the open label extension Study CS11 (the SHINE trial).

### **Study CS4 (the *CHERISH* trial)**

Study CS4 (the *CHERISH* trial) was a Phase III, double blind, randomised, sham procedure controlled study of 126 patients to investigate the clinical efficacy, safety, tolerability and pharmacokinetic of multiple doses of IT nusinersen in patients with later onset SMA conducted over 15 months, including a 9 month treatment period. Patients had to have documentation of 5q SMA (homozygous or compound heterozygous gene deletion or mutation), be 2 to 12 years of age with SMA symptoms and signs at > 6 months age, sitting independently but not walking independently, an expanded HFMSE of  $\geq 10$  to  $\leq 54$  at screening, and an estimated life expectancy of  $\geq 2$  years. Exclusion criteria were numerous but included respiratory insufficiency requiring ventilation for > 6 hours of every 24 hours, a history of brain or spinal cord disease that would interfere with lumbar puncture procedures or CSF circulation (including a CNS catheter or shunt for CSF drainage), and clinically significantly abnormal haematology or clinical chemistry that would render the patient unsuitable for inclusion, a history of bacterial meningitis, injury or surgical procedure that impacted the patient ability to perform outcome measure testing required in the protocol and from which the patient had not fully recovered or established a stable baseline. A sample size of 105 (70 in the nusinersen group and 35 in the control group) would have given at least 90% power to detect a 3 point difference in HFSME score between control and treated groups (SD 4.4, 2 sided t test with alpha 0.05).

Patients had a median age of 3 years (range 2 to 9 years) and 84% were < 6 years of age. Most were white (75%) and female (53%). Median age at symptom onset was 11 months (range 6 to 20 months), the median age of diagnosis was 18 months and the median time from disease onset to enrolment was 35.7 months (range 8 to 94 months). The patients in the nusinersen group had more advanced disease (13% versus 29% had stood without support, 24% versus 33% had walked with support, 76% versus 69% used a wheelchair), and 88% had 3 copies of the SMN2 gene and 8% had 2 copies. Baseline median HFSME score at Baseline was 20.5 in the nusinersen group and 18.0 in the control group. Patients received 12 mg IT nusinersen (n = 84) under anaesthesia or sedation, or sham procedure (n = 42) at Days 1, 29, 85 and 274. The study terminated early based on the favourable interim efficacy results in the nusinersen group, 1 patient in the nusinersen group had discontinued before the final loading dose in the initial dosing sequence because of study closure. The study period including follow-up was completed by 79% of the nusinersen group and 81% of the control group, and 21% and 19% of the nusinersen and control groups, respectively completed until the early termination point of the study because of favourable efficacy outcomes in the nusinersen group.

The primary efficacy endpoint was the change from Baseline in HFSME at 15 months. The control adjusted LS mean score difference from Baseline for nusinersen was 4.9 (95% CI: 3.1, 6.7). Pre-specified sensitivity analyses gave similar results.

Secondary efficacy endpoints:

- Proportion of patients who at 15 months achieved  $\geq 3$  point increase HFSME from baseline: 56% nusinersen versus 26.3% control (odds ratio for nusinersen versus control 5.59 (95% CI: 2.09, 14.91)).
- Proportion of patients who achieved any new motor milestone at 15 months: 19.7% nusinersen versus 5.9% control (p = 0.0811).
- Number of motor milestones achieved per subject at 15 months: 0.2 nusinersen versus -0.2 control; differences emerging after 3 months treatment.
- Change from baseline in Upper Limb Module Test at 15 months (Revised upper limb module test): Control adjusted LS mean difference from baseline 3.7 (95% CI: 2.3, 5.0).

- Proportion of patients who achieved standing alone at 15 months: 2.5% control and 1.5% nusinersen (1 patient each group).
- Proportion of patients who achieved walking with assistance at 15 months: 1.5% nusinersen (1 patient) versus 0% control.

Tertiary endpoints included the caregiver burden as measured by the Assessment of Caregiver Experience with Neuromuscular Disease reduced in the nusinersen group compared with the control group, with the greatest change in the domain of mobility; and the number of disease related hospitalisations was lower in the nusinersen versus the control group (rate ratio 0.385 95% CI: 0.153, 0.968).

Patients from this study were eligible to transition to the open label Study CS11 (the SHINE trial).

### **Study CS3A**

Study CS3A was an interim analysis to Day 694 of an ongoing Phase II, open label, multiple dose study of infants aged 36 to 120 days with documented 5q SMA homozygous gene deletion or mutation with no specified number of SMN2 copies. The 20 patients were dosed in 2 cohorts: 6 mg scaled equivalent loading dose and 12 mg maintenance dose or 12 mg scaled equivalent loading dose and 12 mg maintenance dose. The loading doses were on days 1, 15, 85 and maintenance doses were on Day 253 and every 4 months thereafter, and are planned to continue to Day 1261. All of cohort 1 (4 patients) and 13/16 patients of cohort 2 had 2 SMN2 copies, 2/16 had 3 copies and 1 died prior to gene evaluation. Overall 80% were White, 60% were male and the median age was 155 days (range 36, 210). The median weight was 6.5 kg and the median length was 65.1 cm. The median age at diagnosis was 81 days, and the median time between diagnosis and enrolment was 64 days. The median CHOP INTEND score at Baseline was 26 in Cohort 1 and 28 in Cohort 2. HINE score at Baseline. Twenty patients received study treatment, 4 died due to SAEs related to SMA disease progression, 1 voluntarily withdrew and 15 were continuing at the time of the report.

The primary endpoint was the HINE score:

- 65% achieved a milestone improvement: 2 achieved walking, 5 achieved standing, 8 achieved sitting and 9 achieved full head control.
- Mean increases from Baseline of 0.53, 1.78, 3.76, 4.8 and 9.4 milestones were achieved at days 29, 92, 253, 379, and 694. The 4 patients reaching Day 820 had a mean increase of 12.5 milestones from Baseline.

At the time of data-lock for the interim report 65% patients were alive, free of permanent ventilation and continuing the study. Seven patients (35%) died or needed permanent ventilation: 6 had 2 SMN2 copies (1 was unknown) and developed symptoms at  $\leq 12$  weeks of age. CHOP INTEND score increased from Baseline: 55% had score 4 points from Baseline, 41.2% of patients with 2 SMN2 copies, and 37.5% with symptom onset  $\leq 12$  weeks of age. CMAP: Day 692 mean amplitude increase in ulnar (0.425 mV) and peroneal (1.85 mV) nerves whereas the expected amplitude for Type I SMA was  $< 1$  mV with no improvement over time. Endpoint improvements for CHOP INTEND and CMAP were earlier and were larger in patients with a 12 mg equivalent loading dose.

### **Study CS12**

Study CS12 was a Phase 1, open label study to test the safety tolerability and pharmacokinetic of 12 mg doses of nusinersen in 47 patients (22 with Type II SMA and 25 with Type III SMA) who had completed the Phase I Studies CS2 or CS10 (6 to 13 months previously). Nusinersen was given on Days 1, 169, 351 and 533. Data were included for 715 days treatment in Study CS12. Efficacy endpoints were exploratory. Overall, the mean change from baseline in HFSME ranged from 0.29 to 1.27. 12 patients had a  $\geq 3$  point

increase and 4 subjects were  $\leq 3$  points from Baseline. Mean changes from Baseline in Type II SMA was 0.32 to 1.95 and -1.04 to 1.12 for Type III SMA. The majority of Paediatric Quality of Life Inventory (PedsQL) total scores or individual components were within 2 points of Baseline, with positive scores for the total, communications, and family resources scored for the Neuromuscular Model, and the patient scores were greater than the parent scores. The Upper Limb Module scores were measured in non-ambulatory patients (mean increased from Baseline 0.26 to 0.96) with more favourable scores in Type II SMA patients. Myometry was similar to baseline. None of the Type II SMA patients that were non-ambulatory became ambulatory. 21 /25 ambulatory patients were able to participate in the 6 minute walk test (6MWT): 11 patients (50%) could walk  $\geq 10\%$  further than at screening, 3 unable to complete the 6MWT at Baseline were later able to complete it during the study. Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) scores showed the caregiver impact was generally stable during the study.

### **Study SM201 (CS5) (the NURTURE trial)**

Study SM201(CS5) (the NURTURE trial) was the third interim analysis report of an ongoing Phase II open label, single arm study to assess the efficacy, safety, tolerability and pharmacokinetic of IT nusinersen in genetically diagnosed but pre-symptomatic spinal muscular atrophy. Patients were studied from near birth to age 2 years, but most were  $\leq 6$  weeks of age at the first dose. Patients were 5q SMA homozygous deletion or mutation or compound heterozygotes and 2 or 3 copies of SMN2, and would receive 10 doses of IT nusinersen scaled to the equivalent of 12 mg based on the child's estimated CSF volume (2 years treatment with follow, up to 2.5 years) on Days 1, 15, 29, 64, 183, 302, 421, 540, 659 and 778. The study had recruited 20 patients at the time of data lock for the interim report, 18 were included in the efficacy set. Nusinersen was administered in 4 bolus doses on Days 1, 15, 29, 64 and 4 monthly thereafter for a total of 10 treatments.

The primary endpoint is the time to death or respiratory ventilation (invasive or noninvasive ventilation for  $\geq 6$  hours/day continuously for  $\geq 7$  days, or tracheostomy); 1 subject with respiratory distress was ventilated 4 to 6 hours a day for 9 days but no patients died or met the above ventilation criteria.

The secondary efficacy endpoints of the study (to be assessed at 13 and 24 months of age):

- Proportion of patients who develop clinically manifested SMA: 4 patients up to 6 months of age manifest SMA symptoms at Day 183, 4 patients up to 13 months of age manifest SMA symptoms at Day 365
- Proportion of patients alive; all patients were alive at the analysis
- Attainment of motor milestones assessed as part of the HINE, Section 2
  - 13/18 head control, 13/18 kicking, 10/18 sitting
  - 72% were responders at Day 64 and 100 % at Days 183, 302, 365 and 421.
- Attainment of motor milestone by the WHO criteria: all gained motor milestones were maintained.
- Change from Baseline of CHOP INTEND: 7 of the 18 achieved the highest attainable CHOP-INTEND score at the interim analysis cut-off. Mean CHOP INTEND scores were 54.3, 59.9, 58.2 and 55.2 at days 64, 183, 302, 365 and 421. A decrease of  $> 4$  points was seen in 1 patient.

## **Supportive studies**

### *Study CS1*

Study CS1 was an open label Phase I dose escalation study to evaluate the safety, tolerability and pharmacokinetic of a single IT dose of 1, 3, 6, or 9 mg nusinersen in 28 patients with later onset SMA.

### *Study CS2*

Study CS2 was an open label Phase I/IIa study to evaluate the safety, tolerability and pharmacokinetic of multiple doses of nusinersen in Study CS1 patients (later onset SMA). The study was completed by 33 of the 34 enrolled patients (1 discontinued because of the study procedures). Patients from Study CS2 were included in Study CS12, described above.

### *Study CS10*

Study CS10 was an open label Phase I study open to patients with later onset SMA from Study CS1 to evaluate the safety, tolerability and pharmacokinetic of a single IT dose of 6 mg (n = 4) or 9 mg (n = 14) of nusinersen. Patients from this study were eligible for inclusion in Study CS12.

### *SM202 (CS7) (the EMBRACE trial)*

SM202 (CS7) (the EMBRACE trial) is an ongoing Phase II, double blind, randomised, sham procedure controlled study of nusinersen patients with SMA not eligible to participate in Studies CS3B or CS4. Eligible patients will have symptoms onset  $\leq$  6 months of age and 3 SMN2 copies, symptom onset at  $\leq$  6 months of age, age  $>$  7 months at screening and 2 SMN2 copies, symptom onset  $>$  6 months,  $\leq$  18 months of age at screening and 2 or 3 SMN2 copies. Patients on ventilation for  $\geq$  16 hours per day continuously for  $>$  21 days are excluded. Up to 21 patients are planned for enrolment. Efficacy data were not presented in the submission.

### *Study CS11 (the SHINE trial)*

Study CS11 (the SHINE trial): A progress report from this ongoing Phase III, open label extension study of the long term safety, tolerability and efficacy of repeated doses of nusinersen in patient with SMA that have previously participated in Studies CS3b, CS4 and CS12 did not include any efficacy data.

## **Safety**

### **Exposure**

A total of 260 patients have received nusinersen by IT and an additional 21 infants and children are participating in ongoing studies. Of those, 100 patients had infantile onset SMA, 20 patients with presymptomatic SMA, 140 patients had later onset SMA. The median duration of exposure was 453 days in later onset types (Types II and III) and 301.5 days in infantile onset (symptomatic and presymptomatic, Type I) patients. Among all treated patients, 95% had treatment emergent adverse events (TEAE). Studies CS3b and CS4 were sham procedure controlled. In Study CS3b (nusinersen versus control) upper respiratory tract infection (URTI) (30% versus 22%), pneumonia (29% versus 17%), nasopharyngitis (19% versus 10%), respiratory tract infection (11% versus 5%), urinary tract infection (9% versus 0%), bronchitis (8% versus 2%), upper respiratory tract congestion (8% v2%) viral bronchitis (6% versus 0%) influenza (6%v 0%), constipation (35% versus 22%), teething (18% versus 7%) occurred more commonly in the nusinersen group. In study CS4 the most common events were (nusinersen versus control) pyrexia (43% versus 36%), headache (29% versus 7%), vomiting (29% versus 12%), epistaxis (7% versus 0%) and back pain (25% versus 0%). The headache, vomiting and back pain were attributed by the sponsor to lumbar puncture. In the uncontrolled

studies infections and infestations were the overall the most common adverse events. In Study CS12 all patients experienced at least 1 TEAE, mostly URTI (44.7%), headache (31.9%), post lumbar puncture syndrome (29.8%) and back pain (25.2%). 5 events (2 post lumbar puncture syndrome and 1 each of CSF white cell count increased, heart rate increased, and headache) were considered potentially related.

In Study CS3B deaths occurred in 13 patients of the nusinersen group and 16 patients in the control group (respiratory disorders 9% versus 29%, respiratory failure 5% versus 20%, acute respiratory failure 1% versus 2%, respiratory arrest 1% versus 0%, and respiratory distress 1% versus 5%). Three patients in each group had a cardio-respiratory arrest. 2 patients in the nusinersen group died of nervous system disorders, 1 with a hypoxic brain injury post cardiac arrest and one due to hypoxic ischaemic encephalopathy after aspiration. One in the nusinersen group died of general physical health deterioration, and one died of unknown causes. In Studies CS4 and CS12 there were no deaths. In Study CS12 the 12 serious adverse events were considered unrelated to the study medication.

### *Haematology*

Thrombocytopenia was more common in the nusinersen group in Study CS3B (13% versus 0% of the control group). The mean change from Baseline at Day 394 was -89.5 (range -465.0, 341.0) and was lowest on Day 302 (-228.0). However, in Study CS4 the lowest median decrease in platelet count from Baseline was -13.5 (range 250, 78) at Day 2, and -5.0 (range -353, 335) at Day 169 but decreases occurred in 18% of the nusinersen group versus 24% of controls). In Study SMN201 11% versus 0% control had a shift to low platelets. 4 patients in Study SM201 experienced haemorrhages near the thecal space, all associated with multiple lumbar puncture attempts. In Study CS3B, 1 patient had gastrointestinal and tracheal bleeding events, and 6 patients in Study CS4 had epistaxis; 4 events within 72 hours of study treatment. All had normal platelets at the time of these events.

### *Renal function*

Proteinuria occurred in 33% of Study CS3b patients and 20% of the control group, and 70% of the Study CS4 patients and 41% of controls. Of the other studies renal function was not reported or was within normal limits for all patients.

### *Clinical chemistry*

Low serum sodium was seen in 1% of patients, and low serum chloride in 7% of the nusinersen group in Study CS3B but no Grade 3 or 4 changes were seen in Study CS4. Two patients had hyponatraemia in Study CS3A but in the remainder of the studies hyponatraemia was not a feature of the adverse events. Shifts in alkaline phosphatase (ALP) from normal to low were seen with nusinersen in Study CS3B (14% versus 7%) and Study CS4 (12% versus 3%), conversely a shift from normal to high ALP was seen with nusinersen in CS3B (4% versus 0%).

### *ECG abnormalities*

In Study CS3B ECG abnormalities occurred in 26% of the nusinersen group and 15% of the control group, 12% of the nusinersen group and 0% of the control group had clinically significant abnormalities post-baseline, including one patient with ventricular tachycardia, although no clear pattern of abnormalities was demonstrated. In Study CS4, ECG abnormalities occurred in 36% of the nusinersen group and 39% of the control group, and 0% and 6% of the changes were considered clinically significant. In Study CS3A the ECG abnormalities were suggestive of ventricular hypertrophy.

### *Growth*

Growth may be considered a safety outcome but in some of the studies growth was an efficacy endpoint and growth failure is associated with SMA. In Study CS3B, no improvement in growth was demonstrated in this tertiary efficacy endpoint in the nusinersen group compared to the control group, although the nusinersen group was slightly older and with a greater duration of disease at baseline. Growth was not a safety or efficacy endpoint in Study CS4. In Study 232SM201, although there was not control group weight for age data were compared with the WHO child growth standards. 4 of the 20 patients had weight-based growth failure (3 with 3 copies of SMN2 and 1 with 3 copies). Growth will be measured in Study 232SM202.

### *Neurologic events*

In Study CS3A, 3 patients had autopsies conducted after death. The neuropathological findings were consistent with SMA. No vacuoles similar to the vacuoles observed in the nonclinical monkey toxicity study were observed. There was no signal for acute neurological events. In Study CS3b, 1 patient had an adverse event of seizure in the context of hypoxic brain injury following cardiopulmonary arrest, and another patient with a family history of epilepsy (uncle) on Day 158 had 3 seizures in the context of a complicated series of events including an admission to the paediatric intensive care unit for coronavirus bronchiolitis requiring a tracheostomy and complicated by methicillin sensitive *Staphylococcus aureus* bacteraemia and tracheitis. Other nervous system disorders described in the integrated analysis but not readily attributable to the lumbar puncture procedure include muscle contractions involuntary (7), hypoaesthesia (2), hypotonia (2), clonus (1), dysgeusia (1), hyperreflexia (1), hypoxic ischaemic encephalopathy (1) and myoclonus (1). Some of these events such as hypotonia may be attributable to underlying disease. In studies such as Study C3B the number of nervous system disorder adverse events was higher in the nusinersen treatment group compared to placebo (11% versus 5%) but no single event contributed to the higher incidence. Nervous system disorders were also more common in the nusinersen treatment group in Study CS4 (33% versus 17%) although the difference was largely accounted for by headache. Other events in this System Organ Class that were reported in a higher percentage of nusinersen treated subjects compared to control subjects were dizziness and myoclonus (1% versus 0%).

### *Immunogenicity*

Immunogenicity information was derived from 229 patients. Overall 6% developed treatment emergent anti-drug antibodies (ADA). In Study CS3B, 3 subjects had treatment emergent ADA positive results, one transiently, one at the last time point of collection and 1 without 16 weeks of negative data beyond that point. In Study CS4 6 patients had treatment emergent ADA+, 3 with a persistent response (but titres ranging from 1 to 16). There were no discernible effects on the plasma or CSF concentrations of nusinersen and there was no loss of efficacy. In Study CS12 2 of the 47 patients had specific ADAs to nusinersen (one present as screening that persisted and the other was a transient response). Hypersensitivity reactions were not a feature of the adverse event reports for nusinersen.

### *Skin reactions*

Rash was found in three patients, and although vasculitis was raised as a possibility vasculitis was not confirmed.

### *Post market data*

No post-market data were included in the submission.



### Clinical evaluator's recommendation

The clinical evaluator recommended approval of an amended indication:

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

### Risk management plan

The TGA has evaluated EU-RMP (Version 1.0; 26 September 2016; DLP 15 July 2016 at the first round and Version 5.0, dated 24 April 2017; DLP 16 December 2016 at the second round) with Australian Specific Annex (Version 1.0; November 2016 at the first round and Version 2.0, dated June 2017 at the second round).

Table 13 below presents the summary of safety concerns in the EU-RMP v5.0 Changes to the Australian Specific Annex have been requested by the evaluator and amendments have been recommended by the nonclinical evaluator. The sponsor is encouraged to resolve the outstanding RMP issues with the RMP evaluator.

**Table 13: Summary of safety concerns (EU-RMP, version 5.0)**

Summary of safety concerns (EU-RMP v5.0)	
<b>Important identified risks</b>	None
<b>Important potential risks</b>	Thrombocytopenia and coagulation abnormalities
	Renal toxicity
<b>Missing information</b>	Safety profile in patients > 18 years of age
	Safety profile in patients with severe and progressive scoliosis
	Safety profile in patients receiving repetitive lumbar punctures
	Safety profile in patients with long-term exposure to 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 (for example, Type 0 and Type IV SMA).

European pharmacovigilance activities include the engagement with established SMA registries. The sponsor has indicated that no Australian patients will be included in the European registries.

## Risk-benefit analysis

### Delegate's considerations

SMA is a rare condition. In its most severe forms it is a life limiting disorder, and for most patients results in some degree of disability. In Australia, currently there are no treatments approved for use in this condition.

The sponsor presented data from 260 patients treated with nusinersen, with a median duration of exposure of 453 days in later onset types (Types II and III) and 301.5 days in infantile onset (symptomatic and pre-symptomatic, Type I) patients. The studies were conducted in patients of different ages, the endpoints although age and disability appropriate differed, and the dosage regimens also differed somewhat across all the studies.

All but Studies CS3B and CS4 were single-arm studies, so the most robust efficacy evidence is derived from patients with Types I to III SMA. Nusinersen in Types I to III has shown a benefit. In infantile onset disease Study CS3b showed an improvement in motor milestones and survival or permanent ventilation, and the numbers needed to treat equalled 2 for the HINE response and 4 for survival/time to onset of permanent ventilation. In Study CS4 in Type III SMA patients there was a statistically and clinically meaningful improvement in motor function in patients as measured by the HFMSSE score.

Improvement in motor function is supported by the outcomes of supporting studies, and three studies are underway that will collect additional data. The exploratory endpoints of carer burden and patient perspective measurements show a positive trend for nusinersen treatment. Response was variable between individual patients and deaths, permanent ventilation and loss of motor function as demonstrated with permanent gastrostomy still occurred in the nusinersen treated patients, albeit at a significantly reduced rate compared to control patients in studies with a control group. There is promising evidence in patients who were pre-symptomatic at treatment commencement. The sponsor is continuing to collect efficacy evidence from ongoing studies in Types I to III SMA, including pre-symptomatic patients.

The optimal dose has not been determined: the 12 mg dose is at the top of the dosage range chosen. Although a rationale has been provided it is still unclear whether improved results would be achieved with a larger dose. Greater CSF concentrations and exposure were achieved with the requested dose in infants than older children; however, because equivalent doses have not been tested in older children any further comment would be speculative. There has not been comprehensive testing of the optimal dose frequency, but this is limited somewhat by the IT route of administration and the risks associated with the procedure and sedation. 4 monthly dosing is consistent with the slow elimination of nusinersen from CSF and plasma, but there has been no head to head comparison of different dosage regimens to determine which provides more favourable outcomes.

There are resource implications for the IT administration of nusinersen: it needs to be delivered by experienced staff. Children with SMA can develop scoliosis and have contractures that lead to technical difficulty with the lumbar puncture procedure and skilled and experienced personnel will be needed to perform the procedure. The need for sedation in addition to the need for skilled proceduralists is expected to limit the number of centres across the country at which nusinersen treatment will be offered. There is a risk if lumbar puncture cannot be performed that doses will be missed, and spinal deformities may require the use of imaging to assist in the procedure. There is a demonstrated risk of local complications where multiple lumbar puncture attempts are needed.

Not all types of SMA have been studied. The clinical trial program has included Type I to Type III patients. Type 0 patients have very severe disease and it is unclear whether

treatment would provide sufficient SMN2 to improve survival. Similarly, Type IV patients have milder disease, a normal life expectancy and often remain ambulant, and the benefit versus risk profile for these patients is unclear. A trial of nusinersen for any patient with SMA would be permitted under the proposed indication and the committee is requested to comment on this proposal. Based on first principles and extrapolation of the results to the untested SMA 5q Type 0 and IV this may be reasonable, and if approved would be guided by the prescriber. The Delegate considers nusinersen should be initiated and supervised by specialists in the diagnosis and management of SMA, and the Advisory Committee on Medicines (ACM) is requested to comment. The sponsor has not demonstrated or provided a rationale for use of nusinersen in other types of SMA, in which the underlying pathology is not SMN1 deficiency and a non-compensatory number of SMN2 copies. The evaluator has recommended the wording of the indication be amended to include only 5q SMA patients and this is supported.

There are some notable gaps in the efficacy data. The patients enrolled were predominantly young children, with few patients reaching > 18 years and none reaching > 65 years. Some data on the use in adults may be collected from registry data, but this is outside the clinical trial setting. There are uncertainties about on the impact of nusinersen on growth and development. It is unclear whether the improvements in motor function will be sustained over time, or whether for at least some patients there will be a gradual decline in function, and whether the decline would parallel the natural history of SMA. Additional information will be gained from long term studies.

Overall nusinersen was reasonably well tolerated. Consistent with a rare disease, patient numbers in the treatment arms of the studies were small and the controlled studies were not powered to detect small differences in safety between nusinersen and the control groups. Respiratory adverse events were more common in young children in the nusinersen arm, as were constipation and teething. In older children pyrexia, headache, vomiting and back pain were all more common, and while these symptoms could be attributed to the intrathecal administration of nusinersen, there may be also be some local effects of nusinersen in the CSF. Few of the adverse events were considered adverse reactions and there were few serious outcomes attributed to nusinersen treatment. When comparing the safety of nusinersen with placebo the nature of the placebo should be taken into account. The control groups did not receive the same sedation (light sedation was given to children in the control arm), did not have a lumbar puncture and so had no CSF removed or fluid injected intrathecally.

Concerns about neurological events based on CNS findings in monkeys, and the acute neurological effects in rodents, the absence of long term safety data and the lack of long term 'real world' experience has led to recommendations from the nonclinical and clinical evaluators that the sponsor should develop a plan to ensure it actively collects and analyses neurological events and includes acute neurological events in the ASA of the RMP. There are also uncertainties about thrombocytopenia. Reductions in platelet counts were noted in the clinical studies in the nusinersen groups more than the controls. Although there was no mechanistic explanation for this observation, measurement of the platelet count prior to lumbar puncture would seem a reasonable step. The sponsor has proposed a warning statement for the PI and the ACM is requested to comment. Systemic antisense oligonucleotide therapy has resulted in proteinuria. There was an imbalance in patient numbers with proteinuria and the sponsor proposes to include a general precautionary statement in the PI.

Immunogenicity was investigated by the sponsor. Across the clinical development program 6% of patients developed ADA post-baseline, the clinical significance of which is unclear. There was no apparent efficacy or safety signal related to the presence of ADAs.

The characterisation and limits of the impurities in the formulation was of concern to both the quality and nonclinical evaluators. After three rounds of evaluation the evaluators

found the risks of the formulation acceptable provided risk mitigation strategies were put in place. Most of the impurities are now considered qualified by the nonclinical evaluation, and although most are not expected by the sponsor to have any clinical impact both the nonclinical and chemistry evaluators were cautious because these assumptions are not fully based on direct evidence. In addition, the requested limits of the impurities exceeded those in the commercial batches to date. The impurities include [information redacted]. The normal ranges of concentrations of [information redacted] in CSF have not been well studied, particularly in infants and children. In considering impurities the acceptable daily dose or the acceptable annual dose are taken into consideration. An averaged exposure over the dose interval means the exposure may possibly be taken to be within acceptable limits, particularly as the actual amounts to date are below the requested limits. Animal toxicity studies and human safety observations were not conducted with nusinersen formulated with impurities at the upper limit of the impurities requested by the sponsor for the formulation, limiting the conclusions that can be drawn.

### **Indication**

The clinical evaluator at the second round proposed an amendment to the indication to only include the 5q types of SMA. This request would align the indication with the clinical trial populations studied. The preliminary view of the Delegate is agreement with the clinical evaluator and a proposed modification of the indication as follows:

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

### **Dose**

The proposed dose of 12 mg is based on test doses of 3, 6, 9 and 12 mg dosing in Study CS2. The dosage regimen was designed to achieve target therapeutic doses in all parts of the spinal cord, based on pre-clinical studies, within 3 months of initiation of therapy. The clinical studies included dosage regimens of 3 loading doses over 3 months, 4 loading doses over 2 months and then maintenance dosing every 6 months or 4 months. Studies CS3A, CS3B, and SM201 used an adjusted dosing regimen based on age and CSF volume to 12 mg equivalence, with children > 24 months receiving the 12 mg dose whereas dosing in Study CS4 was 12 mg. In the updated population pharmacokinetic analysis comparable exposure for fixed dose and age adjusted dosing was shown, although the  $C_{max}$  was higher in the youngest age group. Based on the sponsor’s rationale the dose for all patients is 12 mg, and this dose has been agreed by other major regulators that have approved nusinersen. However for an infant the necessitated withdrawal and replacement of 5 mL of CSF to deliver the 12 mg dose is significant. The 4 monthly dosing regimen is consistent with the long half-life of nusinersen.

### **Data deficiencies**

There are no data from patients with Types IV and Type 0 SMA. There are minimal data in adult patients, and there are no data in patients transitioning puberty. There are no data in older adults and the elderly. There are no data in patients with chronic kidney disease, or hepatic impairment. There are no data in patients with concomitant disease associated with increasing age. No drug-drug interaction studies have been conducted. The characterisation and qualification of impurities in the formulation has not been fully conducted to the satisfaction of the nonclinical evaluator. There are gaps in the preclinical program including the completion of carcinogenicity studies and gaps in the genotoxicity studies.

### **Delegate’s preliminary assessment**

There are limitations to the clinical data consistent with the rare nature of the disorder, the evolving nature of the clinical development program and the constraints in the design of the control arm. There are limitations in the duration of treatment, and treatment with conditions more often associated with increasing age. There are limitations in the

pharmacology with no drug interaction studies having been undertaken although a rationale has been provided. There is uncertainty about the clinical implications of impurities in the formulation and missing information about carcinogenicity and deficiencies in the genotoxicity nonclinical work-up. Nusinersen is given intrathecally, requiring skilled administrators and limiting the clinical setting in which patients can be offered treatment. Finally, there is uncertainty regarding the dosage regimen and whether the optimal dosage regimen has been determined. This is balanced against the efficacy demonstrated in the clinical studies for Types I to III SMA, that there are ongoing studies to inform the longer term efficacy and safety in the clinical trial setting, and that the sponsor has made undertakings internationally to address some of the safety concerns with further nonclinical studies and analysis. The efficacy is weighted more heavily because of the unmet clinical need, the life-limiting nature of SMA and the impact incremental changes in motor function can have on the function and quality of life for patients. There are a number of issues for which the ACM's advice is sought for this submission and a number of conditions of registration are already proposed to deal with the uncertainties and potential risks. Subject to the advice of the ACM, the preliminary view is that, although finely balanced, the benefit risk balance is favourable.

### **Conditions of registration**

The following is an outline of the conditions of registration on which the sponsor is invited to comment.

- There will be a condition of registration to implement a RMP in Australia. The exact wording of that condition will be provided to the sponsor for comment after the version to be implemented has been agreed with the RMP team.
- The sponsor is to review and tighten the limits for specified, unspecified and total oligonucleotide impurities and elemental impurities for the drug substance and drug product specifications using the ALARP principles, when data from at least ten commercial scale batches of drug substance become available.
- Provide the final study reports for each of the following studies:
  - Study CS11 (SHINE trial)
  - Study SM201 (NURTURE trial)
  - Study SM202 (EMBRACE trial)
  - The final study report of Study CS3A.
- The sponsor is to conduct a study to investigate the carcinogenicity of nusinersen in a rodent model.
- The sponsor is to provide empirical data to investigate whether 2'MOE nucleotide monomers are poor substrates for human DNA polymerase.

### **Proposed action**

The Delegate had no reason to say at the time that nusinersen should not be approved for the modified indication of:

*'Spinraza (nusinersen) is indicated for the treatment of 5q spinal muscular atrophy.'*

### **Questions for the sponsor**

1. Please comment on the risk of a confidential elemental impurity in the CSF
2. Please comment on the known activity of 15-mer metabolites of nusinersen. Do other metabolites have off target effects?

3. A concern of the clinical evaluator was the long term pharmacokinetics of nusinersen. Has the sponsor planned any additional pharmacokinetic analyses, including after more than one year of therapy?
4. In the disposition table for Study CS3b a proportion of patients terminated the study early. The study report does not clearly detail the reason for early termination of the study. Please provide this information.
5. Given the open label nature of the ongoing studies, and the limitations of postmarket adverse event reporting, how does the sponsor propose to distinguish the long-term safety of nusinersen from the natural history of SMA and complications of treatment, in particular, neurological abnormalities?
6. Why does the US have instruction to give Dose 4 of the loading dose at 30 days from the last dose and the EU, Health Canada and the proposed dosing for Australia has the fourth dose 35 days after the third dose (Day 63)?
7. Please provide an update on the progress of the ongoing studies and the international post market commitments for nusinersen, including the post-approval carcinogenicity study that was required by the FDA for nusinersen.
8. Please provide a summary of the post marketing adverse events to date, following the approval of nusinersen internationally. In this summary please provide an estimate of the numbers of patients treated.

### **Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

1. The nonclinical and chemistry evaluators have concerns with the impurities in the formulation.
  - a. Can the committee comment on the qualification of the impurities by the sponsor.
  - b. Can the committee comment on the proposal to revisit the impurity limits in the formulation with data from 10 commercial batches.
  - c. Can the committee comment on the limits of the elemental impurities proposed for the formulation.
2. Can the committee comment on the proposal to include patients with Type 0 to IV with SMA in the indication. Is a statement that Types 0 and IV have not been studied sufficient for the precautions section of the PI?
3. Has sufficient evidence been provided to support the proposed dosage regimen?
4. The Delegate proposes to limit to medical specialists with experience in the diagnosis and management of patients with SMA. Is this reasonable in the context of the likely use of nusinersen in clinical practice?
5. The clinical and nonclinical evaluations raised concerns about acute neurological adverse events and each proposes the RMP should be the mechanism for collecting additional information. Is this sufficient? Has sufficient evidence been provided to support a precautionary statement in the PI in this regard?
6. Are the warning statements included in the Precautions section sufficient to manage the potential risks of thrombocytopenia and proteinuria?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

## Response from sponsor

### ***Proposed indication***

The Delegate has recommended that nusinersen should be approved for the modified indication of:

*'Spinraza is indicated for the treatment of 5q spinal muscular atrophy (SMA).'*

The sponsor agrees with the proposed indication as proposed by the Delegate. Similarly, the sponsor agrees with the Delegate and as discussed in the overview that nusinersen has demonstrated a positive risk-benefit profile consistent with the proposed indication.

### ***Sponsor comments on the questions posed to ACM***

1. *The nonclinical and chemistry evaluators have concerns with the impurities in the formulation:*
  - a. *Can the committee comment on the qualification of the impurities by the sponsor?*
  - b. *Can the committee comment on the proposal to revisit the impurity limits in the formulation with data from 10 commercial batches?*
  - c. *Can the committee comment on the limits of the elemental impurities proposed for the formulation?*

Impurity qualification for nusinersen was completed based on the totality of nonclinical studies. The impurity specification limits were justified based on the qualification data, risk assessment, relevant ICH guidelines, starting material data and control strategy, and process capability. The global chemistry, manufacturing and controls strategy as presented has been approved in the US, EU and Japan and assures that product of high quality is released to all markets consistently. The applicant commits to further review and, if justified, tightens the limits for specified, unspecified and total oligonucleotide impurities and elemental impurities for the drug substance and drug product specifications when data from at least ten commercial scale batches of drug substance become available.

2. *Can the committee comment on the proposal to include patients with Type 0 to IV with SMA in the indication. Is a statement that Types 0 and IV have not been studied sufficient for the precautions section of the PI? The company has agreed to make the changes in the PI.*

The use of nusinersen for the treatment of the broad SMA population is supported by its mechanism of action, which is the same across all patients, regardless of SMA type, SMN2 copy number, or age at onset of disease. As an increase in SMN protein correlates with an increase in functional neuromuscular junctions, muscle fibril size, and muscle strength a therapeutic approach which increases the levels of full length SMN2 mRNA by promoting inclusion of exon 7 in the SMN2 transcript and thereby increasing the net amount of full length SMN protein is expected to provide benefit in all forms of SMA.<sup>64</sup> Given the relatively rare incidence and poor prognosis of Type 0 SMA, it was not considered feasible to enrol these patients in a clinical trial. As patients with Type IV SMA also have a relatively rare incidence and have much later onset of disease and normal life expectancy, it was considered that it would be difficult to adequately evaluate efficacy in the clinical trial setting in these patients. However, based on its similar mechanism of action and the consistent results observed across the clinical development program, it is considered that nusinersen represents a safe and effective treatment option across the broad spectrum of the disease.

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<sup>64</sup> Passini M, et al. (2011). Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. *Sci Transl Med.* 2011; 3: 72ra18.

3. *Has sufficient evidence been provided to support the proposed dosage regimen?*

While SMA subtypes represent a phenotypic continuum of disease with different severity, the basic biology of SMA and the mechanism of action of nusinersen are the same in all patients, regardless of subtype. The updated population pharmacokinetics model showed that age did not influence nusinersen plasma pharmacokinetics after accounting for the patients growing body weight. Simulations based on the updated population pharmacokinetics model showed that the CSF AUC did not differ by age group. Simulations of CSF concentrations over time supported that administration of 4 loading doses followed by maintenance dosing every 4 months in children and adolescents resulted in CSF exposure targeting the exposure in the pivotal study in infants with SMA given the same dosing regimen (Study CS3B). These simulations also indicate rapid attainment of steady state CSF concentrations and maintenance of trough level. Given the expectation that the relationship between increased CSF trough concentration or overall exposure and improved functional outcomes would exist in all subjects with SMA, the sponsor considers that the 12 mg dose and the more frequent dose regimen are appropriate for all subjects, regardless of age or SMA type. The resulting benefit: risk profile of 4 x 12 mg loading doses followed by maintenance dosing every 4 months is positive in patients with SMA, regardless of age or disease severity. The appropriateness of the proposed dosing regimen will continue to be evaluated in ongoing clinical studies and in post-marketing surveillance.

4. *The Delegate proposes to limit to medical specialists with experience in the diagnosis and management of patients with SMA. Is this reasonable in the context of the likely use of nusinersen in clinical practice?*

Please see the response to question under 'Comments to requested changes to the Product Information' [beyond the scope of the AusPAR].

5. *The clinical and nonclinical evaluations raised concerns about acute neurological adverse events and each proposes the RMP should be the mechanism for collecting additional information. Is this sufficient? Has sufficient evidence been provided to support a precautionary statement in the PI in this regard?*

The sponsor performed a review to look for any signals consistent with lower spinal areflexia in the clinical trials. There were no adverse events of areflexia, hyporeflexia, or decreased reflexes reported. The current ongoing clinical trials have the appropriate neurological examinations to detect any acute neurological abnormalities, and these trials are included as part of the pharmacovigilance plan. In addition, these studies are the quickest and most thorough way to obtain detailed neurological information both from an acute perspective, and a latent perspective, as these clinical trial participants will have been longest exposed to therapy. In the absence of a clinical signal, the sponsor considers there is no additional need for a precautionary statement in the PI or update to the RMP required.

6. *Are the warning statements included in the 'Precautions' section sufficient to manage the potential risks of thrombocytopenia and proteinuria?*

As described in response to clinical safety questions [see Attachment 2], no cases of acute severe thrombocytopenia nor cases of renal toxicity have been reported in patients exposed to nusinersen in clinical trials or the post-marketing setting to-date. Acknowledging these findings have been reported with other subcutaneously or intravenously administered anti-sense oligonucleotides, the sponsor has agreed to include warning statements in the PI. The sponsor will continue to monitor for thrombocytopenia, coagulation abnormalities, and renal toxicity in ongoing clinical trials and through routine pharmacovigilance.



**Questions from the Delegate for the sponsor to address**

1. *Please comment on the risk of a confidential elemental impurity in the CSF.*

The sponsor provided a response that explained that the oxidation process in the CSF would involve nusinersen before the elemental impurity.

2. *Please comment on the known activity of 15-mer metabolites of nusinersen. Do other metabolites have off target effects?*

The possible 15-mer metabolites of nusinersen have not been extensively characterised. One in particular, ISIS 396449, was tested both in vitro and in vivo. It is the most potent of the 15-mers tested at nusinersen's binding site (ISS-N1). It resulted in exon 7 inclusion in SMN2 mRNA in patient fibroblasts when transfected at 100 nM. Similarly, both splice correction and phenotypic improvements were observed in the SMN mouse model when ISIS 396449 was delivered ICV. Notably, ISIS 396449 is not an expected metabolite, as it lacks the first three nucleotides from the 5' end of nusinersen. The primary metabolic pathway appears to involve 3'exonucleases.

As noted in the Written Summary, a Bowtie analysis identified only four possible off-targets for 15-mer derivatives of nusinersen. All putative off targets are uncharacterised transcripts and all are Model genes, predicted by an automated pipeline without manual curation. Should one of these transcripts be bound by a metabolite, it will not result in the degradation of the target RNA.

3. *A concern of the clinical evaluator was the long term pharmacokinetics of nusinersen. Has the sponsor planned any additional pharmacokinetic analyses, including after more than one year of therapy?*

Long term nusinersen pharmacokinetic data have been collected and summarized in clinical study reports for Study CS3A (> 24 months of nusinersen treatment), and were included in the population pharmacokinetic modelling and exploratory exposure-response analysis. Nusinersen pharmacokinetics from Studies CS3B and CS4 have also been summarised, which included data following treatment of approximately 1 year in duration. Long term pharmacokinetic data (> 1 year of therapy) will continue to be collected in the ongoing Study CS11, from which an integrated pharmacokinetic dataset of patients from Studies CS3A, CS3B, CS4, and CS12 since their first initial nusinersen treatment will be generated. The additional pharmacokinetic data collected from the completed and ongoing studies will also be incorporated as appropriate to update the population pharmacokinetic model for nusinersen.

4. *In the disposition table for Study CS3b a proportion of patients terminated the study early. The study report does not clearly detail the reason for early termination of the study. Please provide this information.*

At the interim analysis, the first primary efficacy endpoint was evaluated and found to be statistically significant. The interim analysis results were reviewed by an independent data and safety monitoring board and a joint unblinded senior management team from Ionis Pharmaceuticals and the sponsor, who determined that the study should be terminated early and all subjects should be transitioned to active treatment (as reported in the final clinical study report). After the positive interim analysis performed in August 2016, subjects were invited for end of study visits. As shown in a table of the report for Study CS3b, a total of 52 patients did not complete the follow up period but were considered completed due to the early study termination.

There were also 2 patients who were voluntary withdrawals from Study CS3b. One patient (control) withdrew due to health reasons. The other (active treatment with nusinersen) withdrew from the study during a prolonged hospitalisation for dyspnoea.

5. *Given the open label nature of the ongoing studies, and the limitations of post market adverse event reporting, how does the sponsor propose to distinguish the long-term safety of nusinersen from the natural history of SMA and complications of treatment, in particular, neurological abnormalities?*

The sponsor considers a multi-pronged approach the most prudent and efficient way for understanding the long-term safety of nusinersen, which includes monitoring the post-market setting, continuing data collection via the ongoing clinical trials and additional data gathering by leveraging and building upon existing disease registries as highlighted in the response to the RMP evaluator (Q6). The sponsor acknowledges that distinguishing long-term safety of nusinersen from the natural history of SMA will be a challenge, mostly in the infantile onset population. Nusinersen is changing the natural evolution of SMA by providing an increased survival and an improvement in motor function in this population. Because of the very limited natural history available in the untreated population due to high mortality within the first two years of life, there will be no appropriate comparator group. However, as outlined in the summary of clinical safety, the mechanism of action of nusinersen is not dependent on copy number and therefore, adverse drug reactions are expected to be similar across the different phenotypes of SMA. In order to assess whether events are related to nusinersen or to the natural history of disease, measures such as event frequency compared with the published literature or registry data for SMA across the phenotypes, temporal association, and biological plausibility will be considered. The sponsor is specifically continuing to collect safety data through the ongoing clinical trials. An ongoing open label extension study (Study CS11) will continue to collect long-term safety data on the subjects who were first exposed to nusinersen in earlier studies, both with infantile onset and later-onset SMA, and will provide a mechanism for better understanding the long term safety of nusinersen. In addition, Studies SM201 and SM202 are ongoing and will continue to collect long-term safety data as well. These studies continue to collect relevant measures of motor function and cognition, and neurological examinations.

6. *Why does the US have instruction to give Dose 4 of the loading dose at 30 days from the last dose and the EU, Health Canada and the proposed dosing for Australia has the fourth dose 35 days after the third dose (Day 63)?*

The loading dose regimen approved in the EU and Canada and proposed in Australia includes 4 doses administered on Days 0, 14, 28, and 63, and is consistent with the loading dose regimen administered in Study CS3B (Protocol Days 1, 15 (+/- 1 day), 29 (+/- 1 day), and 64 (+/-7 days). The US FDA suggested a more simplistic dosing schedule whereby the fourth loading dose is administered 30 days after the last dose.

7. *Please provide an update on the progress of the ongoing studies and the international post market commitments for nusinersen, including the post-approval carcinogenicity study that was required by the FDA for nusinersen.*

The TGA have already received final CSRs for Studies CS1, CS2, CS10, CS12, CS3B and CS4. Interim data has been provided for Studies CS3A, SM201, SM202 and CS11. [Further details regarding the studies and also the post marketing commitments are beyond the scope of this AusPAR].

8. *Please provide a summary of the post marketing adverse events to date, following the approval of nusinersen internationally. In this summary please provide an estimate of the numbers of patients treated.*

Cumulatively since US approval (23 December 2016), there have been 597 patients in the US who have received nusinersen, representing 49.75 patient years. In clinical studies, to date, there have been 281 patients treated with nusinersen, representing 388 patient years and 664 enrolled in worldwide EAP with 334 currently active. As of 31 July 2017, there are a total of 1,578 post marketing reports received; of which 1,052 are serious

events and 526 are non-serious events. Cumulatively, the 3 most common System Organ Classes represented are infections and infestations (n = 468), respiratory, thoracic and mediastinal disorders (n = 404), and nervous system disorders (n = 119). The most common serious events reported were respiratory events and infections, which are consistent with complications due to underlying SMA. The most common adverse events received include preferred terms of respiratory distress and respiratory failure (both, n = 82; 82 serious, 0 non-serious), Pneumonia (n = 92; 91 serious, 1 non-serious), and Headache (n = 77; 1 serious, 76 non-serious). Most individual case safety reports received to date describe events consistent with the known complications of SMA or that may have been due to other confounding factors such as pre-existing conditions or concurrent infections.

Since approval in the US, there has been one case of bacterial meningitis reported caused by *Streptococcus salivarius* contamination. On the basis of this single event of bacterial meningitis associated with the lumbar puncture procedure to administer Spinraza, the sponsor has updated the adverse events section to reflect post marketing experience of Spinraza regarding lumbar puncture complications including serious infections (refer to updated the provided updated PI). As the event was associated with lumbar puncture, the term serious infection has been used to encompass events including, but not limited to, meningitis. In addition, two serious reports of preferred term hydrocephalus have been reported in two patients who have received nusinersen. Hydrocephalus has been assessed as a new important potential risk, and updates to the RMP, core data sheet, and IB are in progress. As such, the line listings have been included in the Adverse Reactions update as part of this response. Based on the data available for all post-marketing reports received, including cases of preferred term hydrocephalus and meningitis, the overall benefit-risk profile for nusinersen remains favourable and unchanged.

### Advisory Committee Considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Spinraza solution for injection containing 12 mg/5 mL of nusinersen to have an overall positive benefit-risk profile for the Delegate's amended indication:

*'Spinraza (nusinersen) is indicated for the treatment of 5q spinal muscular atrophy.'*

In making this recommendation, the ACM noted that:

- SMA is rare disease that is associated with significant morbidity and mortality.
- there are no other registered treatments for SMA in Australia.
- Spinraza has been registered by a number of international regulators of medicines including the US FDA, EMA and Health Canada.
- there are no current specific guidelines for the evaluation of quality aspects of antisense oligonucleotide products such as nusinersen.
- the sponsor has made commitments to the TGA and other international regulators to refine limits of impurities and undertake ongoing quality assessment of subsequent product batches. The limits of impurities will be revised when 10 commercial batches become available.
- no clinical data was provided to the TGA on use of Spinraza in 5q SMA Types 0 and IV.
- Spinraza would be used by medical practitioners who specialise in the treatment of SMA.

### ***Proposed conditions of registration***

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- the limits of impurities should be revised after consideration of data from 10 commercial batches.
- the carcinogenicity of nusinersen should be determined.
- the genotoxicity of nusinersen should be determined.

### ***Specific Advice***

The ACM advised the following in response to the Delegate's specific questions on the submission: The committee is requested to provide advice on the following specific issues:

1. *The nonclinical and chemistry evaluators have concerns with the impurities in the formulation.*
  - a. *Can the committee comment on the qualification of the impurities by the sponsor?*

The ACM considered that the impurities in Spinraza, including the revised limits, are adequately qualified at this stage.

- b. *Can the committee comment on the proposal to revisit the impurity limits in the formulation with data from 10 commercial batches?*

The ACM considered that the proposal to review the impurity limits in the formulation with data from ten commercial batches is appropriate. The committee recommended that this action should be described as a condition of registration of Spinraza on the ARTG.

- c. *Can the committee comment on the limits of the elemental impurities proposed for the formulation.*

The ACM considered that the sponsor's revised limits of impurities are currently appropriate. The committee noted that lower limits may be set in the future with further commercial batch testing.

2. *Can the committee comment on the proposal to include patients with Type 0 to IV with SMA in the indication. Is a statement that Types 0 and IV have not been studied sufficient for the precautions section of the PI?*

The ACM noted that no clinical data has been provided on the use of Spinraza in 5q SMA Types 0 and IV, though it was agreed that efficacy may be extrapolated to these patient groups based on first principles. The committee did not recommend that specific 5q SMA disease types should be described in the indication, noting that Spinraza has been approved by the EMA and Health Canada for 5q related SMA. The decision to use Spinraza in patients with 5q SMA Types 0 and IV is likely to be made after careful clinical consideration by specialist medical practitioners who are experienced in the treatment of SMA. It was recommended that a statement should be added to the 'Precautions' section of the PI advising that the efficacy of Spinraza has not been established in patients with SMA Types 0 and IV.

3. *Has sufficient evidence been provided to support the proposed dosage regimen?*

The ACM considered that the proposed dosage of Spinraza is appropriate. The committee noted that use in clinical practice has been well tolerated.

4. *The Delegate proposes to limit to medical specialists with experience in the diagnosis and management of patients with SMA. Is this reasonable in the context of the likely use of nusinersen in clinical practice?*

The ACM agreed that the use of Spinraza should be limited to specialist medical practitioners with experience in the diagnosis and management of SMA. The committee advised that this was appropriate because the treatment of SMA involves multiple facets of care and is not limited to drug therapy.

5. *The clinical and nonclinical evaluations raised concerns about acute neurological adverse events and each proposes the RMP should be the mechanism for collecting additional information. Is this sufficient? Has sufficient evidence been provided to support a precautionary statement in the PI in this regard?*

The ACM recommended that concerns of acute neurological events should be addressed in the RMP. The committee also suggested that international data should be collected to monitor this risk. The committee did not think that a precautionary statement on acute neurological risks was warranted at this time, based on the available evidence.

6. *Are the warning statements included in the 'Precautions' section sufficient to manage the potential risks of thrombocytopenia and proteinuria?*

The committee has noted that the sponsor has agreed to the TGA requested changes to include precautions on the potential risks of thrombocytopenia and proteinuria and that this advice is sufficient.

- *The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Spinraza nusinersen (as heptadecasodium) 12 mg/5 mL solution for injection vial.

The approved indication for Spinraza is:

*'Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).'*

## Specific conditions of registration applying to these goods

- The nusinersen EU-Risk Management Plan (EU-RMP), version 5.0, 24 April 2017; data lock point 16 December 2016 with Australian Specific Annex version 3.0, 26 October 2017, included with submission PM-2016-04042-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- You are to review and tighten the limits for specified, unspecified and total oligonucleotide impurities and elemental impurities for the drug substance and drug product specifications using the ALARP principles, when data from at least ten commercial scale batches of drug substance become available.
- The following final study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission:
  - SHINE (Study CS11)
  - NURTURE (SM201)
  - EMBRACE (Study SM202)
  - The final study report of Study CS3A.

- You are to conduct a study to investigate the carcinogenicity of nusinersen in rodent model and submit the final study report to the TGA as a Category 1 submission.
- You are to provide empirical data to investigate whether 2'MOE nucleotide monomers are poor substrates for human DNA polymerase and submit the final study report to the TGA as a Category 1 submission.

## **Attachment 1. Product Information**

The PI for Spinraza approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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