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EMA/289068/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spinraza

International non-proprietary name: nusinersen

Procedure No. EMEA/H/C/004312/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

CFU	Colony Forming Units
CNET	= N^3 -(2-Cyanoethyl)thymine; ADP = N^2 -Acetyl-2,6-Diaminopurine; IDP = N^2 -Isobutyryl-2,6-Diaminopurine
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CSP	cerebrospinal fluid
DMT	5'-O-4,4'-dimethoxytrityl
EP	European Pharmacopoeia
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-HS	=Gas chromatography with head space injection
HDPE	High Density Polyethylene
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	=inductively coupled plasma-mass spectrometry
ICP- OES	=inductively coupled plasma-optical emission spectroscopy
IPC	In-process control
IP-HPLC-TOF-MS	= Ion pair-high performance liquid chromatography-time of flight-mass spectrometry
IP-HPLC-UV-MS	= Ion pair-high performance liquid chromatography with ultraviolet and mass spectrometry detection
IU	International Units
JP	Japanese Pharmacopoeia
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAM	= N -Methylacetamidomethyl
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
QTPP	Quality target product profile
RSD	Relative standard deviation
RTU	ready to use
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 7 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Spinraza, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

Spinraza was designated as an orphan medicinal product EU/3/12/976 on 02 April 2012 in the following condition: Treatment of 5q spinal muscular atrophy.

The applicant applied for the following indication: Spinraza is indicated for the treatment of Spinal Muscular Atrophy (SMA).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Spinraza as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that nusinersen was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0251/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP Decision P/0251/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a

condition related to the proposed indication.

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance nusinersen contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 13 December 2012. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Greg Markey

- The application was received by the EMA on 7 October 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 15 September 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 26 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 4 January 2017. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 January 2017.
- During the meeting on January 2017, the CHMP agreed on the consolidated List of Questions to be addressed in writing and/or in an oral explanation by the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2017.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 March 2017.
- During the CHMP meeting on 22 March 2017, the outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 23 March 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017.
- During the meeting on April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Spinraza on 21 April 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition, Epidemiology and risk factors, screening tools/prevention

The applicant proposed the following wording for the product indication:

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

SMA is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk.

SMA diagnosis is suspected when a patient presents with flaccid muscle weakness. Genetic diagnosis is the most common form of diagnosis, which allows for premorbid diagnosis in siblings where one previously affected member has been identified.

SMA is an autosomal recessive neuromuscular serious, debilitating, and life-threatening rare disease, with a global incidence of 8.5 to 10.3 per 100,000 live births characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. Historically, SMA has been categorized into Types I, II, III, and IV which range in severity from babies who are born with severe impairment and die within weeks of birth (Type I) to disease which manifests in adult life with proximal muscle weakness (Type IV). The most common variants (Types I, II and III) all present with a pre-symptomatic period and can be classified prospectively based on age of symptom onset and SMN2 gene copy number as infantile-onset (closely resembling Type I) and later-onset (Type II and III).

Current medical care is supportive, focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery (Wang 2007). As there are currently no approved therapies for the treatment of SMA, a significant unmet clinical need exists for these patients.

2.1.2. Biologic features, Aetiology and pathogenesis

SMA is a result of reduced levels of the SMN protein, caused by homozygous deletions and, infrequently, by mutations within the SMN1 gene. The lack of SMN protein causes dysfunction and eventually death of motor neurons. Despite being a rare disorder, SMA is the most common genetic cause of infant mortality and a major cause of childhood morbidity [Pearn 1973a; Pearn 1973b; Sugarman 2012].

The SMN1 gene lies in a duplicated, inverted region of the chromosome that includes a nearly identical copy of the SMN1 gene, called SMN2. Although both genes encode proteins with identical amino acid sequences, SMN2 differs from SMN1 by 5 to 11 nucleotides [Lorson 1999; Monani 1999]. One of these nucleotide differences, a cytosine-to-thymine substitution, occurs in exon 7 of the SMN2 gene, resulting in an alternative splicing pattern that favours skipping of exon 7. Eighty to 90% of the transcripts produced from the SMN2 gene lack exon 7 [Cho and Dreyfuss 2010; Wirth 2013], resulting in a truncated protein product that is defective and unstable [Cho and Dreyfuss 2010; Wirth 2013]. 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 [Hua 2010]. Humans have a variable number of copies of the SMN2 gene (0 to 8 copies). SMN2 copy number is an important predictor of SMA disease severity, and patients with more copies generally have a less severe form of the disease. Furthermore, among families with more than one affected child, siblings with SMA have been found to have high concordance for SMA subtype [Jones 2016; Medrano 2016].

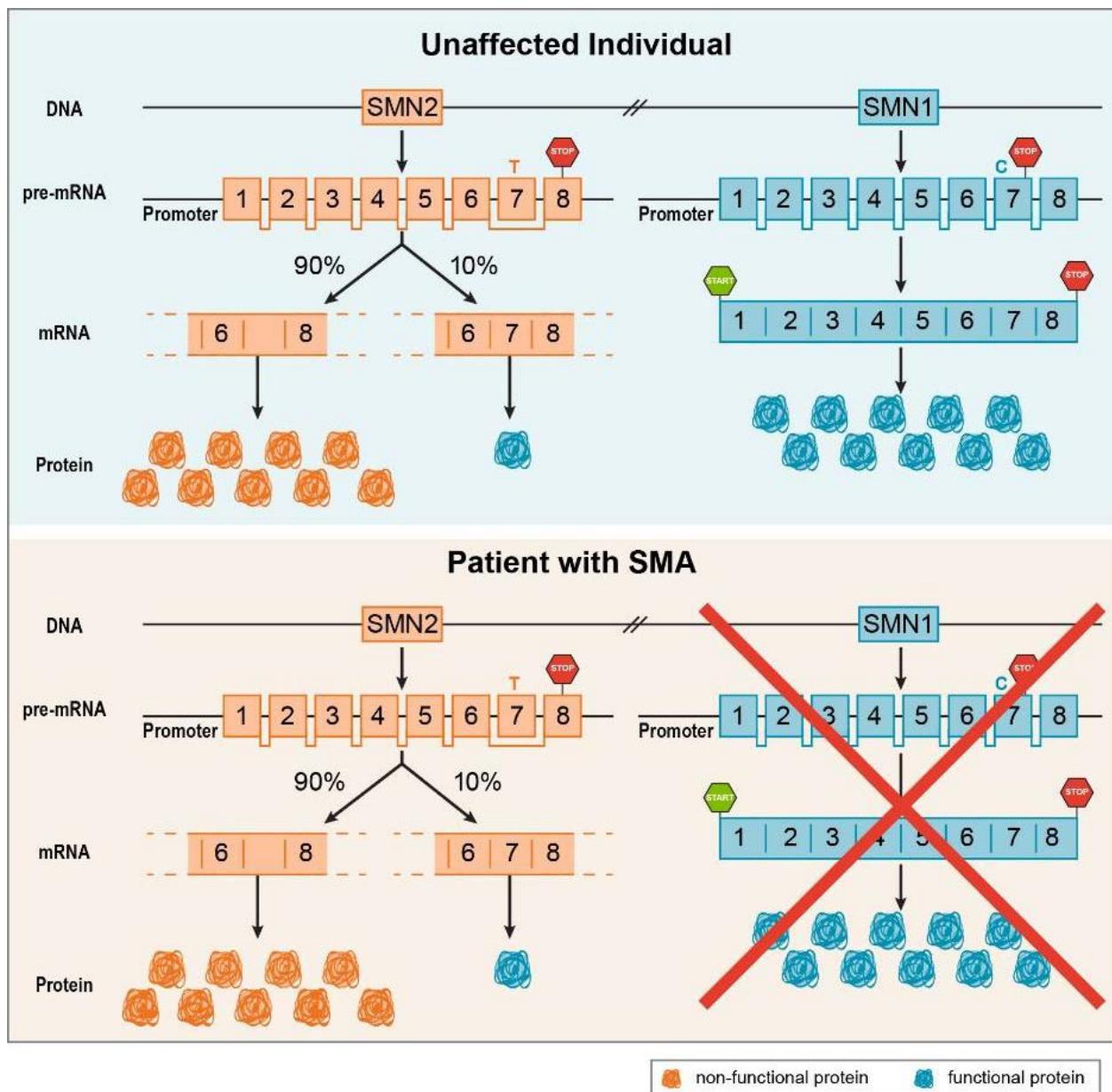


Figure 1 Genetics of Spinal Muscular Atrophy

SMA = spinal muscular atrophy; SMN = survival motor neuron.

Sources: [Arnold [2015]; Cho and Dreyfuss [2010]; Wirth [2013]].

2.1.3. Clinical presentation, diagnosis and stage/prognosis

SMA has been categorized into Types 0, I, II, III, and IV based on age of symptom onset and maximal achieved motor abilities [Finkel 2015]. In general, symptom onset and severity of SMA correlate with SMN2 gene copy number in this genetic disorder [Arnold 2015].

- Type 0 or prenatal SMA is a rare type in which infants are born with clinical signs of disease, such as major joint contractures and respiratory compromise that often leads to the need for mechanical ventilation at or shortly after birth [Dubowitz 1999; Finkel 2015; MacLeod 1999; Mercuri 2012]. These patients usually have 1 copy of the SMN2 gene. Death or permanent ventilation typically occurs within weeks after birth.
- Type I SMA is the most common form of SMA, occurring in approximately 58% of cases [Ogino 2004]. Patients with Type I SMA usually have 2 or 3 copies of the SMN2 gene, with 2 copies of the SMN2 gene as the most common genotype [Feldkötter 2002]. Symptom onset occurs within the first 6 months of life. The earlier the symptom onset, the worse the prognosis [Thomas and Dubowitz 1994]. SMA Type I can be further divided into subtypes based on age of symptom onset: Patients with Type IA SMA have symptom onset in utero and are diagnosed within the first 2 weeks of birth; patients with Type IB SMA have symptom onset during infancy and are diagnosed by 3 months of age; and patients with Type IC SMA have symptom onset during infancy and are diagnosed between 3 and 6 months of age [Finkel 2015].
- Type II SMA represents approximately 29% of SMA cases [Ogino 2004]. Patients with Type II SMA usually have 3 copies of the SMN2 gene, but this can vary from 2 to 4 copies [Feldkötter 2002]. Symptom onset occurs after 6 months but before 2 years of age. Patients have a reduced life expectancy, ranging from 2 years to more than 40 years of age [Faravelli 2015].
- Type III SMA occurs in approximately 13% of cases [Ogino 2004]. Patients with Type III SMA usually have 3 or 4 copies of the SMN2 gene [Feldkötter 2002]. Patients with Type III SMA generally have a normal life expectancy [Arnold 2015; Wang 2007]. SMA Type III can be further divided into Type IIIA (diagnosed at 18-36 months; patients walk but never run or jump well) and Type IIIB (diagnosed at 3-10 years; patients are able to walk, run, jump, and participate in sports) [Finkel 2015].
- Type IV SMA (adult-onset SMA) is the mildest form of SMA and occurs in <5% of the cases [Arnold 2015]. Patients with Type IV SMA usually have 4 or more copies of the SMN2 gene. Patients are ambulatory, and their life expectancy is normal [Faravelli 2015].

The definition of SMA types as described by Finkel et al was used in the clinical development program for nusinersen [Finkel 2015]. The studies of nusinersen included genetically diagnosed subjects with infantile-onset (Type I) SMA, presymptomatic SMA (Type I or Type II) and subjects with later-onset (Type II and Type III) SMA.

2.1.4. Management

At present there are no SMA specific treatments and only supportive care is provided to patients.

Management Patients with SMA have an urgent unmet need as no therapy has been approved to date that can reverse, delay, or halt the progressive decline in motor function and disability associated with all types of SMA.

A consensus statement for the standard of care in SMA is intended as a guideline for the care of patients with SMA [Wang 2007]. 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 (Bi-PAP). Acute respiratory infections are often lifethreatening 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.

2.1.5. About the product

Nusinersen or nusinersen is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO) consisting of 18 nucleotides with high specificity for the intron downstream of exon 7 in the SMN2 pre-mRNA, a region of SMN2 pre-mRNA normally occupied by heterogeneous nuclear ribonucleoproteins A1/A2 (hnRNPs) and referred to as intron splicing silencer N1, 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 spinal muscular atrophy (SMA). The therapeutic approach to treat SMA patients is based on increasing the amount of full-length protein produced from the SMN2 gene by modulating its mRNA splicing pattern. Nusinersen was designed for intrathecal (IT) chronic administration, independent of clinical phenotype.

2.1.6. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the unmet medical need as currently there are no approved treatments for SMA, the presented therapeutic rationale, and the early data available from the development programme, demonstrating that nusinersen has the potential to address the need in SMA.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a single use, unidose, sterile, clear and colourless isotonic solution for injection for intrathecal administration containing 12mg of nusinersen (as nusinersen sodium) (the sodium salt of a 18-mer 2'-O-methyl-phosphothioate oligoribonucleotide) as active substance.

Other ingredients are: sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydroxide, hydrochloric acid and water for injections

The product is available in a type I glass vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap. The deliverable volume is 5 mL.

2.2.2. Active Substance

General information

The active substance, nusinersen (also cited as ISIS 396443), is a uniformly modified 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide consisting of 18 nucleotide residues with the sequence 5'-MeU^{Me}CA^{Me}C^{Me}U^{Me}U^{Me}U^{Me}CA^{Me}UAA^{Me}UG^{Me}C^{Me}UGG-3'.

The chemical name of nusinersen sodium is 2'-O-(2-methoxyethyl)-5-methyl-P-thiouridyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioguananyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)-P-thioguananyl-(3'-O→5'-O)-2'-O-(2-methoxyethyl)guanosine corresponding to the molecular formula C₂₃₄H₃₂₃N₆₁O₁₂₈P₁₇S₁₇Na₁₇ and has a relative molecular mass 7501.0 g/mol and the following structure:

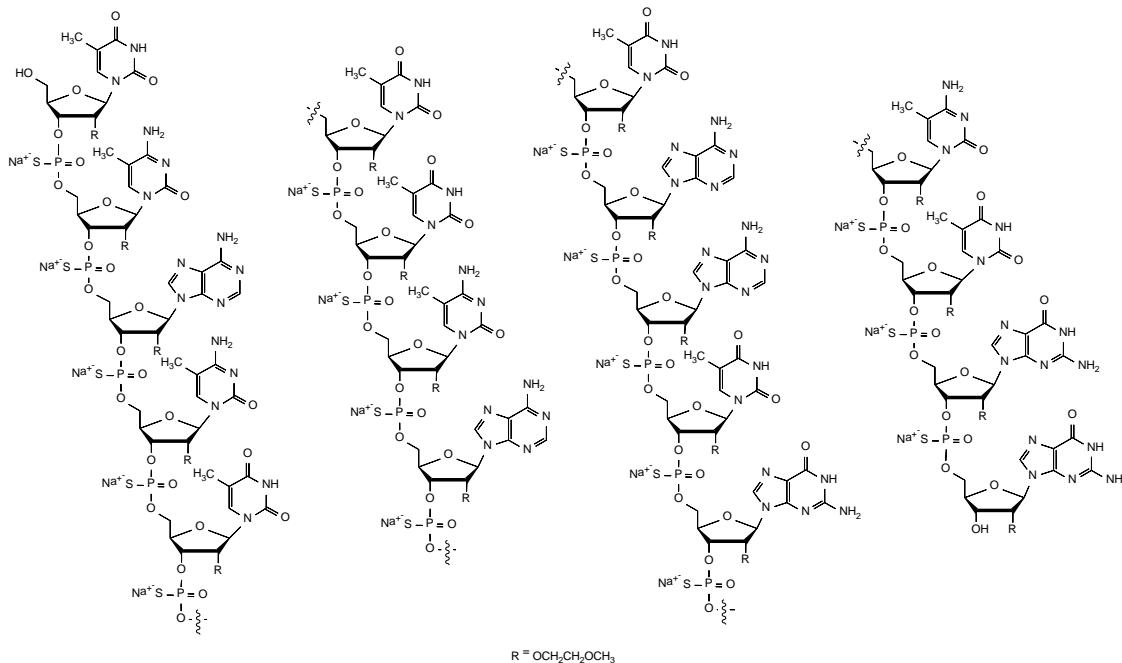


Figure 2. Structural formula of nusinersen sodium.

The molecular weight, empirical formula, and molecular structure of nusinersen were confirmed by nuclear magnetic resonance (¹H NMR, ¹³C NMR, ³¹P NMR) spectroscopy, mass spectrometry (MS), elemental analysis by inductively coupled plasma-optical emission spectrometry (ICP-OES) and

combustion analysis, and Fourier transform infrared spectroscopy (FTIR). The nucleotide sequence of nusinersen was determined by failure sequence analysis (using IP-HPLC-TOF-MS).

Nusinersen exhibits stereoisomerism due to the presence of multiple chiral centres. The absolute configuration of each pure, commercial available starting material is well defined and is maintained in the final active substance as no racemization occurs. Since the coupling reactions for the 17 phosphorothioate diester internucleotide linkages are non-stereospecific, the active substance is a mixture of 2¹⁷ diastereoisomers. Evidence from experimental data and literature were provided to demonstrate that the diastereoisomeric composition of the active substance remains constant from batch to batch regardless of scale, when it is manufactured using the proposed manufacturing process.

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

Manufacture, characterisation and process controls

Nusinersen is a synthetic 2'-O-methyl phosphorothioate oligoribonucleotide. It is manufactured in one manufacturing site. Its manufacturing process consists of four process stages.

1. Solid-phase synthesis (production of crude intermediate):
2. Purification
3. Final detritylation
4. Freeze drying (production of active substance): The drug substance solution obtained from Step 3 is freeze dried yielding a lyophilized solid nusinersen active substance.

The commercial batch size for nusinersen active substance is defined as the amount of drug substance produced in a single freeze drying run.

Specifications and control methods for reagents, crude nusinersen, and intermediates isolated following synthesis, purification, and detritylation have been established to confirm the manufacturing step is successfully controlled and that nusinersen active substance with the intended quality is produced. Batch data for the intermediates from multiple batches were provided. Compliance with the proposed specification was verified in all cases.

Adequate in-process controls are applied during the synthesis.

Holding periods were established for all intermediates based on adequate stability data. No alternate processing or reprocessing are to be performed in the production of commercial batches of nusinersen active substance.

The critical quality attributes (CQAs) of nusinersen directly impacted by manufacturing parameters have been described and the relationships between the steps of the manufacturing process and each CQA have been also indicated. Other CQAs of the active substance, not impacted directly by the manufacturing process have also been described. The CQAs are: appearance identity, assay, purity, oligonucleotide impurities: non-degradation and degradation products, residual solvents, elemental impurities, bacterial endotoxins and total aerobic microbial count.

Process development studies were conducted to determine the critical process parameters (CPPs) that impact one or more CQAs of the active substance, and define proven acceptable ranges (PARs) for the

CPPs. The ranges reported for all of the CPPs during the process qualification were well within the PARs, indicating that the process is consistent and suitably controlled.

A failure mode and effect analysis (FMEA) risk assessment was applied to the manufacturing process, procedures, and controls used in the synthesis of the active substance. The risks at various control points across the active substance manufacturing process were identified, evaluated and mitigated to control the risk to acceptable levels. The control strategy consists of control of material attributes, control of the CPPs, equipment - including synthesizers, columns, synthesis solid support and column packing, and extractables of the solid support and the purification resin, and synthesis parameters - in process controls and release testing. The manufacturing process performance will be evaluated for out of trend results as part of the continued process verification during the life cycle.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

As mentioned above, nusinersen exhibits stereoisomerism due to the chirality of the phosphorothioate backbone. The coupling reactions employed in the synthesis of the oligonucleotide are not stereospecific producing a mixture of two stereoisomers at each linkage. The solid phase synthesis can thus produce up to 2^{17} diastereoisomers in a reproducible manner. It has been demonstrated that the active substance stereoselectivity is under control and the diasteromeric distribution of nusinersen is reproducible.

The potential impurities were critically discussed taken in account the maximum dose of Spiranza (12 mg every 4 months) to calculate the TTC acceptable daily intake limit for individual impurities and for total impurities). The impurities of nusinersen consist of:

- 1) impurities derived from starting material and reagents
- 2) process-related impurities, namely process-related oligonucleotide impurities arising from side reactions during the manufacturing process and by-products of the deprotection reactions and unwanted side reactions residual solvents and elemental impurities from the use of equipment; and
- 3) degradation products, including process-related oligonucleotide impurities and degradation products observed only under forced degradation studies as no evidence of degradation is observed under long-term or accelerated storage conditions.

The qualification of oligonucleotide impurities was done in the 53-week repeat dose intrathecal toxicology study in juvenile monkeys. For all critical impurities the acceptance limit within the active substance specification is usually well below than the qualification level.

The identified and the potential small molecule impurities of nusinersen active substance were evaluated in respect to their potential genotoxic risk as per the ICH M7 guideline. Identified and potential residual solvents, are controlled to the PDE values of ICH Q3(R5) guideline. Impurities with structures with unknown carcinogenic and mutagenic risks were analysed. The risk assessment concluded that relevant solvents are adequately purged during downstream processing. This was confirmed by batch analysis data.

Process validation was achieved by assessing the CPPs, CQAs and yield of four batches of crude nusinersen intermediate (solid-support synthesis), batches of nusinersen intermediate and three batches of nusinersen active substance (freeze drying). These data demonstrate that each unit operation and thus the entire process is controlled and can produce active substance in compliance

with the proposed specification. The yields obtained for each stage of the synthesis of the active substance underline the consistency of the manufacturing process. The proposed plan for continued process verification is considered adequate.

The platform used for the manufacture of nusinersen was optimized and scaled up during development. A summary of the changes implemented and their rationale has been presented. The optimization led to the reduction of the levels of various impurities, , and to the consequent increase in the overall purity.

The active substance is stored in a multi-component container closure system. The bags comply with the EU Commission Directive 10/2011, and specifications and certificates of analysis for them were provided.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (most abundant mass: IP-HPLC-UV-MS; sequencing: IP-HPLC-TOF-MS; sodium counterion: ICP-OES), assay (IP-HPLC-UV-MS), purity (Full Length n) (IP-HPLC-UV-MS), impurities (IP-HPLC-UV-MS), residual solvents (GC), elemental impurities (ICP-MS), sodium acetate (HPLC), water content (Karl Fisher), bacterial endotoxins (Ph. Eur.) and microbial enumeration test (Ph. Eur.).

The active substance specification is based on the active substance CQAs: appearance identity, assay, purity, oligonucleotide impurities: non-degradation and degradation products, residual solvents, elemental impurities, bacterial endotoxins and total aerobic microbial count.

A justification for each attribute and the respective acceptance criteria in the active substance specification was provided. Specification limits are based on ICH requirements, process capability and variability, starting material batch data, active substance and finished product stability data and analytical control strategies, including those developed for starting materials and reagents.

A justification for the omission of a biological activity test on the basis of the antisense mechanism and the inclusion of a test to verify the correct nucleotide sequence was provided and accepted.

Based upon batch analysis and stability data provided the applicant was requested to tighten the limits for some oligonucleotide impurities and residual solvents. These were revised by the applicant taking into consideration the data available from production scale batches available at the time of opinion, representative small-scale batches, process variability and toxicology data. The applicant committed to review the limits for specified, unspecified and total oligonucleotide impurities, and further tighten them as appropriate, once data from ten commercial scale batches of active substance become available.

The justification for only including some residual solvents in the specification has been provided. The scientific principles, fates and estimated purge factor knowledge were provided as a support for not testing other solvents in the final active substance according with ICH M7 – Option 4.

For elemental impurities a risk assessment approach has been performed on drug substance.

Adequate justifications were provided for the exclusion from the active substance specification of other solvents , pH, and deamination control .

Although sodium acetate and water content are not CQA, these are used in calculations for the formulation of the finished product. Therefore, the applicant was requested to include these parameters in the active substance specification.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards testing has been presented. The reference standards, primary and working reference standards, as well as working solution standards have been adequately described.

Batch analysis data on one pilot scale batch (manufactured before optimization of the process) and three commercial scale process validation batches of the active substance were provided. The results demonstrated compliance with the specifications and consistency in the manufacturing process.

Stability

Stability data on three primary production scale active substance batches from the proposed manufacturer stored in a container closure system representative of that intended for the market for 24 months under long term conditions at $-20 \pm 5^\circ\text{C}$ and for up to 6 months under accelerated conditions at $5 \pm 3^\circ\text{C}$, according to the ICH guidelines, were provided. Data from 3 months storage at $30 \pm 2^\circ\text{C}/65 \pm 5\% \text{ RH}$ to simulate temperature excursions were also provided.

Supportive stability data on one pilot scale batch manufactured by the same process but stored in a different container for 60 months at $-20^\circ\text{C} \pm 5^\circ\text{C}$ and 12 months at $5 \pm 3^\circ\text{C}$ were also submitted.

All batches placed on stability are representative of the full scale commercial manufacturing process.

The following parameters were tested: appearance, assay, purity, impurities, microbial enumeration test (TAMC and TYMC) and bacterial endotoxins. Deamination (tested by IP-HPLC with time-of-flight-MS) and water content (measured by Karl Fischer) were monitored on the primary stability batches. However, these attributes are not proposed for the commercial specification.

All results remained within the proposed specification limits and no significant changes were observed. No meaningful trends in assay, purity or impurities occurred over the 24 months at any storage condition. Process-related impurities that may also be degradation products were assessed for trends at the long term (-20°C), accelerated (5°C) or stressed condition (30°C). Some oligonucleotide impurities showed no change over time at accelerated (5°C) or stressed (30°C) conditions, but showed a slight increase at the long term storage condition of -20°C in all batches. Nevertheless, no impact to the proposed retest period is expected as a result of this minimal increase. Deamination was tested and not detected at the 6 month time point for the accelerated condition of 5°C and the 3 month time point for the stressed condition of 30°C . Although water content increased in all batches over time in all storage conditions, it was demonstrated that it has no impact on the stability of the active substance.

Forced degradation studies were also conducted on one pilot and one production scale batch. Nusinersen was exposed to light, acidic (pH 2), basic (0.1 N NaOH), oxidative (0.03% H₂O₂) and thermal (7 months at 80°C) stress conditions. It was shown that the active substance is susceptible to acidic, oxidative, thermal and photolytic conditions. The results of mass balance calculations support the stability indicating properties of the analytical method for assay and impurities.

Photostability testing following the ICH guideline Q1B (option 2) was performed on one production scale batch. The results obtained indicate that the formation of impurities through photodegradation is slow. This slow degradation rate suggests that the short exposure times to lower intensity room fluorescent lighting associated with dispensing and drug product manufacturing operations will not result in measurable degradation. This is supported by the hold time validation experiments which showed no significant differences in oligonucleotide impurities content between batches. Therefore, no special precautions to protect nusinersen from light during manufacturing, handling, storage and finished product formulation activities are required.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored at -20 ± 5°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Spinraza is a single use, unidose, sterile, preservative-free, clear and colourless isotonic solution for injection intended for intrathecal administration containing 2.4 mg/ml of nusinersen. It is supplied in aseptically filled single use vials that nominally contain 12 mg of nusinersen.

The quality target product profile (QTPP) was defined as a single use, sterile, preservative free liquid isotonic solution for intrathecal injection containing nusinersen formulated in an artificial cerebrospinal fluid (aCSF), stable at 2-8 °C, packaged in Ph. Eur. Type I glass vial, which meets pharmacopoeial requirements for parenteral dosage forms and product specific requirements.

Nusinersen is a synthetic oligonucleotide with a molecular weight of 7501 amu. Due to its polyanionic nature, nusinersen is freely water soluble at physiologic pH, making it straightforward to formulate in aqueous solution. The particle size distribution of the active substance is therefore not critical.

In line with the QTPP, formulation excipients were selected based on the composition, pH and electrolyte levels of cerebrospinal fluid (CSF).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The excipients are: sodium dihydrogen phosphate dihydrate and disodium phosphate as buffers to maintain the pH of the drug product comparable to CSF; sodium chloride to establish the tonicity of the drug product comparable to that of CSF; potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate as electrolytes, sodium hydroxide and hydrochloric acid for pH adjustment and water for injection as vehicle. None of the excipients are of human or animal origin. The applicant completed a risk assessment to determine the potential sources of endotoxin in the manufacturing process. All excipients are tested to meet the requirements in the applicable Ph. Eur. monograph. While endotoxin limits are not included for sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic and potassium chloride, the risk associated with these salts is low as their concentrations in the final finished product are also low. Additionally, raw materials derived from an inorganic origin carry a low risk of measurable endotoxin in general. No endotoxin specifications are provided for sodium hydroxide (NaOH) or hydrochloric acid (HCl). Given this insignificant contribution and the fact that NaOH is often used an agent for endotoxin removal in other processes, the risk of endotoxin introduction from HCl and NaOH is negligible. Based on the results of this assessment and the results of endotoxin testing throughout the process validation at both manufacturing sites, additional controls

for endotoxin were deemed not necessary. The compatibility of the active substance with the formulation excipients was demonstrated as part of the stability studies.

The pharmaceutical development of the nusinersen solution for injection formulation was completed in two stages.

The development of the manufacturing process was described in sufficient detail. The choice of the sterilisation method (sterile filtration) was justified in line with the decision trees for the selection of sterilisation methods (CPMP/QWP/054/98).

Leachables and extractables studies on the container closure systems used for holding the bulk product at the proposed manufacturing sites were also provided.

Nusinersen 12 mg solution for injection is packaged in an ISO 6R Ph. Eur. type I, clear single-use vial sealed with a sealed with a 20-mm fluorinated polymer coated, bromobutyl rubber stopper and capped with a 20-mm aluminium over seal with a plastic flip off cap. The vial contains a nominal volume of 5.0 ml. The specifications, technical drawings, quality control information and certificates of analysis for the proposed container closure system are provided. Confirmation was provided that the rubber stopper material complies with current requirements of Ph. Eur. and European food regulations. Details of depyrogenation and sterilization cycles employed for the primary containers and the vials together with the respective validation reports were submitted. Confirmation was provided that the sterilization of the rubber stoppers and sterilisation/ depyrogenation of the glass vials meet Ph. Eur. requirements (5.1.2). Non-volatile, semi-volatile, volatile and inorganic extractables and leachables were assessed. A risk assessment on the potential for delamination to occur was conducted and concluded that the risk was low. This was supported by stability data. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of ten main steps: receipt and storage of the drug substance at manufacturing site (step 0), temperature equilibration of the drug substance (step 1), excipient dispensing for artificial cerebrospinal fluid preparation (step 2), artificial cerebrospinal fluid preparation (step 3), active substance concentrate preparation (step 4), compounding (step 5), bioburden reduction (step 6), sterilizing filtration (step 7), vial filling, stoppering and crimping (step 8) and 100% visual inspection of filled vials (step 9).

Details regarding the description, duration and holding times of different steps of the manufacturing process have been provided. The process is a non-standard manufacturing process. The validation protocol and report of the manufacturing process of the finished product are provided for three commercial scale batches manufactured at each of the proposed manufacturing sites. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), identification (IP-HPLC-UV-MS), assay, purity and impurities (IP-HPLC-UV-MS), extractable volume (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (high voltage leak detection).

The specifications for Nusinersen 2.4 mg/ml Solution for injection have been established in line with the requirements of the Ph. Eur monographs, ICH guidelines and batch analysis data.

As indicated in the active substance section, a justification for not including a biological activity test based on the antisense mechanism was provided and accepted.

The proposed limits for purity, specified, unspecified and total degradation products in the finished product specification are the same as those proposed for the active substance since no finished product degradation was observed in the long term stability studies. However, as indicated in the active substance section, since these limits are based on a limited number of commercial scale batches the applicant is recommended to review and tighten them once data from ten commercial scale batches of active substance become available. Exclusion of deamination control has been justified based on available stability data, which confirm that deamination does not proceed to any measurable extent at the proposed long term storage condition of 5 °C, or during 6 months storage at the accelerated condition of 25 °C/60% RH, . The absence of deamination control is considered acceptable.

A risk assessment for elemental impurities in the finished product was conducted as per ICH Q3D. It confirmed that elemental impurities testing does not need to be included in the finished product specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for ten production scale batches from both manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three production scale batches of finished product manufactured at one of the proposed manufacturing sites stored under long term conditions for up to 36 months at 5±3°C / 60% RH; up to 36 months at long term condition of 5±3°C / 60% RH followed by 2 weeks at 30±2°C/ 65±5%RH; and for up to 6 months under accelerated conditions at 25±2°C / 60±5%RH according to the ICH guidelines were provided.

Up to six month stability data at the long term storage condition (5°C±3°C) and three month at accelerated storage condition (25 ± 2° C/60 ± 5%RH) on three commercial scale batches of finished product from the other proposed manufacturing site were also provided.

Supportive stability data from six process validation batches (three from each of the proposed manufacturing sites) stored for 12 months or 3 months at 5±3°C / 60% RH, and 9 months or 3 months at 25±2°C/ 60±5%RH, respectively were also presented.

The finished product batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, purity, specified degradation products, unspecified degradation products, total degradation products, pH, particulate matter, bacterial endotoxins, sterility, container closure integrity testing and deamination. The analytical procedures used are stability indicating.

All samples complied with the specification at all time points. No meaningful changes were observed for any product quality attributes after storage at long term or accelerated conditions. The data

obtained through 36 months at the long term storage condition and 6 months at the accelerated condition confirm that deamination does not occur to any measurable extent. The accelerated stability data show no meaningful changes in any attribute when drug product is exposed to temperature excursions up to 25°C (e.g., during shipping) or when the drug product is stored long term at 5 ± 3°C followed by up to 14 days up to 30 °C.

The release (T=0) and 6 month stability data from the proposed manufacturing sites was evaluated and considered comparable.

Data to support the storage of the finished product outside of 2-8°C for two weeks has been presented. It included: i) 36 months of real time stability data at the 2-8°C followed by 2 weeks at 30±2°C/65±5%RH storage condition, ii) 6 months of real time stability data at the accelerated storage condition of 25±2°C/60±5%RH for the primary (registration) batches, iii) 9 months of real time stability data at the accelerated storage condition of 25±2°C/60±5%RH for the process validation batches manufactured at one of the proposed manufacturing sites, and iv) 3 months of real time stability data at the accelerated storage condition of 25±2°C/60±5%RH for the process validation batches manufactured at other manufacturing site.

A confirmation of compliance with CPMP/QWP/072/96 regarding start of shelf life of the finished product has been presented.

In addition, the applicant conducted a study to evaluate the impact of exposure to room temperature and light on the finished product prior to administration. Unopened vials removed from the outer carton were exposed taken out from the refrigerator for six hours six times. The cumulative time outside of secondary package and refrigeration was not less than 36 hours. Minor or no changes in the quality attributes of the finishes products were observed. Therefore it was concluded that prior to administration, unopened vials of Spinraza can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours, at temperature that does not exceed 25°C.

Forced thermal degradation and photo degradation studies designed to determine degradation pathways, structures of degradation products and the inherent stability of the finished product were conducted on three batches. Samples were tested for assay, purity, and degradation products by IP-HPLC-UV-MS and for deamination by IP-HPLC-TOF-MS. The results indicated that the product degrades to a variety of components under stressed conditions. Based on the stability data, none of these impurities are expected to be formed (or increase in the case of process-related impurities) in the finished product stored at the long-term or accelerated conditions. In addition, a photostability study has been performed on one production scale batch of Nusinersen 12 mg solution for injection according to ICH Q1B (option 2) guideline. Samples were tested for appearance, particulate matter, assay, purity, specified degradation products, unspecified degradation products, total degradation products and deamination. Minimal degradation was observed. Exposure did not alter drug product appearance or resulted in an increase in particulate matter. Drug product stored in vials contained within paperboard boxes did not degrade. The results indicate that the degradation rates are slow and special precautions to protect the product during normal handling, for example, during drug product manufacture, are not required. However, for the long term, it is recommended that drug product vials are stored protected from light in secondary packaging.

Based on available stability data, the proposed shelf-life of 36 months stored in a refrigerator (2°C - 8°C) and in the outer carton in order to protect from light as stated in the SmPC (section 6.3) are

acceptable. However, since no degradation was observed under accelerated conditions at $25\pm2^\circ\text{C}$ / $60\pm5\%\text{RH}$, the applicant is recommended to further explore the possibility to store the product at ambient temperature post-approval and revise the storage conditions if appropriate.

If no refrigeration is available, Spinraza may be stored in its original carton, protected from light at or below 30°C for up to 14 days.

Prior to administration, unopened vials of Spinraza can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours, at a temperature that does not exceed 25°C .

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Nusinersen is a uniformly modified 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide consisting of 18 nucleotide residues. The finished product is a solution for injection for intrathecal administration. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Although, the active substance and finished product are in general adequately controlled by the proposed specifications, the applicant is recommended to review and tighten the limits for specified, unspecified and total oligonucleotide impurities in both the active substance and finished product specification when data from ten commercial scale batches of the active substance become available.

The finished product is manufactured by sterile filtration followed by aseptic filling. Since this is a non-standard manufacturing process, process validation data were presented in the dossier to demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Based on available stability data, the proposed shelf-life of 36 months stored in a refrigerator (2°C - 8°C) and in the outer carton in order to protect from light are acceptable. However, since no degradation was observed under accelerated conditions at $25\pm2^\circ\text{C}$ / $60\pm5\%\text{RH}$, the applicant is recommended to further explore the possibility to store the product at ambient temperature post-approval and revise the storage conditions if appropriate.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to review and tighten the limits for specified, unspecified and total oligonucleotide impurities in both the active substance and finished product specification when data from ten commercial scale batches of active substance become available
- The applicant is recommended to further explore the possibility to store the product at ambient temperature post-approval and revise the storage conditions if appropriate.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical program for nusinersen (ISIS 396443) consisted of studies to evaluate the pharmacology, pharmacokinetics (PK) and tissue distribution, and nonclinical toxicology safety (off target) of nusinersen.

2.3.2. Pharmacology

Humans are the only species known to have the SMN2 gene; therefore, the preclinical pharmacological effects of nusinersen can only be studied in genetically modified animal models or human cells. The field has developed several different mouse models of SMA ranging in phenotypic severity. The general approach has been to use genetic engineering to remove the endogenous mouse gene and add various numbers of copies of the human SMN2 gene. Those models with more copies of the SMN2 gene typically have milder phenotypes than those with fewer copies. The pharmacological properties of nusinersen were assessed in multiple models with varying degrees of phenotypic severity. For PK/PD relationships, a mild model expressing 4 copies of the human SMN2 gene was used (Hsieh-LI 2000). The use of the mild model to assess PK/PD relationships minimized potential complications associated with the rapid deterioration and morbidity found in the severe models. Mouse models with more severe phenotypes were used to assess efficacy of nusinersen.

As common laboratory animal species (mice, rats, dogs, macaques) used in toxicity studies lack the SMN2 gene, it was not feasible to evaluate the toxicity of nusinersen in a pharmacologically responsive species. However, since the consequence of modulating splicing of the SMN2 transcript is increased production of the full-length SMN protein, which is already produced in healthy subjects and at insufficient levels in SMA patients, the on-target safety risk is minimal. Thus, the toxicity assessment was focused on non-pharmacologic effects related to exposure to nusinersen.

Although toxicology studies were conducted in several species (CD-1 mice, Sprague Dawley Rats, New Zealand White rabbits, and cynomolgus monkeys), the cynomolgus monkey was chosen as the species for repeat-dose IT toxicology studies as it was considered that the ability to repeatedly administer the

drug in a clinically relevant manner (IT dosing) in monkeys provides the most relevant safety and exposure information for IT dosing in patients.

Conducting a sub-chronic or chronic repeat-dose toxicology study in rodents using IT bolus dosing was not technically feasible. Thus, a 13-week repeat-dose toxicology study was conducted in juvenile CD-1 mice using SC dosing to obtain maximum systemic exposure and to support treatment of pediatric patients. Rats were used for a safety pharmacology study, but the method of administration was continuous IT infusion into the lumbar region, at a slow rate (0.25 µL/hour over 25 days and up to 0.2 mg/day). Reproductive studies were conducted in mice (fertility and developmental toxicity) and in rabbits (embryo-fetal development) using SC dosing to provide maximum systemic exposure.

Conclusions on pharmacology

The results from the nonclinical pharmacology studies described above demonstrate that nusinersen can modulate the splicing of SMN2 to produce an mRNA capable of encoding full length SMN protein. In non-clinical species possessing the human SMN2 transgene, nusinersen is capable of inducing sufficient SMN expression to significantly improve the life span and function of engineered mouse models. This activity supports its potential use in individuals with SMA caused by loss of SMN1.

Safety pharmacology parameters were evaluated in the 14-week and 53-week toxicity studies in monkeys and also in rats receiving 25 days of continuous IT infusion of the test article. There was no sustained effect of nusinersen on safety pharmacology parameters from any of these studies. The only observations were transient changes in lower spinal reflex following IT slow bolus administration of doses ≥3 mg. The safety pharmacology supports the dose levels used in the clinical program.

Considering the specific binding and unique mechanism of action of nusinersen, no secondary pharmacodynamic studies or pharmacodynamic drug-drug interaction studies were performed, which was considered acceptable.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetics of nusinersen were characterized in CSF, plasma, and tissues from single and repeat-dose toxicology/PK studies in monkeys using IT administration. Plasma and tissue concentrations were evaluated from reproductive studies in mice and rabbits following SC bolus dose administration.

Results were obtained from 4 separate *in vivo* studies in monkeys as follows:

- A non-GLP multiple dose toxicity/PK study in adult cynomolgus monkeys (Study 396443-APK01)
- A GLP single-dose IT toxicity study in cynomolgus monkeys (Study 396443-AS01)
- A GLP 14-week IT toxicity study in juvenile cynomolgus monkeys (Study 396443AS03)
- A GLP 53-week IT toxicity study in juvenile cynomolgus monkeys (Study 396443AS06)

Absorption

By bypassing the blood-brain-barrier, IT injection of nusinersen into the CSF allows the drug to be fully available to the target CNS tissues without an initial absorption process. nusinersen administered via IT injection rapidly distributes throughout the CSF space with uptake into CNS tissues with little metabolic clearance in the CNS prior to eventual transfer into the systemic circulation via CSF turnover. Plasma exposure of nusinersen was approximately 1 to 3 orders of magnitude lower than CSF exposure.

Distribution

Multiple-Dose PK Study in Monkeys (Study 396443-APK01)

A comprehensive PK study was conducted utilizing adult male monkeys dosed IT and IV. In the 4-week multiple dose study, cynomolgus monkeys received either four IT lumbar doses (17 male monkeys), administered via an implanted lumbar catheter, or four IV bolus doses (3 male monkeys) at 1 mg/dose on Days 1, 8, 15, and 22. Both CSF and plasma concentrations exhibited multiphasic disposition following IT administration, with a rapid distribution phase followed by slower and prolonged elimination (post-distribution) phase(s) in the same manner as observed after a single IT dose. The terminal elimination half-life from CSF was 102 days. Peak CSF concentrations occurred 1 hour (the first evaluated time point) following IT injection, while plasma concentrations peaked 4 hours after the IT bolus injection. While a substantial distribution advantage in the spinal cord and brain tissues was achieved following direct IT administration, a comparison of plasma exposure after IT and IV administration suggests minimal metabolic clearance of nusinersen in the CNS prior to eventual transfer from the CNS to the systemic circulation.

Following the last dose on Study Day 22, animals dosed IT were sacrificed on Study Days 29, 85, 183, 253 and 365. nusinersen was slowly cleared from CNS tissues with terminal elimination half-lives for various brain and spinal cord regions ranging from 74 to 275 days with a median value of 116 days.

14-Week (396443-AS03) and 53-Week (396443-AS06) Repeat-Dose Toxicology Studies in Juvenile Monkeys

CSF, plasma, and tissue concentrations from the 14-week and 53-week toxicology studies in juvenile monkeys were consistent with the pattern established in the 4-week multiple dose PK study. CSF and plasma concentrations increased in a dose-dependent manner in both studies. The CSF elimination half-life determined in AS06 was 111 days, which is consistent with the elimination half-life in CSF determined from the multiple-dose PK study. CSF measurements were taken 7 days following IT dose administration, so CSF concentrations were well below their expected peak values and were consistent with Day 7 CSF values from the single-dose IT study. Consistent with previous studies, the plasma Tmax occurred approximately 2 to 5 hours after IT bolus administration.

Tissue concentrations were measured for CNS tissues, and consistent values were obtained between the 14-week and 53-week studies after adjusting for the difference in dosing regimens. The dosing regimens differed between the two studies as follows: In the 14-week study, animals dosed at 0.3 and 1 mg received 5 weekly loading doses (SD 1, 8, 15, 22 and 29) followed by biweekly maintenance doses (SD 43, 57, 71, 85 and 99) while animals dosed at 3 mg received 15 weekly IT doses. In the 53-week study, all animals received 5 weekly loading doses (SD 1, 8, 15, 22 and 29) followed by maintenance doses every 6 weeks (SD 71, 113, 155, 197, 239, 281, 323 and 365).

Dosing frequencies in both of these toxicology studies were more frequent than the clinical study and proposed dosing regimen. Thus, the extrapolation of dose exposure in monkeys to humans took into

consideration the difference in CSF volume between species and dose regimen to calculate safety margins.

PK studies established a consistent pattern of distribution and uptake of nusinersen into the critical spinal cord and brain regions needed for pharmacology following IT administration. The long elimination half-lives from multiple-dose PK and repeat-dose toxicology studies support a long dosing interval for IT drug administration to SMA patients.

Metabolism

Nusinersen is metabolized slowly and predominantly via exonuclease mediated hydrolysis (3' and 5' exonucleases). Nusinersen is not expected to be a substrate for CYP450mediated oxidative metabolism. While intact nusinersen was the most abundant ASO detected in monkey tissues, it is noted that the drug-related 17-mer oligonucleotide (N-1 from the 3' end) was detected in a relative abundance of more than 15%. It is scientifically well established that shorter oligonucleotides less efficiently hybridize with their target sequence because the resulting lower melting temperature (Tm) renders the interaction of the hybrid thermodynamically less. Accordingly, the 17-mer metabolite should less effectively interact with the target sequence compared to the parent oligonucleotide. Based on comprehensive *in silico* analyses by the Applicant, the potential for interaction of parent substance and 17-mer metabolite with "off-target"-sequences is also low, particularly because these "off-target"-mRNAs would have to be transcribed in the same temporal and site-specific manner. Moreover, the sequence of the 17-mer metabolite is in antisense orientation like in the parent oligonucleotide, which excludes duplex formation of parent substance and metabolite. For this reason, it is accepted that the 17-mer metabolite can neither reduce, nor antagonise the pharmacodynamic effect of the parent oligonucleotide.

Excretion

Nonclinical urinary excretion evaluation of nusinersen has not been conducted. The chain shortened oligonucleotides are expected to be excreted in urine following slow metabolism in tissues which represents the major pathway for whole body clearance of these compounds and thus also expected for nusinersen (Geary 2003). The absence of excretion studies was considered acceptable.

Pharmacokinetic drug interactions

The potential for nusinersen to have drug-drug interactions is low. While nusinersen is highly bound to plasma proteins, the binding sites of ASOs (hydrophilic) differ from the binding sites for small molecule hydrophobic drugs. Thus, the likelihood of drug-drug interactions due to competition with plasma protein binding is low. Nusinersen is not a substrate or inhibitor of a variety of human transporters (Study ISIS 396443-IS12) and is unlikely to interact with other drugs due to competition or inhibition of the transporters. The metabolites of nusinersen observed in CSF, plasma and tissues are consistent with slow and predominantly exonuclease mediated hydrolysis. Based on previous experience (Geary 2008, Yu 2007), nusinersen is not expected to be a substrate for CYP450-mediated oxidative metabolism. In addition, *in vitro* studies with cultured cryopreserved human primary hepatocytes have demonstrated that nusinersen is not an inducer or inhibitor of major CYP450-mediated oxidative metabolism (Studies ISIS 396443-IS13 and ISIS 396443-IS14) and therefore should not compete with other drugs for this metabolic pathway.

Conclusions on pharmacokinetics

Nusinersen administered via IT injection rapidly distributes throughout the CSF space with uptake into CNS tissues followed by transfer to systemic circulation via CSF turnover. Plasma concentrations remain well-below CSF concentrations following IT administration. The estimated CSF terminal elimination half-life is 102 to 111 days in adult and juvenile monkeys. CSF concentrations seemed to be in equilibrium with CNS tissue concentration as terminal elimination half-lives from CNS tissues ranged from 116 to 174 days.

The long elimination half-lives from multiple-dose PK and repeat-dose toxicology studies support a prolonged dosing interval for IT administration in SMA patients. The concentrations measured in the CNS tissues in the toxicology studies exceeded the expected efficacious range (2 to 10 µg/g) confirming that the toxicology studies had been dosed high enough to provide appropriate safety margins in support of the clinical studies.

The chain shortened oligonucleotides are expected to be excreted in urine following slow metabolism in tissues which represents the major pathway for whole body clearance of these compounds and thus also expected for nusinersen.

The potential for nusinersen to have drug-drug interactions is low.

Nusinersen is metabolized slowly and predominantly via exonuclease mediated hydrolysis (3' and 5' exonucleases). Nusinersen is not expected to be a substrate for CYP450mediated oxidative metabolism.

2.3.4. Toxicology

The toxicology program for nusinersen was designed by the applicant to support chronic IT administration for treatment of Spinal Muscular Atrophy (SMA).

The route of administration for the core repeat-dose toxicity studies was a slow IT bolus injection into the lumbar space, which matches the route of administration used in the clinical program. The reproductive toxicity studies in mice and rabbits used SC dose administration to ensure maximum systemic exposure of the adult animals and fetuses to nusinersen.

Nusinersen was well tolerated in single and repeat-dose studies in monkeys except for acute, transient deficits in lower spinal cord reflexes at the highest doses tested. There was no mortality and no effects on body weight, food consumption or persistent clinical observations. The acute transient deficits in lower spinal cord reflexes occurred only at the highest dose levels tested (7 mg in the single-dose study, 3 mg in the 14-week study, 4 mg in the 53-week study, and at 5 mg in the 6-week investigational study). These effects were observed within several hours post-dose, resolved generally within 48 hours post-dose and did not seem to progress with repeated administration.

A 13-week toxicity study was conducted in juvenile CD-1 mice using SC dose administration to provide additional safety data related to systemic exposure margins for use of nusinersen in pediatric patients. SC dosing was initiated on postnatal day (PND) 4 and occurred once weekly for 4 weeks (PND 4 through PND 25) and then every other week until the final dose on PND 95. Dose levels were vehicle, 1, 10, and 50 mg/kg/dose. Nusinersen was well tolerated at all dose levels. There were no effects on morbidity, mortality, clinical findings, body weights, food consumption, ophthalmic examinations, hematology, clinical chemistry, or gross findings at necropsy. There were also no apparent effects on

growth or development. Test article-related histopathologic findings were seen at 50 mg/kg in male liver (Kupffer cell hypertrophy) and in male and female lymph nodes (vacuolated macrophages), which correlated with higher organ weights for those 2 tissues. Higher spleen weights were seen at 10 mg/kg in males and at 50 mg/kg in males and females. The range of effects observed in juvenile animals was comparable to that documented in adult animals. Based on these results, the NOAEL should be 10 mg/kg and is still well above the human equivalent dose (0.6 to 2 mg/kg) used in the maintenance phase of the clinical studies (IT administration every 4 months).

In the 14- and 53-week studies in the monkey, physical examinations, clinical pathology evaluations, ophthalmic examinations, cardiovascular evaluations, maturation of the skeletal system, and immune system parameters were within normal limits for animals this age. There were also no effects on systemic organ pathology. Although nusinersen was detected in liver and kidney, the absence of any treatment related findings is consistent with the relatively low concentrations in liver (<120 µg/g at the highest doses tested by IT) compared to the threshold for concentration in monkey liver in systemic administration toxicity studies (>1000 µg/g) for other compounds (Henry 2008). There were no treatment-related effects on neurobehavioral or learning parameters.

Microscopic changes associated with administration of nusinersen were limited to the inferior hippocampal region of the brain, where the primary finding was minimal to mild focal neuronal vacuolation. This alteration appears to be related to histological fixation and sample preparation in the presence of formalin. Hippocampal vacuolation was absent in brain sections processed using alternative fixation methods. The incidence and severity of these fixation-induced vacuoles was greatest in the 14-week monkey IT study which had the most intensive dosing schedule (45 mg total dose in 14 weeks) and achieved the highest concentrations in lumbar spine and cerebral cortex (169 and 166 µg/g, respectively). Per the applicant, further support for the lack of significance of the hippocampal vacuoles was provided by an investigational study conducted in cynomolgus monkeys using 6 weekly IT doses (Study 396443-AS11). Based on this investigational study, vacuoles in the hippocampus may not represent an adverse toxicological finding; instead, the observation of vacuoles could be linked to the method of tissue preservation and the presence of ASO in endosomes or lysosomes, like that described in the kidney (Engelhardt, 2016). The microscopic findings in repeat dose studies in the monkey could be consistent with oligonucleotide uptake and/or cellular activation and cytokine production due to pro-inflammatory effects. The consequences of such uptake and of the potential pro-inflammatory effects were discussed and substantiated with published evidence to support the reduced risk of long term adverse effects.

Table 1 Comparison of Hippocampal Vacuolation (Terminal Necropsy) with Total Dose in Monkeys

Study Duration	Mg/Dose	Total Dose	Incidence of Hippocampal Vacuolation
14 Weeks	0.3	3 mg	None
	1	10 mg	1 of 7
	3	45 mg	7 of 7
53 Weeks	0.3	3.9 mg	None
	1	13 mg	2 of 10
	4	52 mg	5 of 10 ^a

^a 3 of 4 recovery animals (4 mg dose group) had neuronal vacuolation in the hippocampus with a similar microscopic scoring grade to those seen at the terminal necropsy

In the 14-week study, 1 of 7 high dose group animals also had a necrotic neuron, and in the 53-week study, some necrotic non-neuronal cells and cellular debris were observed in one mid-dose male and in 3 of 7 high-dose males. Based on a 5-point microscopic severity grading scale, the hippocampal vacuolation findings from both studies were mainly slight (Grade 1) and minimal (Grade 2) with one mild (Grade 3). In the opinion of the study pathologist, the histologic findings in the hippocampus were unlikely to cause any clinical signs or influence the animals' ability to function. This interpretation, based on the microscopic severity, was supported by the lack of effects on neurobehavioral assessments in these animals.

The 53-week monkey study was designed to achieve an intermediate level of exposure compared to the 14-week study and determine if there was any progression or additional toxicities seen with chronic exposure. The total dose in the first 3 months of this study was 24 mg, which produced lumbar spinal cord and cerebral cortex concentrations of 106 and 71 µg/g, respectively. The neuronal vacuolation in the inferior hippocampus was present at this level of exposure, but there was no evidence of progression in severity of the histologic changes compared to the 14-week study.

An investigational study was conducted in cynomolgus monkeys, which provided support that the hippocampal vacuoles contain nusinersen and do not represent an adverse histopathological finding. Indeed, the observation of vacuoles is linked to the method of tissue preservation in the presence of drug, thereby allowing these to be called fixation-induced vacuoles. Vacuolation in the inferior hippocampus was absent in tissues immersion-fixed in Carnoy's or perfusion-fixed with Karnovsky's fixative.

Results of the two developmental and reproductive toxicity studies were negative for drug-related effects on fertility and embryo-fetal development. Biodistribution results indicated that nusinersen did not cross the placenta and, therefore, maternal exposure does not lead to any toxicologically relevant exposure in the developing fetus.

Nusinersen was non-genotoxic when tested in the bacterial reverse mutagenesis assay, in vitro chromosomal aberration assay in CHO cells and the in vivo mouse micronucleus assay. Therefore, nusinersen was interpreted to be neither mutagenic nor clastogenic.

Carcinogenicity studies have not been conducted with nusinersen. Nusinersen is not genotoxic and does not have a direct mechanism for tumor induction. There is no reason to believe that the pharmacological action of nusinersen, i.e., restoration of full-length SMN protein via the SMN2 gene, poses a carcinogenic risk for SMA patients. Based on a weight-of-evidence assessment, nusinersen does not pose a meaningful carcinogenic risk for patients.

The safety margin for comparing monkey toxicology results to the dose administered to patients is based on the cumulative dose administered in a set period. The cumulative doses in the 53-week study were 3.9, 13 and 52 mg (Table 20). The cumulative doses in the monkey studies were converted to human equivalent doses (HED) based on the nominal volume difference in CSF (approximately 10-fold between monkeys and patients > 2 years old).

Table 2 Safety Margin Calculations for First Year and Chronic (Maintenance) Dosing

Study Duration	Dose Level (mg/dose)	Toxicology Assessment	Cumulative Dose	HED ^a	Safety Margin: Ratio of NOAEL to Adult Dose	
					Total First Year (72 mg) ^b	Chronic Yearly Maintenance Dose (36 mg) ^c
53 Weeks	0.3	NOEL	3.9 mg	39 mg		
	1.0	NOAEL	13 mg	130 mg		
	4.0	NOAEL	52 mg	520 mg	7.2-fold	14.4-fold

^a HED, human equivalent dose is 10 x cumulative dose in monkeys (approximate 10-fold difference in CSF volume)

^b Patients with SMA will receive loading doses on Days 1, 15, 29 and 64 followed by maintenance doses every 4 months (72 mg in first year, adult equivalent)

^c Maintenance dosing will be 36 mg per year (12 mg every 4 months, adult equivalent)

The calculated safety margin for IT doses in monkeys to IT doses in humans is based on the different CSF volumes in the two species (approximately 10-fold greater absolute CSF volume in humans 2 years or older).

SMA patients will receive four loading doses in the first year of treatment to reach CNS steady-state tissue concentrations as rapidly as possible, followed by maintenance dosing every 4 months. This cumulative dose of 72 mg during the first year of treatment results in a safety margin of 7.2-fold (520 mg/72 mg). Thereafter, the safety margin during maintenance dosing will be 14.4-fold (520 mg/36 mg).

2.3.5. Ecotoxicity/environmental risk assessment

An ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00) was performed. A PEC surface water (1.87×10^{-6} µg/L) based on a DOSEAI of 12 mg/inhabitant/day and a fraction market penetration of 3.12×10^{-7} (based on SMA prevalence of 0.0019%), resulted very low and did not trigger the action limit calculation. An evaluation of PBT properties is required if the log Kow is greater than 4.5, and a study supporting the partition coefficient data was in the process of being finalised during the assessment. The preliminary data indicated that the experimental log Dow determined to be less than 4.5.

Because of the above considerations, Spinraza is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Nusinersen is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO) for the treatment of spinal muscular atrophy (SMA). Nusinersen is intended to be chronically administered for the treatment of patients with SMA via the intrathecal (IT) route. As humans are the only species known to have the SMN2 gene and it was not possible to evaluate the toxicity of nusinersen in a pharmacologically responsive species. The nonclinical program for nusinersen consisted studies to evaluate the pharmacology, pharmacokinetics (PK) and tissue distribution, and nonclinical toxicology safety (off target) of nusinersen. The activity of nusinersen was investigated in patient fibroblasts and in

transgenic mouse models of SMA models in which the human SMN2 gene is integrated into the mouse genome.

Pharmacology studies evaluated the ability of nusinersen in promoting increased amounts of full-length SMN protein from the SMN2 gene using in vitro and in vivo studies. In some of these studies (Study 396443-NP04 and Study 396443-NP05) it is unclear as to what doses and which tests were carried out at which dose within these studies. The applicant is asked for clarification. In safety pharmacology studies male albino rats were given continuous IT Infusions of 0, 0.02, 0.06 and 0.2 mg/day. There were no effects on pulmonary function (respiratory rate, tidal volume, and minute volume), blood pressure (systolic, diastolic, and mean arterial) and heart rate. Safety pharmacology parameters were also evaluated in single (1, 3, and 7 mg) and repeat-dose toxicology studies in juvenile cynomolgus monkeys. Transient deficits in lower spinal reflexes were seen at \geq 3 mg in the 53 week study, which affected lower spinal reflexes (patellar, grip, and anal). The most significant findings were observed after the first IT dose (Day 1) and consisted of reduced or missing reflexes in 4 of 7 females and 1 of 7 male animals in the 4 mg dose group. In general, these changes were reversible within 48 hours following dosing. There were no test article related effects on neurobehavioral or learning parameters. Details of the deficit in lower spinal reflexes are included in section 5.3 of the SmPC. These findings could have been procedure related. This could be monitored in a long term registry study.

While intact nusinersen was the most abundant ASO detected in monkey tissues, it is noted that the drug-related 17-mer oligonucleotide (N-1 from the 3' end) was detected in a relative abundance of more than 15%. The pharmacological effects of this metabolite, including its putative antagonist effects against nusinersen, were asked to be further clarified. The applicant explained that nusinersen is metabolized slowly, and predominantly via exonuclease hydrolysis (3' and 5' exonucleases). The 17-mer (n-1 from 3' end) is expected to have the same physical properties as the parent ASO. Since it has the identical base sequence with one base removed from the 3' end, the 17-mer metabolite would bind to the same pre-mRNA sequence but with a slightly lower binding affinity (measured by Tm). According to the applicant, the 17-mer metabolite is not expected to interfere with the pharmacological activity of nusinersen, which is binding to a specific site in pre-mRNA and promoting inclusion of exon7 in SMN2 mRNA. Nevertheless, the applicant did not evaluate the pharmacological effects of this metabolite, including its putative antagonist effects against nusinersen, but a 15-mer ASO version of nusinersen was tested in vitro and in the transgenic mouse model, showing similar or slightly less activity. These results suggest that the 17-mer metabolite, if present in the active compartment of the cell, would retain pharmacologic activity and potency similar to (or slightly less) than the parent ASO. The percentage of the 17-mer metabolite is not expected to increase over time. It is agreed that no dose-adjustment is recommended, given that pharmacologic activity and potency (ug/g basis) of the 17-mer metabolite is expected to be only slightly less than the parent ASO.

Both the parent ASO and the 17-mer metabolite are uniformly modified polymers with 2'-MOE at each residue. This modification prevents the parent and the 17-mer from forming duplexes which would be degraded by RNase H. Thus, there is no potential for the 17-mer metabolite to promote degradation of other mRNA sequences from non-target genes.

nusinersen non-clinical pharmacokinetics were assessed following single IT lumbar bolus injections (1 to 7 mg) in adult monkeys and following multiple IT lumbar bolus injections for 4, 14 or 53 weeks in juvenile monkeys. The dosing regimen used during the first 4 weeks of the 14-week study was once weekly administration for all dose groups and was intended to provide a loading period. Following a single nusinersen IT dose at 1, 3 and 7 mg in adult monkeys, both CSF and plasma concentrations exhibited multiphasic disposition, with a rapid distribution phase followed by slower and prolonged elimination (post-distribution) phase(s). Mean nusinersen CSF concentrations measured 7 days after dosing were dose-dependent and typically increased during periods of weekly or bi-weekly dosing as

would be expected with multiple dosing in both the 14-week and 53-week studies and is consistent with the observed CNS tissue accumulation and long-term elimination half-life. The 16-mer (N-2, 3'-Deletion) oligonucleotide can be regarded as a human specific metabolite, based on the levels detected in human urine ($7.89\% \pm 12.25\%$) when compared to maximum levels observed in monkey lumbar spinal column ($2.96\% \pm 0.32\%$).

The single-dose toxicity/PK study and core repeat-dose (14-weeks and 53-weeks) studies were conducted in a single species, cynomolgus monkeys. In the non-human primate studies transient deficits in lower spinal cord reflexes were noted. In the 14 week study these effects were seen at 3 mg and 4mg in the 53 week study. In the 14 week study, these effects consisted of negative responses for cutaneous (left and right sides), sensory foot (left and right), and/or tail reflexes. There were no effects on cerebral reflexes, general sensory or motor function parameters during the study, at any dose (0.3, 1 or 3 mg). In the 53 week study lower spinal reflexes affected patellar, grip, and anal were seen at 4 mg. The most significant findings were observed after the first IT dose (Day 1) and consisted of reduced or missing reflexes in 4 of 7 females and 1 of 7 male animals in the 4 mg dose group. In general, these changes were reversible within 48 hours following dosing. Details of the deficit in lower spinal reflexes are included in section 5.3 of the SmPC. These finding could have been procedure related . This could be monitored in a long term registry study.

In the 14-week monkey toxicity study, 1/7 animals at 3 mg had a necrotic neuron in the hippocampus. Another animal at this dose had some necrotic glial cells, which were also seen in 1 recovery animal at this dose. In the 53-week study, some necrotic cells and cellular debris were observed in the hippocampus in 1 male at 1 mg and 3/7 males at 4mg. Rare necrotic cells were also noted (in the hippocampus) in one recovery male at 4.0 mg. The Applicant goes onto say that based on a 5-point microscopic severity grading scale, the hippocampal vacuolation findings from both studies were mainly slight (Grade 1) and minimal (Grade 2) with one mild (Grade 3). In the opinion of the study pathologist, the histologic findings in the hippocampus were unlikely to cause any clinical signs or influence animal ability to function. This interpretation, based on the microscopic severity, was supported by the lack of effects on neurobehavioral assessments in these animals. As a result 4 mg was considered the NOAEL in the 53 week study and 1 mg in the 14 week study.

It is accepted that the 14-week and 53-week toxicology studies were conducted in juvenile monkeys to support treatment of paediatric patients and were appropriately conducted in this respect. The Applicant states that the highest dose of 3 mg/dose was administered IT every week for 15 consecutive weeks (total dose of 45 mg, which is equivalent to a human dose of 450 mg in 14 weeks, based on the 10-fold difference in CSF volume between monkeys and humans). In the 53-week study, animals received 5 weekly IT doses, followed by maintenance dosing every 6 weeks. The loading/maintenance dosing regimen in the 53-week study is more frequent than the proposed clinical treatment, which envisions 6 loading doses in the first year followed by 3 maintenance doses per year, thereafter. Animals at 4 mg/dose were given 52 mg in one year, which is equivalent to a human dose of 520 mg in one year.

In both toxicology studies, observed microscopic changes (either a necrotic neuron, necrotic glial cells, or cellular debris) were limited to the inferior hippocampal region of the brain in animals exposed to the highest dose (3 or 4 mg per dose). The histological findings in the hippocampus were associated with hippocampal ASO concentrations of 149 and $88.9 \mu\text{g/g}$ in the 14-week and 53-week studies, respectively.

The Applicant argued that these histological changes were not associated with any functional or clinical consequence in either of the toxicology studies and there was no progression. However the lack of functional or clinical consequence in relation to microscopic findings such as these, is not a sufficiently

robust end-point on which this safety assessment can be based, and as the Applicant has stated, the long-term consequences of the persistence of ISIS396443 in neurons in the brain is not known. However reassurance is gained from the fact that the ASO tissue concentrations in the hippocampus achieved at the highest doses in monkeys (3 or 4 mg/dose) were above the target concentrations needed to produce a pharmacological effect in spinal motor neurons from animal models (between 2 and 10 µg/g) and the proposed dose in human, 12 mg/dose, is intended to achieve the pharmacologically active tissue concentration in spinal motor neurons, while hippocampal concentrations remain well below the hippocampal concentrations measured in the toxicology studies at the highest doses and the proposed dose to patients with SMA, 12 mg/dose, would result in a yearly dose (36 mg/year), which is below the human equivalent dose administered to monkeys in the high dose group (4 mg) from the 53-week study (520 mg/year, human equivalent).

Regarding the potential cellular activation and cytokine production due to pro-inflammatory effects evidence was provided that there was no indication of cellular activation and cytokine production due to pro-inflammatory effects in the animal studies and none in the clinical setting.

Long term data are not available. Patients will be followed up long term via the planned and ongoing studies outlined in the risk management plan, in Part III and IV of the document.

In a single combined fertility and early development study conducted in CD-1 mice (SC 3, 10, and 25 mg/kg), no significant changes to morphology, motility or concentration of sperm was noted. In female mice there were no significant effects noted on fertility, oestrous cycling, fetal weight, fetal death and there evidence of treatment-related malformations. The fertility sub-heading in Section 4.6 of the proposed SmPC was revised to reflect the lack of knowledge on the human effects.

Two studies embryo-fœtal development were conducted in New Zealand White rabbits. There were no findings to suggest treatment-related effects on embryo-fetal development following treatment with nusinersen at any dose (0, 6, 12.6 or 25 mg/kg (0, 21, 44.1, and 87.5 mg/kg/week) on Gestation Days (GD) 6, 8, 10, 12, 14, 16 and 18). The proposed wording of the pregnancy part of section 4.6 in the SmPC is adequate.

The pre- and post natal development study has been completed in female pregnant CD-1 mice treated subcutaneously with nusinersen at doses of 1.4, 5.8, and 17.2 mg/kg (5, 20 and 60 mg/kg/week) over gestation day 6 through to day 20 of lactation. Reduction in kidney/liver/spleen absolute weights was observed in the high dose group (17.2 mg/kg), and increased kidney weight was observed in the mid-dose level (5.8 mg/kg). Changes in organ weights are thought to be attributed to treatment with oligonucleotides and due to dose accumulation. Similar findings were observed in other developmental studies in mice and rabbits however these changes are unlikely to affect development or growth to the F1 generation offspring. There was no evidence of adverse effects to pups in terms of mortality, sexual maturation, motor activity, learning or ability to mate/reproduce. The NOAEL for maternal toxicity and development is 17.2 mg/kg (60 mg/kg/week).

In the study, concentrations of nusinersen in breast milk from lactating pregnant females were measured. These levels increased in a dose-dependent manner and ranged from 0.00847 to 0.0552 µg/mL. These levels were very low compared to that detected in liver samples and had no significant effect on pup development.

The applicant did not propose changes to the warnings in section 4.6 of the SmPC/PL because of this study, and this was agreed. Wording of all sections of 4.6 have been updated to bring into line with the Guideline on Risk assessment of medicinal products on human reproduction. It is unknown if nusinersen/metabolites are excreted in breast milk and the limited evidence in nursed mice suggest

no effect on development. Use of nusinersen during breastfeeding may be appropriately covered in the warnings in section 4.6.

Conventional studies of genotoxicity (Ames test in *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay, In Vitro Chromosomal Aberration Assay in Chinese hamster ovary (CHO) cells and a bone marrow micronucleus assay following SC administration to CD-1 mice revealed no genotoxic potential of nusinersen.

Carcinogenicity studies have not been conducted with nusinersen. The carcinogenic risk of nusinersen for patients was evaluated using a weight-of-evidence approach, which considered key principles for carcinogenicity assessment. Humans already make full-length SMN protein from the SMN1 gene and make varying percentages of full-length protein from the SMN2 gene.

2.3.7. Conclusion on the non-clinical aspects

No further concerns require clarification from a non-clinical point of view. For this reason, from a non-clinical point of view, no further issues preclude the granting of a marketing authorisation for nusinersen.

2.4. Clinical aspects

2.4.1. Introduction

The nusinersen clinical development program was designed to evaluate nusinersen across a range of SMA phenotypes to address the unmet medical need in a general population of patients with SMA. The studies conducted to date include 3 completed and 7 ongoing clinical studies: 2 studies in symptomatic infantile-onset SMA, 5 studies in symptomatic later-onset (Type II and Type III) SMA, 1 study in patients with genetically diagnosed, presymptomatic SMA, and 2 studies in patients with symptomatic infantile- and later-onset SMA (**Figure 3**). Unless stated otherwise, multiple doses of nusinersen were studied.

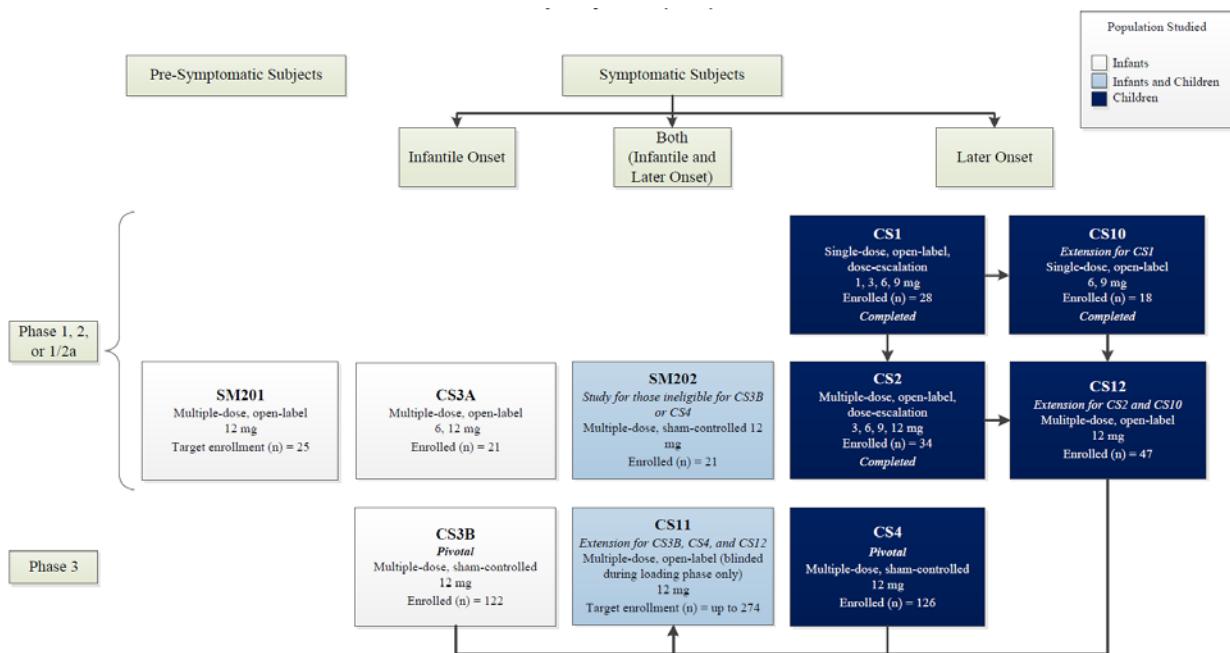


Figure 3 Clinical Development Plan for nusinersen Flow of Subject Population by Study

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Study ID Study population	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary / Secondary Endpoint
Study CS3B Subjects with symptomatic infantile-onset SMA	31 centers Australia: 5 Belgium: 1 Canada: 6 France: 8 Germany: 10 Italy: 9 Japan: 3 South Korea: 1 Spain: 11 Sweden: 3 Turkey: 5 UK: 5 US: 54	Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled	ISIS 396443: 12 mg scaled equivalent dose IT injection by LP or sham-procedure (2:1) Loading dose: Days 1, 15, 29, 64 Maintenance dose: Days 183 and 302 Total duration: approximately 14 months	Efficacy, safety, tolerability, and PK	August 2014 Completed 122 subjects (111 subjects)	Ongoing 153 (166) days (20 to 211 days)	45% male 55% female 153 (166) days (20 to 211 days)	Infantile-onset Male and females with genetic documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: 2 Age at onset of clinical signs and symptoms consistent with SMA: ≤6 months (180 days) of age	Motor milestones (HINE Section 2) / CHOP INTEND, CMAP, overall and event-free survival, growth
Study CS3A Subjects with symptomatic	4 centers US: 18 Canada: 3	Phase 2, Open-label, multiple-dose	ISIS 396443 IT injection by LP:	Safety, tolerability, efficacy, and PK	May 2013 Completed 21 subjects (20 subjects)	Ongoing 155 days	60% male 40% female 155 days	Infantile-onset Male and females with genetic	Motor milestones (HINE Section 2) /

Study ID Study population	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary / Secondary Endpoint
infantile-onset SMA			Cohort 1: <input type="checkbox"/> 6 mg scaled equivalent loading dose and 12 mg maintenance dose Cohort 2: <input type="checkbox"/> 12 mg scaled equivalent loading dose and 12 mg maintenance dose Loading dose: Days 1, 15, and 85 Maintenance dose: Day 253 and every 4 months thereafter.			(36 to 210 days)	documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: Not specified Age at onset of clinical signs and symptoms consistent with SMA: ≥21 days and ≤6 months	CHOP INTEND, CMAP, overall and event-free survival, growth	
Study CS4 Patients with Later-onset Spinal Muscular Atrophy	multiple centers worldwide	Phase 3, Randomized, Double-Blind, Sham Procedure Controlled Study	12 mg ISIS 396443 or sham procedure control group	To examine the efficacy of ISIS 396443 administered intrathecally to patients with lateronset SMA.	Approx. 117 intended	The total duration of participation in the study is approximately 16 months. Study ongoing at the time of this report	Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote) Onset of clinical signs and symptoms consistent with SMA at >6 months of age Males and females 2 to 12 years of age Can sit independently, but has never had the ability to walk independently	PEP: Change from baseline in HFMSE (Hammersmith Functional Motor Scale – Expanded) score at 15 months	
Study SM201 Presymptomatic subjects with genetically diagnosed SMA	10 centers Australia: 1 Germany: 1 Italy: 2 Taiwan: 1 US: 12	Phase 2, Openlabel, multipledose, single-arm	ISIS 396443: 12 mg (scaled equivalent) IT injection by LP Loading dose: Days 1, 15, 29, and 64 Maintenance dose: Days 183, 302,	Safety, tolerability, efficacy, and PK	20 May 2015 Ongoing 11 subjects (25)	Ongoing	65% male 35% female 21.9 (19) days (8 to 42 days)	Male and females with genetic documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: 2 or 3 Age at onset of clinical	Time to death or respiratory intervention / Development of clinically manifested SMA, motor milestones, CHOP INTEND, CMAP, overall and

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary / Secondary Endpoint
			421, 540, 659, and 778 Total duration: approximately 2.4 yrs					signs and symptoms consistent with SMA: NA Baseline CMAP: ≥1 mV at Baseline	event-free survival, growth
Study CS1 Subjects with symptomatic later-onset SMA	4 centers US: 28	Phase 1, Openlabel, escalating dose	ISIS 396443 1, 3, 6, and 9 mg single dose IT injection by LP	Safety, tolerability, dose finding, efficacy	05 Dec 2011 Completed 28 subjects (NA)	Completed	39% male 61% female Mean 6.1 yrs (2-14 yrs)	Male and females with genetic documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: Not specified	HFMSE / PedsQL™, CMAP, MUNE
Study CS10 Subjects with symptomatic later-onset SMA	4 centers US: 18	Phase 1, Openlabel, single dose	ISIS 396443 IT injection by LP Cohort 1: 6 mg on Day 1 Cohort 2: 9 mg on Day 1	Safety, tolerability, efficacy, and PK	10 Jan 2013 Completed 18 subjects (NA)	Completed	28% male 72% female Mean 6.6 yrs (2-11 yrs)	Male and females with genetic documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: Not specified Age at onset of clinical signs and symptoms consistent with SMA: >6 months	HFMSE / PedsQL™, CMAP, MUNE
Study CS2 Subjects with symptomatic later-onset SMA	4 centers US: 34	Phase 1, openlabel, doseescalation, multiple dose	ISIS 396443 IT injection by LP: Cohort 1: 3 mg on Days 1, 29, 85 Cohort 2: 6 mg on Days 1, 29, 85 Cohort 3: 9 mg on Days 1, 85 Cohort 4: 12 mg on Days 1, 29, 85 Total Duration: approximately 8 months	Safety, tolerability, efficacy, and PK	12 Oct 2012 Completed 34 subjects (NA)	Completed	59% male 41% female 7.4 yrs (2-15 yrs)	Male and females with genetic documentation of 5q SMA homozygous gene deletion or mutation SMN2 Copy Number: Not specified Age at onset of clinical signs and symptoms consistent with SMA: >6 months	HFMSE / PedsQL™, CMAP, MUNE ULM, myometry, 6MWT, ACEND
Study CS12 Subjects with	4 centers US: 47	Phase 1, Openlabel, multipledos	ISIS 396443: 12 mg IT injection by	Safety, tolerability, efficacy, and	30 January 2014 Completed	Ongoing	49% male 51% female	Male and females with	ULM, 6MWT, CMAP

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary / Secondary Endpoint
symptomatic later-onset SMA		e, singlearm	LP Doses on Days 1, 169, 351, and 533 Total duration: approximately 1.5 yrs	PK	47 subjects (NA)		8 years (3-17 yrs)	genetic documentation of 5q SMA homozygous gene deletion or mutation Age at onset of clinical signs and symptoms consistent with SMA: >6 months	

2.4.2. Pharmacokinetics

The key findings for nusinersen pharmacokinetics and drug interaction potential were evaluated based on data from in vitro studies using human biomaterials and data from clinical studies.

Ten studies comprise the nusinersen clinical program. To date, 3 studies have been completed and 7 studies are ongoing. For this application, the PK and clinical pharmacological properties of nusinersen have been characterized using data from the 3 completed studies in later-onset 5q spinal muscular atrophy, as well as data from 4 of the 7 ongoing studies: 1 in later-onset SMA, 2 in infantile-onset SMA and 1 in infants genetically diagnosed with SMA but presymptomatic at study start. The PK data from the remaining 3 ongoing studies were not available for evaluation since those studies were still ongoing and/or blinded.

Over the course of the development program, nusinersen treatment was initially evaluated in studies of subjects with later-onset SMA and subsequently in studies of infants diagnosed with SMA. The population of subjects with later-onset SMA includes subjects \geq 2 years old at screening and the population of infants diagnosed with SMA includes subjects with infantile-onset SMA (subjects \leq 7 months of age at screening) and infants with genetically diagnosed and presymptomatic SMA (subjects \leq 6 weeks of age at the time of first dose).

Nusinersen was evaluated in vitro for binding to proteins in human CSF and plasma, inhibition or substrate activity of human BCRP, P-glycoprotein (P-gp), OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, and BSEP mediated transport, and cytochrome P450 (CYP450) induction or inhibition. An ultrafiltration method was used to evaluate the extent of protein binding of nusinersen in whole plasma and CSF in vitro, where the concentrations in plasma, CSF and ultrafiltrate were determined using a nuclease-dependent hybridization ELISA detection method. Transporter interactions were evaluated with nine major transporters, and transporter activity was assessed by radiometric detection of movement of radiolabeled substrate across a polarized cell monolayer or membrane vesicles expressing the transporter. CYP450 interactions were evaluated with seven major enzymes, and enzyme activity was assessed by liquid chromatography-mass spectrometry/mass spectrometry of hepatocyte culture medium (for enzyme activity in the presence of substrate) and by reverse transcriptase polymerase chain reaction of RNA isolated from the cells (for gene expression)

The in vivo PK of nusinersen have been characterized in 4 open-label studies in subjects with later-onset SMA; these include the completed Studies CS1, CS2, and CS10 and ongoing Study CS12. Subjects who completed treatment in CS1 were permitted to enrol in CS2 or CS10 and subsequently into CS12. The cut-off date for the CS12 PK data that are included in this summary is 07 April 2016.

The PK of nusinersen in infants with SMA have been evaluated using data from 2 studies in subjects with infantile-onset SMA, studies CS3A and CS3B and 1 study in genetically diagnosed and presymptomatic infants with SMA, study SM201. All of these infantile-onset SMA studies are ongoing. Data cut-off dates for the PK data are 26 January 2016, 15 June 2016, and 08 June 2016 for Studies CS3A, CS3B, and SM201, respectively.

In addition to PK analyses for individual studies, PK data from Studies CS1, CS2, CS10, CS3A and CS12 were pooled and analyzed using a population PK approach.

PK data from the remaining 3 ongoing studies comprising the clinical program (Studies CS4, Study SM202 and CS11) are not yet available for inclusion.

Nusinersen was administered via an intrathecal (IT) injection in all studies. A single dose of drug was administered in Study CS1. In Study CS10, a single additional dose of nusinersen was administered after the initial dose on Study CS1. Studies CS2, CS12, CS3A, CS3B and SM201 are multiple-dose studies.

Two formulations of nusinersen have been used in the clinical development program. For Studies CS1, CS2, CS10, for Study CS12 prior to 17 February 2016 or 22 February 2016 depending upon the clinical site, and for Study CS3A prior to 15 December 2015, nusinersen was supplied in a 2-vial configuration, with a vial of a concentrated aqueous solution of nusinersen at a dosage strength of 20 mg/mL (2.5 mL per vial) and a vial of diluent. The drug in the concentrated solution was diluted at the clinical site to the required concentration for injection (range: 0.2 to 2.4 mg/mL), with the diluent composition designed so that the final solution approximated the salt concentrations in naturally-occurring human CSF. For Study CS12 beginning 17 February 2016, for Study CS3A beginning 15 December 2015, and for Studies CS3B and SM201, nusinersen was supplied in a ready-to-use, single-vial formulation at a dosage strength of 2.4 mg/mL (5.0 mL per vial). This formulation was supplied at the appropriate drug concentration for injection, with the drug dissolved in an aqueous solution approximating the salt concentrations in naturally occurring human CSF. The administered drug product is identical for both formulations; the 2 configurations differ only in primary packaging and the requirement for dilution. Nusinersen was administered at doses ranging from 1 mg to 12 mg as an IT bolus injection by lumbar puncture. For subjects over 24 months (2 years) of age at the time of dosing, the injection volume was fixed at 5.0 mL (12-mg). For subjects 24 months of age or younger at the time of dosing, the injection volume was adjusted according to subject age based on relative CSF volume.

Nusinersen concentrations in human CSF and plasma were measured by a validated hybridization enzyme linked immunosorbent assay method for Study CS1 and by a validated hybridization electrochemiluminescence assay method for the other 6 studies.

Noncompartmental methods were used to calculate PK parameters from the single- and multipledose clinical studies when feasible. The PK data from Studies CS1, CS2, CS10, CS3A and CS12 were combined and analyzed using a population PK approach.

Absorption

IT injection of nusinersen into the CSF allows the drug to be administered in close proximity to the site of action within the CNS.

Following IT administration, nusinersen is rapidly transferred from CSF into the systemic circulation, with a median time to maximum concentration (Tmax) of 1.7 to 6.0 hours in plasma in both later-onset subjects and infants diagnosed with SMA.

Distribution

IT-administered nusinersen appears to be widely distributed into CNS tissues (including the target spinal cord tissues), and is cleared through transfer into the systemic circulation.

Nusinersen trough concentrations in plasma were relatively low compared to those in CSF. After reaching the peak level, plasma concentrations of nusinersen declined rapidly followed by a much slower decline, indicating a biphasic disposition in plasma. The rapid decline in plasma concentrations is likely due to extensive distribution to systemic tissues.

Elimination

The metabolites of nusinersen observed in CSF, plasma, and urine samples from subjects with later-onset SMA following multiple IT administrations suggest that nusinersen is metabolized slowly by exonuclease (3'- and 5')-mediated hydrolysis, which is not dependent on the liver.

Less than 0.5% of the administered dose was excreted into urine in the first 24 hours in subjects with later-onset SMA. While urine was only collected for a small fraction (<2%) of the half-life of nusinersen, the primary route of elimination is likely by urinary excretion for nusinersen and its metabolites.

In subjects with later-onset SMA, the terminal elimination half-life in CSF is approximately 135 to 177 days supporting infrequent (e.g., 4 to 6 months) maintenance dosing. Due to the lack of data available from post dose samples, the half-life could not be calculated in infants diagnosed with SMA. However, the population PK estimates for median terminal half-life was 163 days for the overall population and ranged from 160 to 163 days for the later-onset subjects and 159 to 172 days for infantile-onset subjects, all within the range of the observed values.

The terminal elimination half-life in plasma was estimated to be 63 to 87 days in subjects with later-onset SMA and could not be calculated in infants due to the limited sample collection postdose. Based on peak (Cmax) or total exposure (AUC0-4hr, AUC0-6hr, and AUC0-20hr), no accumulation of nusinersen was evident in plasma after multiple doses. Comparison of plasma PK in different days of administration was performed in study CS2 (Day 1 vs Day 85) showing similar behaviour and negligible accumulation.

Dose proportionality and time dependencies

Overall, after accounting for differences in body weight, the PK characteristics of nusinersen in the CSF and plasma were similar across studies and appear to be similar in subjects with later-onset SMA and infants diagnosed with SMA (i.e., infantile-onset SMA and presymptomatic SMA infants).

CSF drug concentrations appeared to increase proportionally from 1 mg to 12 mg in subjects with later-onset SMA (subjects 2 years of age or older at screening) and dose proportionally over doses from 6 mg to 12 mg in infants diagnosed with SMA (subjects 7 months or younger at screening). nusinersen trough concentrations in the CSF accumulated approximately 1.4 to 3.0-fold and reached steady state after multiple 12 mg loading and maintenance doses at around 22.5 months in both later-onset subjects and infants diagnosed with SMA. No further accumulation in CSF or CNS tissue concentrations would be expected with additional doses after steady state.

There was an approximately dose proportional increase in maximum concentration (Cmax) and area under the concentration-time curve (AUC) values in plasma over the evaluated dose range. Cmax and AUC were greater in infants diagnosed with SMA than in subjects with later-onset SMA given the same dose, consistent with their lower body weight.

Special populations

Covariates that may influence the disposition of nusinersen were initially explored in Study CS1, and further evaluated by a population PK analysis using data from Studies CS1, CS2, CS10, CS12, and CS3A. The major conclusions were that the central volume in the CSF and in plasma and the CL in plasma are related to increasing body weight of an infant or child as they grow during a clinical study. CL in CSF is not related to body weight. Gender is unlikely to affect the PK of nusinersen. Race is unlikely to affect the PK of nusinersen noting that the majority of subjects identified as Caucasian.

Considering the PK of nusinersen and the 2-O-(2-methoxyethyl (2'-MOE) antisense oligonucleotide (ASO) class, the natural history of the target population, the fact that nusinersen is metabolized by exonuclease-mediated hydrolysis (which is not dependent on hepatic function), maturation of renal function in infants (where renal function is approximately 50% of adults and increases to adult levels by 1 year of age), hepatic and renal effects are not anticipated. Renal or hepatic impairment conditions are not commonly seen in patients with SMA, making the pool of potential subjects very small, therefore studies in these populations were not performed. In addition, within the limited range of the hepatic and renal chemistry markers evaluated in clinical studies, the markers did not contribute to intersubject variability in PK among the subjects studied in the Population PK analysis.

Pharmacokinetic interaction studies

The potential for drug interactions with nusinersen is low. The metabolites of nusinersen observed in CSF, plasma, and urine samples from subjects with later-onset SMA following multiple IT administrations suggest that nusinersen is metabolized slowly by exonuclease (3'- and 5')-mediated hydrolysis.

Pharmacokinetics using human biomaterials

In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism and therefore should not interfere with other drugs for these metabolic pathways. Given that drug-drug interactions are not expected for nusinersen, specific drug-drug interaction studies were not conducted and an analysis of extrinsic factors such as the effect of other drugs on nusinersen was not performed.

Nusinersen is not a substrate or inhibitor of human BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or BSEP transporters, although these transports were evaluated at very high concentrations due to analytical limitations. Therefore, the likelihood of drug-drug interactions due to competition with or inhibition of these transporters is very low.

Nusinersen is highly bound to human plasma proteins (> 94% bound) at clinically relevant or higher plasma concentrations (100 ng/mL and 5 µg/mL), which limits glomerular filtration (reducing renal clearance of the drug) and therefore facilitates distribution to systemic tissues. However, protein binding in plasma for this class of ASOs is relatively weak and the binding sites for these types of hydrophilic drugs differ from the binding sites of low molecular weight hydrophobic drugs. Therefore, the likelihood of drug-drug interactions due to competition with plasma protein binding is very low. In addition, nusinersen binding to human CSF proteins seems to be low (< 25%).

2.4.3. Pharmacodynamics

Antisense oligonucleotides are synthetic nucleic acid analogues that bind to a target RNA through Watson-Crick base pairing and interfere with RNA-splicing. The antisense oligonucleotide needs to be (about) 20- to 25-bases long to ensure that it binds to a specific, known site on the target mRNA.

Spinal muscular atrophy is caused by homozygous deletion of the gene for 'survival of motor neuron 1' (SMN1). Humans carry a near identical gene called 'survival of motor neuron 2' (SMN2) which differs from the SMN1 gene by 11 nucleotides. One of the nucleotide changes occurs in an exon splicing enhancer region of exon 7 of SMN2 leading to loss of exon 7. About 90% of the mature transcripts of SMN2 are missing exon 7 and are translated into a truncated protein that is rapidly degraded.

Nusinersen targets an intronic region of the SMN2 pre-messenger RNA (mRNA) normally occupied by heterogeneous nuclear ribonucleoproteins (hnRNP) A1/A2 proteins [Hua 2008; Rigo 2012]. nusinersen displaces these proteins, thereby promoting inclusion of exon 7 into the SMN2 mRNA, resulting in higher levels of full-length transcripts. This in turn results in the increased production of full-length, functional SMN protein.

No available PD biomarker currently exists for nusinersen. CSF SMN protein levels were explored in several clinical studies but no clear relationships were identified with nusinersen. Because nusinersen is administered intrathecally and levels achieved peripherally are not thought to be therapeutic, peripheral SMN protein levels were not explored. Several reasons may explain why no association has been identified between CSF SMN protein levels and nusinersen including that the role of SMN protein in the CSF is not currently known; there are differences in CSF SMN protein levels between healthy

controls and SMA patients; and the optimal time to measure the effect of nusinersen on SMN protein in the CSF is not known.

PD characteristics of nusinersen were determined from studies of available autopsy samples collected from infants with SMA. Autopsy samples from 3 infants with infantile-onset SMA treated with nusinersen in Study CS3A had higher levels of full-length SMN2 mRNA in the thoracic spinal cord compared to infants with SMA who did not receive nusinersen. Full length SMN2 mRNA and SMN protein were also identified in other regions of the spinal cord and CNS.

The current product binds to the SMN2 transcript before the splicing machinery recognizes exon 7 in order to modulate mRNA processing and so increase the inclusion of exon 7 resulting in the production of a full-length product to take the place and function of the missing SMN1 product. In addition, the product was modified by 2' -O-methoxyethyl additions to prevent the actions of RNase H or RNA interference mechanisms in the pharmacology studies.

Nusinersen was identified after screening over 500 potential candidates by in vitro assays of activity. The preferred site to promote exon 7 inclusion was found to be (about) 10 nucleotides downstream from the intron / exon junction, also referred to as the intron splicing silencer N1 (ISS-N1). In the absence of treatment, approximately 30% of the SMN2 transcripts in patient fibroblasts cells are full length, i.e. contain exon 7.

The proposed mechanism of action was considered plausible based on the data available from published literature.

Primary pharmacodynamics of the current product were studied in the pre-clinical component of the development programme.

It is understood that human-related pre-clinical studies were conducted in fibroblasts only (because of the nature of the underlying disease) whereas studies of transgenic mice were more extensive in terms of tissues studied.

Treatment of patient fibroblasts with the lead candidate nusinersen increased the amount of full length transcript expressed and decreased the amount of transcripts missing exon 7 ($\Delta 7$) in a concentration-dependent manner. Treatment of patient fibroblasts with nusinersen also increased the amount of SMN protein produced in these cells. Treatment of SMA fibroblasts with nusinersen increased the number of punctate nuclear structures containing SMN protein ('Gems').

The company stated that although nusinersen likely increases SMN protein levels at the site of action within the neuron, a measurement of the increase in tissue in subjects is not feasible. The closest concentrations that can be measured are CSF concentrations, which are highly variable in the infant population due to marked changes in SMN protein in utero and early neonatal period. In addition, since no data are available from control subjects, the actual change in SMN protein concentrations in CSF could not be assessed. In light of these limitations, no relationship was observed between CSF concentrations of nusinersen and SMN protein concentrations in the CSF.

In vivo pharmacology was carried out in mouse models. Nusinersen is predicted to bind uniquely to the ISS-N1 sites present only in the SMN1 and SMN2 pre-mRNA transcripts. Furthermore, nusinersen is not homologous to any other regions of the human transcriptome with 17 or 16 consecutive nucleotides matches.

Three additional potential transcripts were identified with homology to nusinersen. All are uncharacterised transcripts and all are Model genes, predicted by an automated pipeline without manual curation. Using current techniques, the company has not been able to demonstrate that nusinersen may have targets other than the proposed target; this is acceptable. There were not any other studies carried out on secondary pharmacodynamics; this was considered acceptable

2.4.4. Discussion on clinical pharmacology

Despite the lacking information on some aspects like e.g. the mechanism of cellular uptake, it can be concluded that there is a good understanding of the pharmacokinetics of the product.

Further deliberation may be provided on the POPPK model, particularly on the determination of the effect of age on PK which should include any new data, to support the proposed dose per age group. Additional PKPD analysis for the older onset children would be useful and both of these should be considered in the post-approval programme. The Applicant is required to study the effect of age on PK as a post-approval measure.

The pharmacodynamics of nusinersen is considered as relatively well understood despite the fact that it relies heavily on data generated in animal models.

2.4.5. Conclusions on clinical pharmacology

No specific concerns regarding pharmacodynamics are identified as outstanding, but some issues in the pharmacokinetics have led to the need for a post-approval measure (PAM), required to provide further data.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- A PopPK model update- the updated popPK model should include a larger number of subjects with short- and long-term dosing with nusinersen
- The company should explore whether higher doses of nusinersen could show greater efficacy, also providing further understand the PK/PD relationship including in later-onset patients (related to Pop PK model update)
- Long – term PK data to be collected from the ongoing studies – SHINE (CS11), NURTURE (SM201) and EMBRACE (SM202).

2.5. Clinical efficacy

The clinical development program of nusinersen was designed to evaluate nusinersen across a range of SMA phenotypes to address the unmet medical need in a general population of patients with SMA. The studies conducted to date include 4 completed and 6 ongoing clinical studies: 2 studies in symptomatic infantile-onset SMA, 5 studies in symptomatic later-onset (Type II and Type III) SMA, 1 study in patients with genetically diagnosed, pre-symptomatic SMA, and 2 studies in patients with symptomatic infantile- and later-onset SMA.

Studies of nusinersen categorised patients according to the presence or absence of symptoms. Among patients with symptoms, studies were further categorised by the age of symptom onset.

Efficacy results from studies in symptomatic patients (2 in subjects with infantile-onset and 4 in subjects with later-onset) and a study in pre-symptomatic patients are used to support the claim of efficacy. Results from the ongoing studies in symptomatic patients with later-onset SMA (interim analysis results for study CS4) and progress reports for the infantile-onset and later-onset SMA studies (SM202 and CS11) were submitted during the procedure. The primary data used by the applicant at submission to support the efficacy of nusinersen in the treatment of SMA derived from a pre-planned interim analysis of Study CS3B. These were later supplemented by the final results of the same study and the submitted data from the interim analysis for study CS4, as well as all available data from the rest of the ongoing studies.

No studies were carried out to describe dependence between dose and response in terms of efficacy.

2.5.1. Main studies

Pivotal study CS3B

"A Phase 3, Randomized, Double-Blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients With Infantile-Onset Spinal Muscular Atrophy."

This was a Phase 3, multicentre, double-blind, randomised, sham-procedure controlled study of nusinersen conducted at 31 centres worldwide.

At the time of the submission of the marketing authorisation application, the Applicant provided only the interim analysis results to inform the assessment. In the course of the procedure the final results became available and were included in the assessment of the B/R ratio of the product.

At the interim analysis, only the first primary efficacy endpoint (proportion of motor milestone responders) was tested. A data cut-off of 15 June 2016 was chosen for this interim analysis, since it was anticipated that by this time approximately 80 subjects would have completed the Day 183 Visit, which is thought to be the minimum amount of time needed to see a meaningful improvement in motor milestones. These predictions were based on the open-label data available from Study ISIS 396443-CS3A. Time to death or permanent ventilation and survival rate were not evaluated in this interim analysis, as it was expected that too few events would have occurred at the interim. The interim analysis results were reviewed by an independent DSMB and a Joint Unblinded Senior Management Team from Ionis Pharmaceuticals and Biogen.

Methods

- Objectives**

Primary Objective

The primary objective of the study is to examine the clinical efficacy of nusinersen administered intrathecally to patients with infantile-onset SMA.

Secondary Objective

The secondary objective of the study is to examine the safety and tolerability of nusinersen administered intrathecally to patients with infantile-onset SMA.

Tertiary Objective

The tertiary objective of the study is to examine the cerebrospinal fluid (CSF) and plasma PK of nusinersen administered intrathecally to patients with infantile-onset SMA.

- **Design**

This study was conducted to test the clinical efficacy, safety, tolerability, and PK of multiple doses of nusinersen administered as IT injections by lumbar puncture (LP) to subjects with infantile-onset SMA. As the study is ongoing, this report presents an interim analysis of the data.

The total duration of subject participation in the study was approximately 14 months. The study consisted of a Screening Period, a Treatment Period, and a Post-treatment Follow-up Period.

Although treatment occurs over a 10-month period, given the long half-life of nusinersen, subjects are considered exposed to nusinersen from the time the first dose was administered to the last day of follow-up (13 months).

A randomised, sham-procedure controlled, double-blind study design was chosen for Study CS3B as the best and most reliable way to collect data to determine the safety and efficacy of nusinersen in an infantile-onset SMA population; this type of study design minimises bias in data collection. A sham procedure was chosen for the control group in order to minimise the risks to subjects randomised to this group. The procedure consists of a small needle puncture on the lower back, but no LP injection or deeper needle insertion was to occur. A 2:1 randomisation (drug to sham procedure, respectively) was used in order to permit more subjects access to active treatment in this life-threatening disease while also having enough sham participants to complete the study with adequate power in a reasonable period of follow-up time.

A length of study of approximately 1 year was considered to be the maximum feasible time for subjects with a life-threatening disease to be without active treatment. It is also the length that would provide the earliest opportunity to see a clinically meaningful improvement in function and survival. Across published natural history studies, the median age of death ranged from 5.9 to 7.4 months in patients who did not receive ventilation [Cobben 2008; Farrar 2013; Gregoretti 2013].

- **Study participants**

Approximately 111 subjects were to be enrolled into the study.

Main Inclusion Criteria:

- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.

- SMN2 copy number = 2.
- Onset of clinical signs and symptoms consistent with SMA at \leq 6 months (180 days) of age.
- Males and females \leq 7 months (210 days) of age at Screening.
- At study entry, receiving adequate nutrition and hydration (with or without gastrostomy), in the opinion of the Site Investigator.
- Body weight \geq 3rd percentile for age using appropriate country-specific guidelines.
- Medical care, such as routine immunisations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis (palivizumab) if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA (Appendix D of the protocol), in the opinion of the Investigator.
- Gestational age of 37 to 42 weeks.

Main Exclusion Criteria:

- Hypoxemia (O₂ saturation awake <96% or O₂ saturation asleep <96%, without ventilation support) during screening evaluation.
- Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening Period of ISIS 396443-CS3B.
- History of brain or spinal cord disease that would interfere with the LP procedures, CSF circulation, or safety assessments

• **Treatments**

Eligible subjects entered the ~10-month Treatment Period for treatment with either a scaled equivalent 12-mg dose of nusinersen or a sham procedure control. Nusinersen was administered using a loading regimen (dosing on Study Days 1, 15, 29, and 64), followed by maintenance dosing once every 4 months (dosing on Study Days 183 and 302). Following the injection/sham procedure on Study Day 1, subjects remained at the study centre for at least 24 hours for safety monitoring. On all other treatment days, subject remained at the study centre for at least 6 hours for safety monitoring.

The dose level and dose intervals of nusinersen for this study were selected based on nonclinical toxicology and PK observations from studies in monkeys using single and repeat IT dosing over a 14-week period, consideration of the target tissue concentration anticipated for drug pharmacology, and safety data in the completed and ongoing clinical studies of nusinersen.

Nusinersen

Subjects randomised to the nusinersen treatment group received a single IT LP injection of study drug as a slow bolus (1 to 3 minutes) using a spinal anaesthesia needle and 5-mL syringe. The target site for needle insertion was the L3/L4 space, but could be 1 segment above or 1 to 2 segments below this level, if needed. Spinal ultrasound could be used for the LP procedure, if it was deemed necessary, but was not required. Prior to each injection of study drug, 4 to 5 mL of CSF was collected for PK analyses.

The volume of injection was adjusted based on the subject's age on the day of dosing as shown in Table 3 such that each subject received a 12-mg scaled equivalent dose based on CSF volume scaling.

Thus, younger subjects were given a lower dose of drug, achieved by injecting a smaller volume that was proportional to estimated CSF volume for age, such that dose volume was equivalent to 5 mL for age 2 years to adult.

Table 3: Study CS3B nusinersen Dose Volume to be Injected

Age	Estimated CSF Volume	Injection Volume	Dose
0 to 3 months (0 to 90 days)	120 mL	4 mL	9.6 mg
3 to 6 months (91 to 180 days)	130 mL	4.3 mL	10.3 mg
6 to 12 months (181 to 365 days)	135 mL	4.5 mL	10.8 mg
12 to 24 months (366 to 730 days)	140 mL	4.7 mL	11.3 mg

CSF = cerebrospinal fluid

Source: [Matsuzawa 2001]

Sham Procedure

In general, the sham procedure consisted of a small needle prick on the lower back at the location where the LP injection was normally made. The needle broke the skin but no LP injection or needle insertion occurred. The needle prick was covered with the same bandage that was used to cover the LP injection normally, thus simulating the appearance of an LP injection. The study subject was kept in the procedure room for the same amount of time that subjects administered study drug were kept, thus simulating the time period of a study drug administration procedure.

Concomitant Therapy

Allowed Therapies

Throughout the study, Investigators or designated licensed physicians involved in the study could have prescribed concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

Disallowed Therapies

Study subjects were prohibited from receiving other experimental agents during the study. This included marketed agents at experimental doses that were being tested for the treatment of SMA (e.g., valproate, riluzole, creatine, sodium phenylbutyrate, hydroxyurea, and salbutamol).

- **Outcomes/endpoints**

Primary Efficacy Endpoints

Primary efficacy endpoints of the study were as follows:

- Proportion of motor milestone responders (Section 2 of the Hammersmith Infant Neurological Examination [HINE])

- Time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event OR tracheostomy).

Motor milestones were assessed as part of the neurological examination conducted by the neurologist at the study centre using Section 2 of the 3-part HINE. The assessments were performed at Screening, Day 64 predose, Day 183 predose, Day 302 predose, and Day 394. The subject's ventilator or BiPAP use (number of hours/day) was recorded daily by the caregivers using a daily ventilator use diary for the duration of the study. This information was obtained during study visits and weekly telephone contacts.

Secondary Efficacy Endpoints

Secondary efficacy endpoints of the study were as follows:

- Proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders.
- Survival rate.
- Percent of subjects not requiring permanent ventilation.
- Proportion of compound muscle action potential (CMAP) responders.
- Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration.
- Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration.

The CHOP INTEND is a validated 16-item, 64-point motor assessment designed specifically to evaluate the motor skills of infants with symptomatic SMA and to accommodate their fragile nature and observed tolerance to item administration [Glanzman 2010]. The test was designed by an expert panel that was guided in item selection by the statistical characteristics of each item as well as by clinical judgment concerning the item's ability to quantify motor behaviour in Type I SMA. The test captures neck, trunk, proximal, and distal limb strength in 14 elicited and 2 observational items and has been established as a safe, reliable, and clinically meaningful measure of motor function in infants with SMA.

Evaluations using the CHOP INTEND motor function scale were performed by physical therapists at the study centres. These evaluations were scheduled at Screening (2 assessments, baseline assessment), Day 64 predose, Day 183 predose, Day 302 predose, and Day 394.

CMAP measurements of ulnar nerve function in the abductor digiti minimus muscle and peroneal nerve function in the anterior tibialis muscle were performed or supervised by a clinical electromyographer at the study centre. Measurements were made at Screening (baseline assessment), Day 64 predose, Day 183 predose, Day 302 predose, and Day 394.

CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles. CMAP is a well validated method for tracking disease progression in neuromuscular disorders such as SMA [Lewelt 2010; Swoboda 2005] and amyotrophic

lateral sclerosis [Shefner 2011] and has been proposed as a potential biomarker of a therapeutic effect in SMA.

Tertiary Efficacy Endpoints

The tertiary efficacy endpoints were as follows:

- Change from baseline in growth parameters (weight for age/length, chest circumference, head to chest circumference ratio, and arm circumference).
- Number of serious respiratory events.
- Number of hours of ventilation support.
- Number and length of hospitalisations.

Growth parameters were assessed by trained site staff at the study centers. The assessments were performed at Screening, Day 29 predose, Day 64 predose, Day 183 predose, Day 302 predose, and Day 394. Body length, head circumference, chest circumference, and arm circumference were measured. Ratios of weight-for-age, weight-for-length, and head-to-chest circumference were also calculated.

Safety Endpoints

Safety endpoints are as follows:

- AEs, including SAEs
- Vital signs and weight
- Neurological examinations
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Electrocardiograms
- Use of concomitant medications

Pharmacokinetic Endpoints

The PK endpoints are as follows:

- CSF levels of nusinersen
- Plasma levels of nusinersen

Plasma and CSF samples were collected for nusinersen PK assessments from all subjects in the study. See Table 6 for a schedule of all PK collection times.

CSF collection occurred predose during the LP procedure on Days 1, 15, 29, 64, 183, and 302.

Some of the collected PK plasma and CSF samples were retained for investigation of possible biomarkers of SMA disease or the pharmacodynamic effects of nusinersen (e.g., CSF mRNA, CSF protein) or for profiling of drug binding proteins, metabolite assessments, immunogenicity assessments, or to assess other actions of nusinersen with plasma and CSF constituents.

Immunogenicity Endpoint

The immunogenicity endpoint is plasma antibodies to nusinersen.

- **Sample size**

For the primary endpoint of motor milestone response, the power was estimated to be approximately 60% to detect a statistically significant difference between treated and sham groups at the time of the interim analysis (N~80 subjects), under the assumptions of having 3 responders in the sham group ($3/26 = 11.5\%$) and 20 responders in the nusinersen group ($20/52 = 38.5\%$), and alpha = 0.035. At the final analysis, with alpha = 0.03, 111 subjects would provide approximately 78% power to differentiate a response rate of 38.5% for the nusinersen group versus a response rate of 11.5% for the sham group.

In addition, the sample size for this study was estimated based on a doubling of median time to death or permanent ventilation for the nusinersen group compared to that of the sham procedure control group. Based on limited available natural history data for the target population (Finkel et al. 2014), it was estimated that the median time to death or permanent ventilation of the sham-procedure control arm is 5 to 6 months from date of randomisation. With 2:1 randomization and 13 months follow-up time, 111 subjects would provide approximately 80% power to detect a doubling in median time to death or permanent ventilation for the nusinersen group versus the sham-procedure control group at an overall 2-sided 5% significance level.

- **Randomisation**

Subjects were randomised after all screening assessments had been completed and after the Investigator and the Medical Monitor had verified that they were eligible. Using an Interactive Voice/Web-Response System (IXRS), eligible patients were randomized 2:1 to receive nusinersen or sham-procedure control, respectively. The randomization was stratified for disease duration (subject's age at screening - age at symptom onset): ≤ 12 weeks vs. > 12 weeks.

A permuted block schedule was used in the randomization.

- **Blinding (masking)**

To allow the study to be blinded, patients who were randomised to the control group underwent a sham-procedure. The study drug or sham procedure was administered by dedicated study personnel who were unblinded to treatment group; this could not be any of the key study site personnel (i.e., the Principal Investigator, study coordinator, or outcomes assessors).

The sham procedure or study drug administration was performed in a dedicated room and the key study personnel and the parents were not present during the procedure to ensure blinding. The sham procedure consisted of a small needle prick on the lower back at the location where the LP injection was normally made. The needle broke the skin but no LP injection or needle insertion occurred. The needle prick was covered with the same bandage that was used to cover the LP injection normally, thus simulating the appearance of an LP injection. The study subject was kept in the procedure room for the same amount of time as subjects administered Study Drug were kept, thus simulating the time period of a Study Drug administration procedure. Study Drug and sham kits were packaged in a blinded fashion. Blinded kits for sham procedure contained artificial CSF (5.0 mL solution per 6 mL vial) that were not injected but were used to simulate CSF samples for that subject.

The Sponsor, parents of the subjects, and key study site personnel were blinded throughout the study. The evaluator (i.e., physical therapist) who performed efficacy evaluations was blinded to study treatment and was not involved in decisions about the subjects' ventilation. Clinicians who were making decisions regarding subjects' ventilation were blinded throughout the study, and did not have access to study treatment assignments or efficacy evaluation results. Study personnel involved in processing and analysing study samples (e.g., blood, urine) were blinded to treatment assignment. To protect against unblinding when analysing blood and CSF samples for drug concentrations and anti-nusinersen antibodies, dummy identification numbers were assigned by vendors. There were both blinded and unblinded monitors in the study.

Data collected during administration of nusinersen and performance of the sham procedure were documented in an unblinded source packet that was kept separate and secured from all other source documents and was accessible only to unblinded study staff.

- **Statistical methods**

General considerations

For the interim analysis only the first primary endpoint was formally statistically tested. For all other endpoints only summary statistics are presented. Following the positive result at the interim analysis a final formal statistical analysis of all endpoints was conducted once the study was completed.

Analysis populations

For the interim analysis the following analysis populations were defined:

ITT Set: All subjects who were randomized and received at least 1 dose of study drug/sham procedure. Subjects were analysed in the treatment group to which they were randomised.

Interim Efficacy Set: The subset of subjects in the ITT Set who had the opportunity to be assessed at the Day 183 Visit. Specifically, the Interim Efficacy Set included all subjects with a Day 183, Day 302, or Day 394 Visit and all subjects with a time difference of at least 190 days (183 days plus a 7-day window) between the date of first dose and the targeted clinical cut-off date of 15 June 2016 for the interim analysis (i.e., dosed on or before 09 December 2015). A subject who had died or withdrawn was included provided that there was a time difference of at least 176 days (183 days

minus a 7-day window) between the date of first dose and the targeted clinical cut-off date of 15 June 2016 for the interim analysis (i.e., dosed on or before 23 December 2015). The interim efficacy set was used for the interim analysis of functional endpoints such as motor milestones.

Safety Set: All subjects who were randomized and received at least 1 dose of study drug/sham procedure. The analyses of safety data were based on the Safety Set. Subjects randomized to receive sham procedure but incorrectly treated with nusinersen were counted in the nusinersen group from the first dose of nusinersen received.

PK Set: All subjects who were randomized and had at least 1 evaluable post-baseline PK sample.

Analysis of the primary endpoint

The primary efficacy endpoints were ranked as follows:

1. Proportion of motor milestone responders.
2. Time to death or permanent ventilation.

Proportion of motor milestone responders

Initially, the main efficacy analysis presented for assessment were the percentages of motor milestones responders in the Interim Efficacy Set. The analysis was based on non-missing values at the later of the Day 183, Day 302, and Day 394 assessments. Subjects who died or withdrew from the study were counted as non-responders.

Baseline is defined as the measurement taken during the screening period.

A motor milestones responder was defined as follows:

- (i) The subject demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
- (ii) among the 7 motor milestone categories (with the exclusion of voluntary grasp), the subject demonstrated improvement in more categories than worsening.

As the number of responders was less than 5 in the control group, the difference in the percentage of responders between the nusinersen and sham-procedure groups was compared using Fisher's exact test, and an exact unconditional confidence interval for the difference in proportions was calculated.

Four sensitivity analyses were planned. Two (numbers one and four) were not relevant, as there were no patients who did not die or withdraw but who had no assessment on days 183, 302 or 394 and no patients who received the incorrect treatment. The other two sensitivity analyses considered different definitions of motor milestones responder:

For sensitivity analysis 2 a motor milestones responder was defined as follows:

- (i) Subject demonstrates at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking, AND

(ii) Among the 7 motor milestone categories (with the exclusion of voluntary grasp), the changes from baseline in total motor milestones score is at least 1 point. The total motor milestones score is calculated as the sum of scores across motor milestone categories, where 0 is the lowest possible score within each motor milestones category.

For sensitivity analysis 3 a motor milestones responder was defined as follows: a 2-point increase in the total motor milestones score, where voluntary grasp is excluded.

Time to death or permanent ventilation

Permanent ventilation was defined as tracheostomy or ≥ 16 hours of ventilatory support per day continuously for >21 days in the absence of an acute reversible event. Time to death or permanent ventilation was determined in a blinded fashion by a central, independent EAC.

The date of first dose/sham administration was used as the reference time point. If the date of first dose/sham administration was incomplete, the date of randomization was used.

At the interim analysis, the second primary endpoint of time to death or permanent ventilation was descriptively reported. In particular, the median times to death or permanent ventilation was estimated using the Kaplan-Meier method. The proportion of subjects who met such an event was estimated from the Kaplan-Meier curve. The hazard ratio (nusinersen versus sham) was calculated based on the Cox regression model adjusted for disease duration at Screening; no confidence interval for the hazard ratio was provided. The analyses for this endpoint were performed in the ITT Population.

Interim analysis

The interim analysis was planned for when approximately 80 subjects had the opportunity to be assessed at the day 183 visit and was conducted with a clinical cut-off date of 15 June 2016.

At the interim analysis only the first primary endpoint, proportion of milestone responders, was tested. To control the type I error rate across the interim and potential final analysis this was pre-specified to be tested at an alpha of 0.032 based on the Lan-DeMets alpha spending function.

Results

- Recruitment Participant flow**

A total of 149 subjects were screened of whom 122 were randomised in a 2:1 ratio to receive nusinersen (81 subjects) or undergo a sham procedure (41 subjects in this control group). As of the data cut-off (15 June 2016), enrolment is complete. Apart from the one subject randomised to receive nusinersen who was withdrawn from the study prior to receiving study treatment, all subjects received study treatment according to their randomization assignment.

The 121 subjects randomised and dosed, and who comprise the ITT Population, were enrolled at 31 sites in 13 countries. Fifty-four subjects (45%) were enrolled at 12 sites in the United States, 11

subjects (9%) at 2 sites in Spain, and 10 subjects (8%) at 2 sites in Germany, which together account for 62% of the population. With the exception of Japan, in which a separate randomization scheme was used, subjects were randomized across sites, i.e., centrally, resulting in an imbalance at some sites in the intended ratio of 2:1 of nusinersen to control.

As of the data cut-off date of 15 June 2016, of the 121 subjects who received treatment, 22 (18%) completed the study (19% of subjects in the nusinersen group and 17% of subjects in the control group). The rate of treatment discontinuation was lower in the nusinersen group (16%) than the control group (29%). Twelve out of 80 subjects (15%) in the nusinersen group and 12 out of 41 subjects (29%) in the control group experienced an adverse event with a fatal outcome. One additional subject in the nusinersen group was withdrawn from the study and discontinued treatment.

One additional subject in the control group was withdrawn from the study after undergoing all the scheduled sham procedures. As of the data cut-off date, 52 out of 80 subjects (65%) in the nusinersen group and 21 out of 41 subjects (51%) in the control group were continuing in the study.

Shortly after the data cut-off date, 1 additional death of a subject in the control group occurred and was reported to the Sponsor. The death was due to an AE that began prior to data cut-off. This subject is included in all analyses of death. The decision to include this death was made prior to the unblinding of the study.

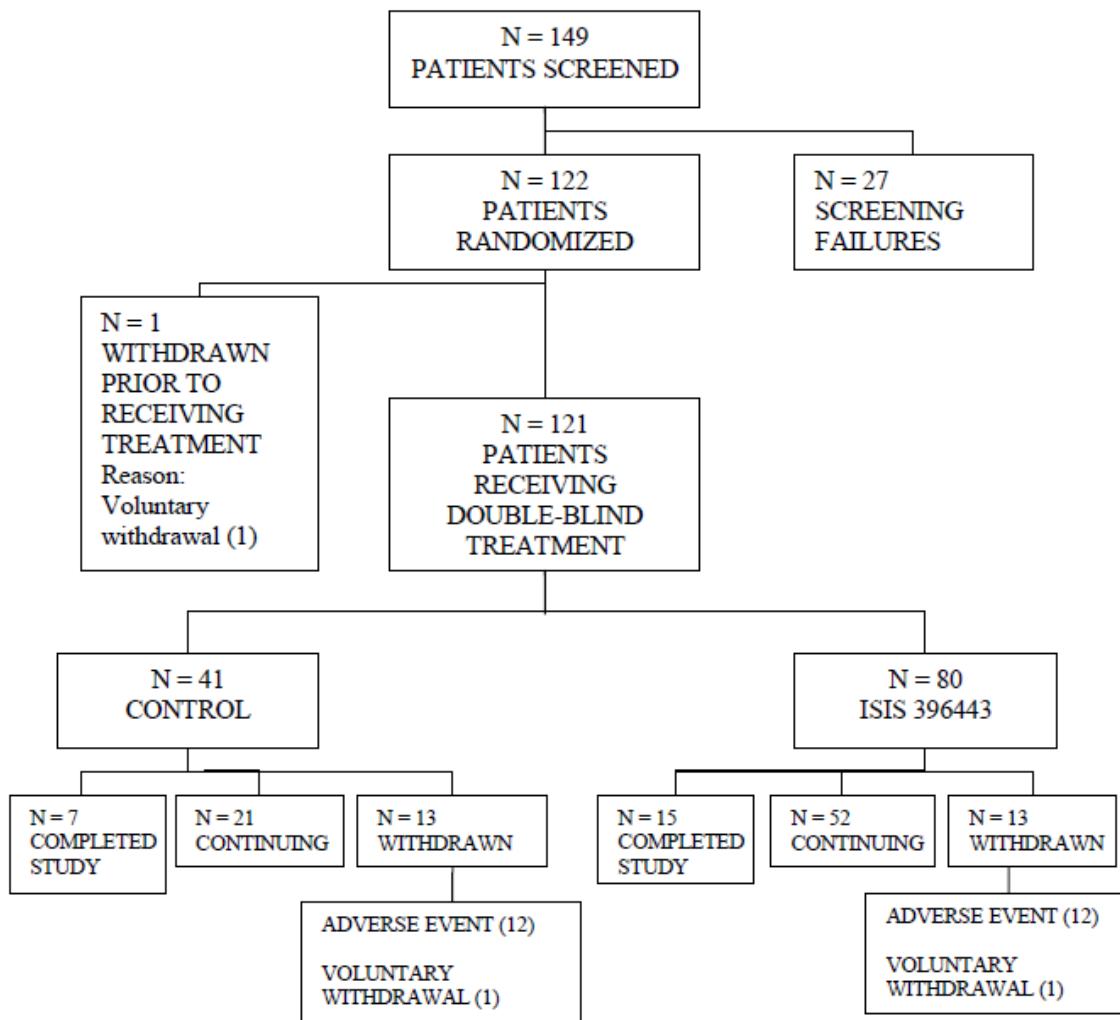


Figure 4 Subject Disposition as of the Data Cut-off Date

- **Conduct of the study**

Major protocol deviations occurred in 15% of subjects and were balanced across treatment groups. Less than 1% (i.e., 1 subject each) had visit schedule deviations, enrolment criteria deviations, or procedure deviations; and 12% had deviations listed as "other." Note that deviations listed under "other" as miscalculations of disease duration by the study sites did not affect statistical analyses because analyses using disease duration were made using actual dates of symptom onset and not on study site calculations. Overall, none of the deviations were considered to affect the analysis of the study results or the conclusions.

- **Baseline data**

Overall, the demographic and baseline disease characteristics and SMA history of the ITT Population is consistent with a population highly likely to develop Type I SMA. At baseline, subjects in the

nusinersen treatment group had a younger age of SMA symptom onset than the sham-procedure control group (median of 6.5 weeks vs. 8 weeks), required more ventilatory support (26% vs. 15%) and exhibited more severe symptoms of SMA such as paradoxical breathing (89% vs. 66%), pneumonia or respiratory symptoms (35% vs. 22%), and swallowing or feeding difficulties (51% vs. 29%).

Of the 121 subjects in the ITT Population, 67 (55%) were female and 54 (45%) were male. Age at first study treatment ranged from 30 to 262 days (median 175 days). One hundred and four (86%) subjects were white.

Baseline demography was balanced between the nusinersen and control groups with the exception of age and geographic region. Subjects in the nusinersen group were on average younger than those in the control group. A greater percentage of subjects in the control group were from North America (54% versus 48%) and Europe (41% versus 38%), while a greater percentage of subjects in the nusinersen group were from the Asia-Pacific region (15% versus 5%).

Both groups were balanced with respect to disease duration and SMN2 copy number. Disease duration was 12 weeks or less for 43% of the subjects and greater than 12 weeks for 57% of subjects. Median disease duration was 13.1 weeks. Ninety eight percent of subjects were documented to have 2 copies of the SMN2 gene.

There was some imbalance in age at symptom onset with 90% of subjects in the nusinersen group and 78% in the control group experiencing symptoms of SMA within the first 12 weeks of life. Median age at symptom onset was 6.5 weeks in the nusinersen group, and 8 weeks in the control group.

A greater percentage of infants in the nusinersen group had a history of paradoxical breathing (nusinersen vs control: 89% vs. 66%), pneumonia or respiratory symptoms (35% vs. 22%), and swallowing or feeding difficulties 51% vs. 29%.

At baseline the majority of subjects had achieved few or no motor milestones. Eighty one percent of subjects were unable to maintain their head upright, 73% were unable to kick, 95% could not roll, and 97% could not sit. No subject was able to crawl, stand, or walk.

Baseline CHOP-INTEND total scores were similar between the control and nusinersen groups ranging from 8.00 to 50.50, with a median of 28.00 (64 is the maximum possible score).

The groups were balanced with respect to CMAP measurements at baseline. Peroneal amplitude at baseline ranged from 0.00 to 1.50 mV (median 0.30 mV) with 75% of the population having amplitudes of 0.5 mV or less. Baseline ulnar amplitude ranged from 0.00 to 0.87 mV (median 0.20 mV) with 75% of the population having amplitudes of 0.30 or less.

Weight-for-age percentiles (based on World Health Organization Child Growth Standards, 2006), a key measure for growth assessment, ranged from 0.57 to 97.78 (median 14.92) at baseline.

Of the 121 subjects treated, 27 (22%) required ventilatory support at baseline, with a greater percentage of subjects in the nusinersen group requiring such support (26% vs 15%).

Mean time on ventilatory support ranged from 1 to 20 hours (median 8 hours) in the nusinersen group and from 1 to 12 hours (median 7 hours) in the control group.

- **Numbers analysed**

There were 121 patients in the ITT population, 80 treated with nusinersen and 41 who underwent the sham procedure. As all treated subjects received correct intervention the ITT and safety populations were identical.

The interim efficacy set (IES) included all subjects who had the opportunity to be assessed at the day 183 visit based on the data cut-off date (i.e. they were dosed early enough such that their day 183 visit had been reached by the time of the data cut-off for the interim analysis). This comprised 78 subjects, 51 treated with ISIS and 27 who received the sham intervention.

- **Outcomes and estimation**

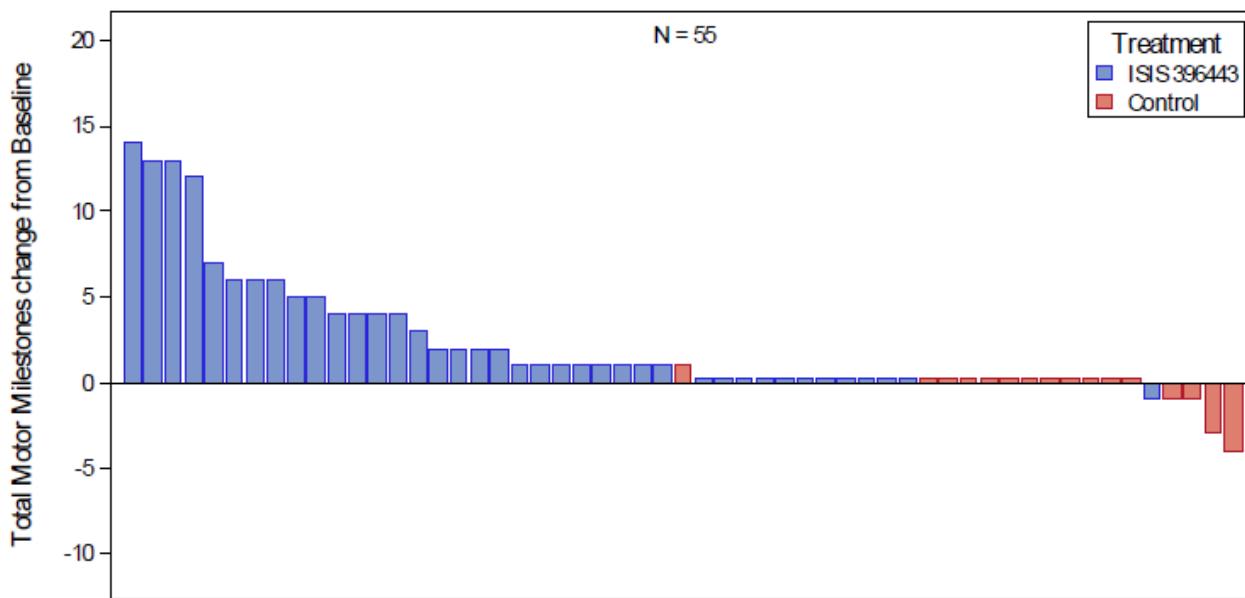
First primary endpoint - motor milestone response

Motor milestones were assessed using Section 2 of the HINE. Eight categories of motor milestones are evaluated, including voluntary grasp, head control, ability to kick, rolling, sitting, crawling, standing, and walking, with 2 to 4 milestones that can be achieved within each category. Voluntary grasp, a category in which none of the milestones require movement against gravity, was excluded from the analysis as some infants with SMA can acquire all milestones in this category.

While attainment of motor milestones is a desired outcome, some infants with SMA can acquire milestones but subsequently lose them. A subject is considered to have responded if the number of motor milestone categories in which there was an improvement from baseline was greater than the number that showed worsening.

There were 21 (41%) subjects in the nusinersen group with a motor mile response at their last possible visit (day 183, 302 or 394 depending on the date they were treated), compared to 0/27 patients on control. This was highly statistically significant ($p<0.0001$ from Fisher's exact test).

The results remained statistically significant when looking at each visit individually.



Note 1: Shortest bars at 0 line indicate 0 value.

Note 2: Out of the 78 subjects in the interim efficacy set, 21 died (11 for active and 10 for control) and 2 withdrew for reason other than death (1 for active and 1 for control) and were therefore not included in this analysis of the IES.

Figure 5: Waterfall Plot for Total Motor Milestones Excluding Voluntary Grasp Change from Baseline to Later of Day 183, Day 302, and Day 394 Study Visit - Interim Efficacy Set

All pre-specified sensitivity analyses using a different definition of response were also positive.

Table 4 Proportion of patients with motor milestone response - interim efficacy set

Time-point	Control	nusinersen	Difference (95% CI)	p-value
Last of day 182, 302, 394	0/27	21/51 (41%)	41.18% (18.16, 61.20)	p<0.0001
Day 183	2/27 (7%)	20/51 (39%)	31.81% (8.67, 52.82)	p=0.0032
Day 302	0/19	17/36 (47%)	47.22% (20.39, 69.96)	p=0.0002
Day 394	0/11	10/23 (43%)	43.48% (9.05, 72.00)	p=0.0135
Sensitivity Analyses for Last of day 182, 302, 394				
Sensitivity analysis 2	0/27	22/51 (43%)	43.14% (20.27, 62.62)	p<0.0001
Sensitivity analysis 3	0/27	19/51 (37%)	37.25% (13.99, 57.63)	p=0.0001

P-values from Fishers exact test. Confidence intervals are exact unconditional confidence intervals.

The data supports the position that nusinersen-treated subjects achieved progressive and sustained increases in total motor milestone over time compared to baseline whereas control group subjects

showed slight improvement at the first assessment (Day 64) followed by a decrease over time. The loss of motor milestones gained prior to symptom onset, as seen in the control group, is consistent with the natural history of Type I SMA, while a gain in motor milestones after symptom onset, as seen in the nusinersen group, is highly inconsistent with Type I SMA natural history.

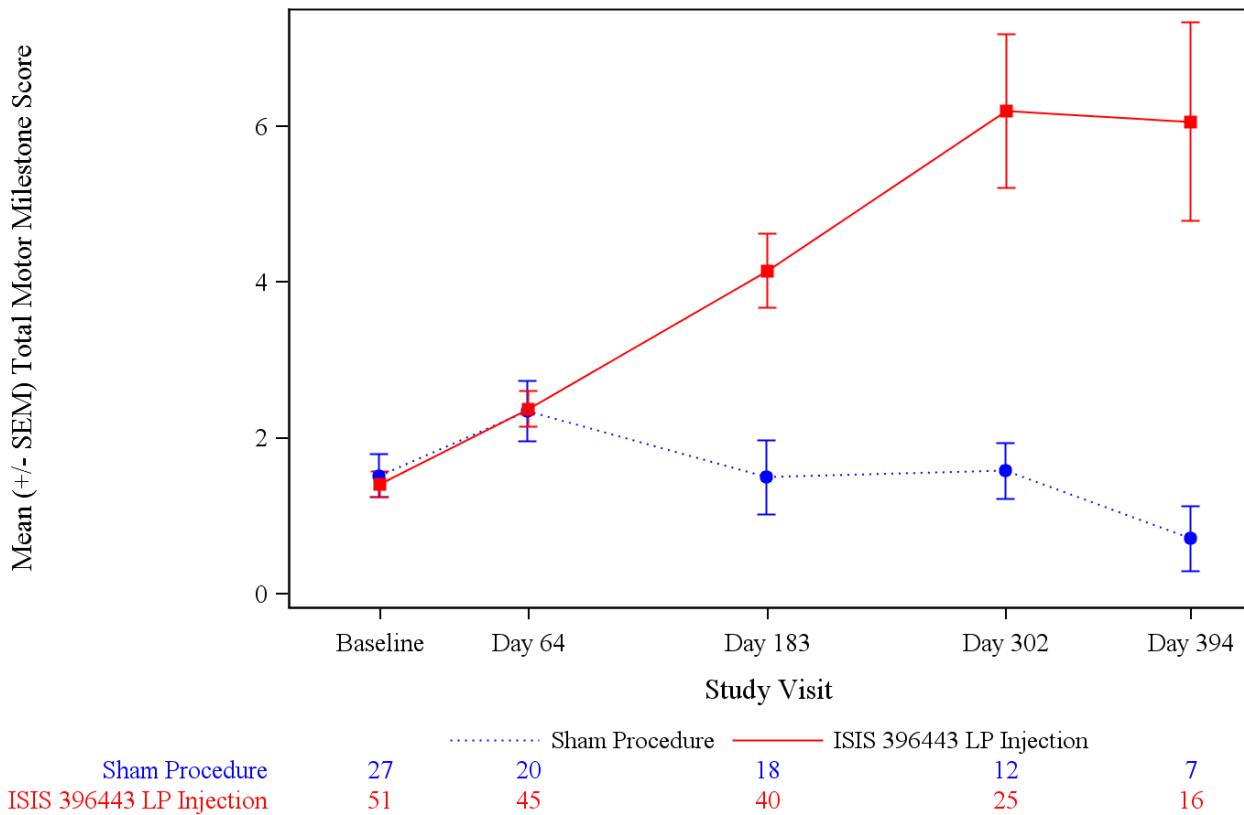


Figure 6: Figure of Total Motor Milestones Over Time: Mean Results - Interim Efficacy Set

Some significant motor milestones were achieved by subjects in the nusinersen group. Nine of the 51 subjects (18%) in the nusinersen group achieved full head control (i.e., the ability to maintain their head upright all the time) versus none in the control group. This is not typically seen in patients with Type I SMA. Independent sitting, i.e., achievement of stable sit or pivoting, was seen in 5 (10%) of nusinersen-treated subjects and none in the control group. The inability to achieve independent sitting is part of the definition of Type I SMA. Standing is never seen in patients with Type I SMA yet 1 subject (2%) in the nusinersen group managed to achieve standing with support.

It is worthwhile to note that although a large treatment difference in favour of nusinersen was observed across subgroups, it is true that a greater treatment benefit was seen in subjects with shorter disease duration at the start of the study.

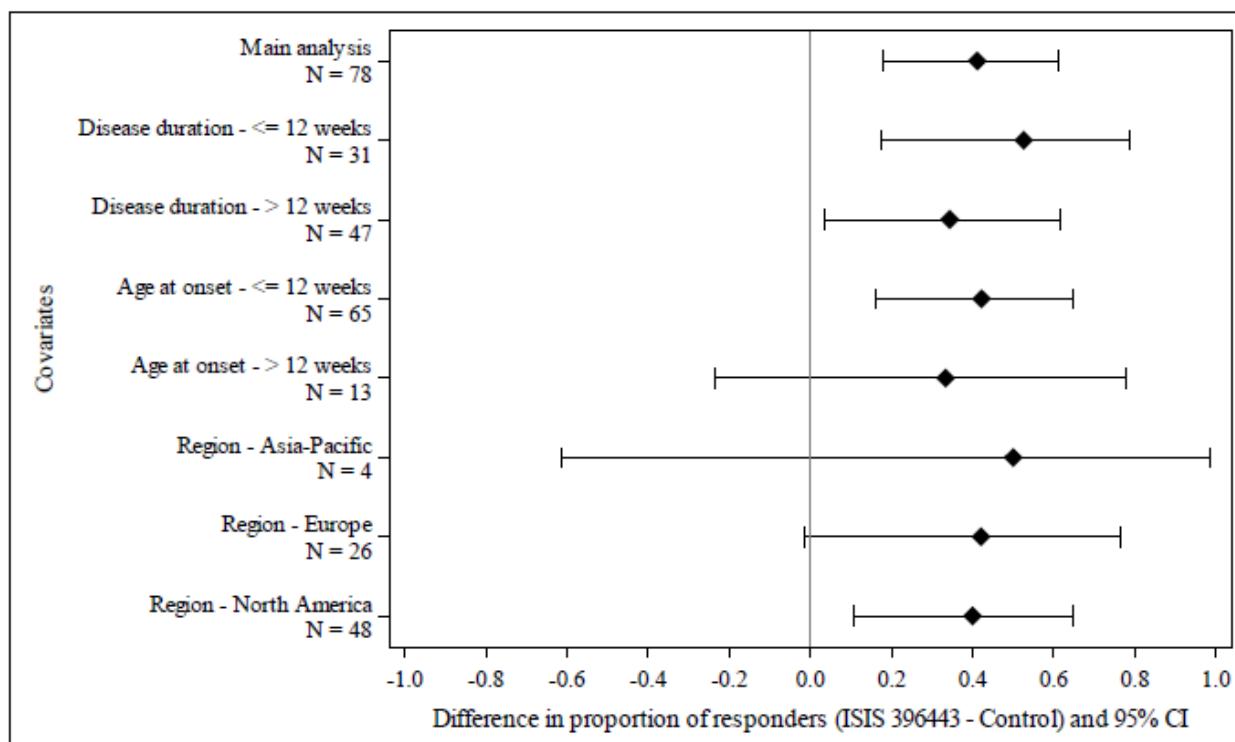


Figure 7: Figure of Difference in Proportion of Responders and 95% Confidence Intervals for Motor Milestones Primary Analysis: Subgroups – Interim Efficacy Set

Second primary endpoint - Event-Free Survival (time to death or permanent ventilation)

In accordance with the statistical analysis plan the second primary efficacy endpoint, time to death or permanent ventilation, was not formally tested statistically at the time of interim analysis. However, a description of the results was provided.

There were 27/80 (34%) patients who died or required permanent ventilation on nusinersen compared to 20/41 (49%) on control. There were 12/80 (15%) deaths on nusinersen, compared to 13 (32%) on control.

From the Kaplan-Meier curve the estimated proportion of patients who died or required permanent ventilation by day 182 was 0.520 on control compared to 0.315 on nusinersen.

This endpoint was not formally analysed as part of the interim analysis, but the trend favoured nusinersen over control, with an observed hazard ratio of 0.71 for time to death or permanent ventilation, and a hazard ratio of 0.44 for time to death.

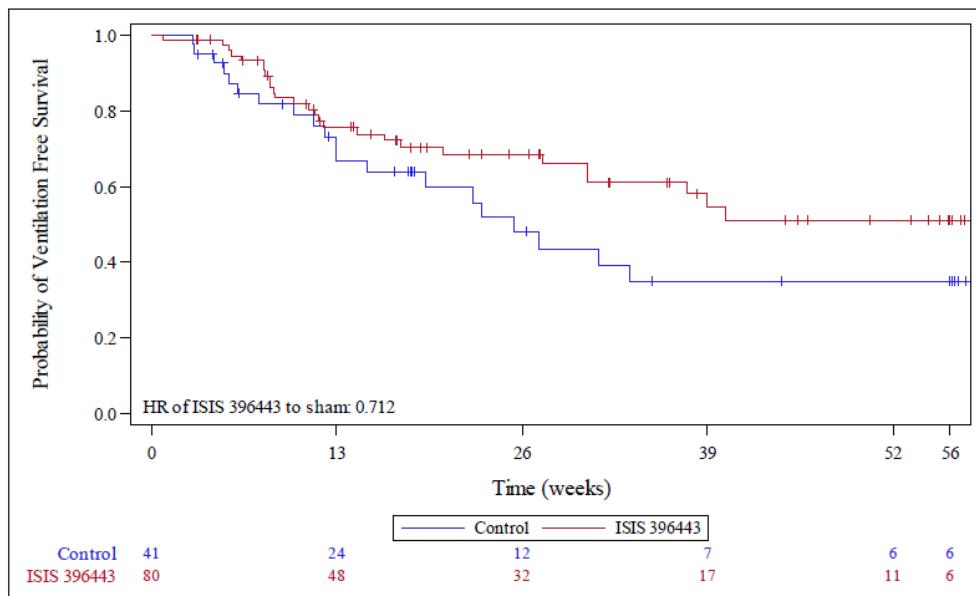


Figure 8: Kaplan-Meier Curves for Time to Death or Permanent Ventilation (EAC-Adjudicated Events) ITT Set

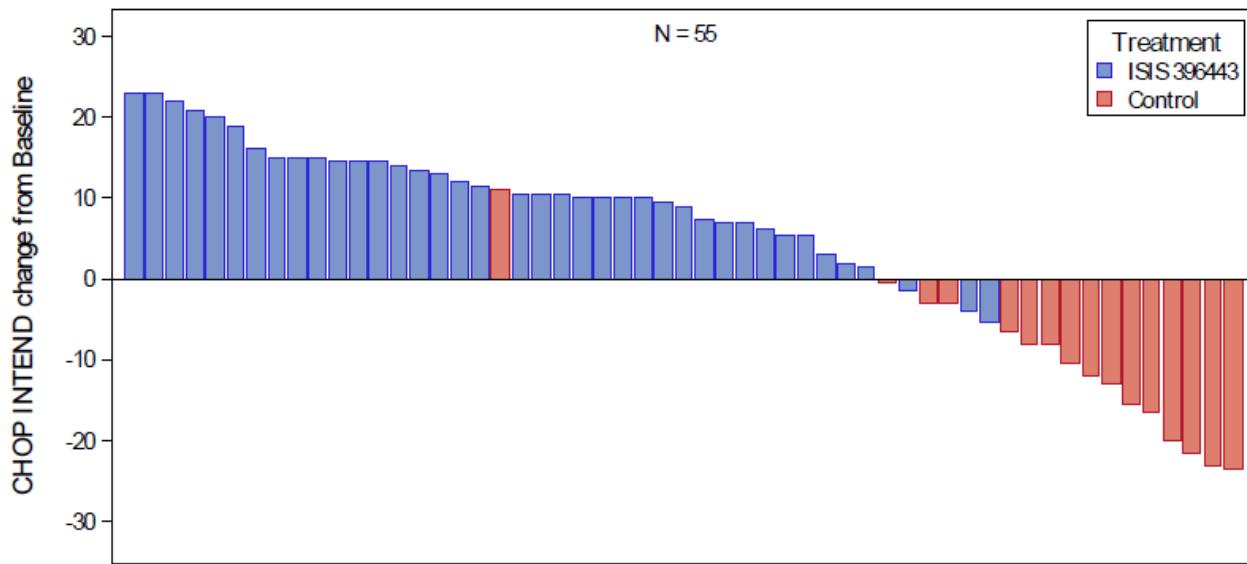
A subject is considered to have received permanent ventilation if a tracheostomy was performed or at least 16 hours of ventilator support per day continuously for more than 21 days was required in the absence of an acute reversible event.

None of the subjects required permanent ventilation at baseline. Compared to the control group, the estimated percentage of subjects requiring permanent ventilation in the nusinersen group was higher early in the study (14.9% versus 6.2%, respectively, by Study Day 91) but consistently lower later in the study.

Using a Cox proportional hazards model adjusting for each subject's disease duration at screening resulted in a hazard ratio of 0.90, indicating a 10% reduction in the risk of permanent ventilation following treatment with nusinersen.

Secondary Endpoint - CHOP INTEND

At baseline, the distribution of the total score was comparable to that of the ITT Population: in the nusinersen group, baseline total score ranged from 8.5 to 48.5 (median, 27.50), and from 10.5 to 50.5 (median, 28.50) in the control group. At the later of the Day 183, Day 302, and Day 394 visits, 71% of nusinersen-treated infants had shown improvement with 65% achieving at least a 4-point improvement from baseline (a secondary endpoint of the study), and 61% showing an improvement of at least 6 points. In contrast, 52% of subjects in the control group showed some degree of worsening, with 44% worsening by 4 points or more. Subjects who died or were withdrawn from the study were considered non-responders.



Note 1: Shortest bars at 0 line indicate 0 value.

Note 2: Out of the 78 subjects in the interim efficacy set, 21 died (11 (22%) for ISIS 396443 and 10 (37%) for Control) and 2 withdrew for reason other than death (1 (2%) for ISIS 396443 and 1 (4%) for Control) and were therefore not included in this analysis of the IES.

Figure 9 : Waterfall Plot for CHOP INTEND Change from Baseline to Later of Day 183, Day 302, and Day 394 Study Visit - Interim Efficacy Set

Secondary Endpoint - Compound Muscle Action Potential

Baseline CMAP measurements were consistent with that of a symptomatic Type I SMA population. Ulnar amplitude ranged from 0.00 to 0.80 mV (median 0.20 mV) in the nusinersen group and from 0.10 to 0.60 mV (median 0.20 mV) in the control group. Peroneal amplitude ranged from 0.00 to 1.50 mV (median 0.30 mV) in the nusinersen group and from 0.00 to 1.30 mV (median 0.205 mV) in the control group.

The secondary endpoint based on CMAP defined a subject as responding if the peroneal amplitude increased to, or was maintained at, 1 mV or more compared to baseline.

Of the 51 subjects in the nusinersen group, 18 (35%) responded versus none in the control group. Indeed 10 subjects (20%) had an improvement of 1 mV or more with 2 subjects (4%) having improved by at least 2 mV. At the Day 183, 302, and 394 Visits, 25%, 25%, and 39% of nusinersen-treated subjects had responded whereas none in the control group had done so.

Tertiary Endpoint - Serious Respiratory Events

Serious respiratory events included all SAEs coded into the respiratory, thoracic, and mediastinal disorders SOC, either as their primary or secondary SOC.

A greater percentage of subjects in the nusinersen group experienced serious respiratory events (nusinersen vs. control: 73% vs. 67%), the duration of observation was twice as long (37.7 vs. 17.9 years), resulting in a lower annualized rate with nusinersen (2.836 vs. 3.065 serious respiratory events per year).

Tertiary Endpoint - Number of Hours of Ventilatory Support

The median percentage of time on ventilatory support was lower in the nusinersen group (27.1%) compared with the control group (43.0%). The ranges were similar in each group 0% to 95.2% and 0% to 91.5% in the nusinersen and control groups, respectively.

Tertiary Endpoint - Number and Length of Hospitalizations

Of the time on study, subjects in the nusinersen group spent a lower percentage of time in hospital (ranging from 0 to 50%, median 8.86%) compared to control (ranging from 0% to 75%, median 13.87%).

Growth Parameters

Similar trends of improvement were observed in both groups in the majority of growth parameters.

Final results of the study CS3B

During the assessment process, the final results from study CS3B became available and were submitted by the applicant. The below paragraphs describe the relevant findings:

Subject Accountability:

A total of 149 subjects were screened of whom 122 were randomized in a 2:1 ratio to receive nusinersen (81 subjects) or undergo a sham procedure (41 subjects in this control group). One subject randomized to receive nusinersen was withdrawn before receiving study treatment. The 121 subjects randomized and dosed, and who compose the ITT Population, were enrolled at 31 sites in 13 countries. Fifty-four subjects (45%) were enrolled at 12 sites in the United States, 11 subjects (9%) at 2 sites in Spain, and 10 subjects (8%) at 2 sites in Germany, which together account for 62% of the population. Of the 121 subjects who received treatment, 89 (74%) completed the study (81% of subjects in the nusinersen group and 59% of subjects in the control group).

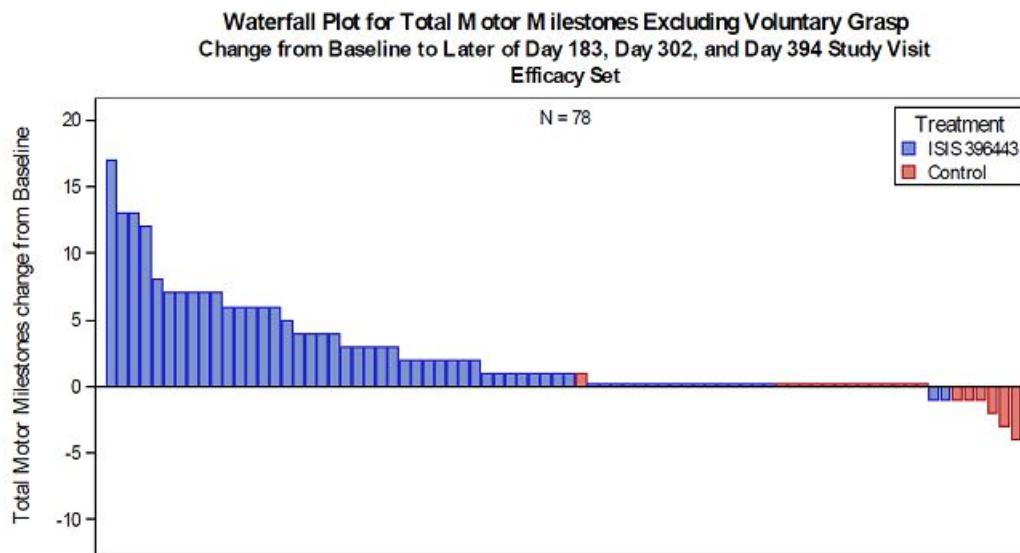
Demographics and Baseline Disease Characteristics:

Overall, the demographic and baseline disease characteristics and SMA history of the ITT Population is consistent with a population highly likely to develop Type I SMA.

Efficacy Results:

- The analysis of the first primary endpoint was done for the interim analysis. A statistically significantly greater percentage of subjects achieved a motor milestone response in the nusinersen group (41%) compared to the control group (0%; p<0.0001). In the final analysis, this percentage improved; 51% of subjects in the nusinersen group achieved a response compared to 0% in the control group (p<0.0001). Responders were subjects with a greater number of motor milestone categories with improvement than worsening. Subjects who died or were withdrawn from the study are considered non-responders. A consistent and statistically significant effect was observed across the group of sensitivity analyses. A

treatment effect was evident in the pre-specified subgroups based on disease duration, age at onset of symptoms of SMA, and geographic region.



Note 1: Shortest bars at 0 line indicate 0 value.

Note 2: Out of the 110 subjects in the efficacy set, 29 died (13 (18%) for ISIS 396443 and 16 (43%) for Control) and 3 withdrew for reason other than death (2 (3%) for ISIS 396443 and 1 (3%) for Control) and were therefore not included in this analysis of the ES.

- Among the non-responders, most subjects in the nusinersen group experienced improvement in CHOP INTEND and CMAP while the non-responders in the sham control group experienced declines.
- As of the data cut-off date, in the nusinersen group (n=73), 16 subjects (22%) achieved full head control, 6 subjects (8%) achieved independent sitting, and 1 subject (1%) achieved standing with support, whereas no subjects in the control group (n=37) achieved any of these milestones.
- Time to death or permanent ventilation was significantly prolonged in subjects treated with nusinersen. Overall, there was a 47% reduction in the risk of death or permanent ventilation compared to control. Notably, nusinersen-treated subjects who were below the median for disease duration at baseline had a markedly decreased risk of death or permanent ventilation (76% reduction in risk) compared with control subjects who were below the median, suggesting that early treatment with nusinersen may confer a strong benefit for event-free survival.
- There was a trend toward a lower percentage of subjects in the nusinersen group requiring permanent ventilation during the study compared with the control group. Overall, the risk of permanent ventilation was 34% lower in nusinersen-treated subjects than in those who

received the sham procedure even though subjects randomized to nusinersen required more ventilatory support and had more history of pulmonary disease at baseline

- Subjects who received nusinersen but required permanent ventilation continued to show improvement in motor function, whereas subjects in the control group who required permanent ventilation showed no improvement in motor function.
 - A significantly lower percentage of subjects in the nusinersen group died compared with the control group. Overall, the risk of death was 62.8% lower in nusinersen-treated subjects than in those who received the sham procedure even though subjects randomized to nusinersen were younger at symptom onset and had more difficulty swallowing and feeding at baseline, all of which confer a worse prognosis for survival.
 - A statistically significantly greater percentage of subjects achieved a CHOP INTEND response in the nusinersen group (71%) compared to the control group (3%; $p<0.0001$). Several nusinersen-treated infants had improvements of 10 points or more in CHOP INTEND total score, but only one in the control group showed improvement. With the exception of this one subject, all subjects in the control group showed no change or worsened.
 - Sustained and clinically significant increases of mean CMAP amplitude of the peroneal and ulnar nerves were observed in the nusinersen group compared with the control group. Through Day 64 (i.e., during the loading-dose period) little separation was observed between the groups, however by Day 183, the nusinersen group was improving steadily, while the control group remained at baseline levels or below.
 - There was a trend toward a lower annualized rate of serious respiratory events in subjects who received nusinersen (2.570) than in subjects who received the sham procedure (4.031).
 - There was a trend toward a lower proportion of time spent on ventilator support in nusinersen- treated infants compared to control.
 - The rate of hospitalization and the proportion of time in hospital were lower in subjects treated with nusinersen.
 - Absolute length and weight improved for subjects receiving nusinersen. Subjects receiving nusinersen appear to have a slower rate of growth compared to age matched controls whereas subjects in the control group have an increased rate of growth over time. The greater increase in mean chest circumference from baseline in subjects in the nusinersen group compared to the control group is noteworthy because this increase likely indicates a decrease in chest deformities seen in patients with SMA.
- **Summary of main efficacy results**

Table 5 Summary of efficacy for trial CS3B

Title: A Phase 3, Randomized, Double-Blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of nusinersen Administered Intrathecally in Patients With Infantile-Onset Spinal Muscular Atrophy		
Study identifier	(ISIS 396443) CS3B	
Design	A Phase 3, multicenter, double-blind, randomized, sham-procedure controlled study of ISIS 396443	
	Duration of main phase:	1 mth screening + 10 mths treatment + 3 follow up
	Duration of Run-in phase:	not applicable
Hypothesis	Duration of Extension phase:	Patients transferred for study CS11 - ongoing
	Superiority	
	Treatments groups	Control
Endpoints and definitions		Sham procedure on days 1, 15, 29, 64, 183 and 302, n=41 randomised
ISIS 396443 (nusinersen)	ISIS 396443 on days 1, 15, 29, 64, 183 and 302, n=81 randomised	
First Primary endpoint	Proportion of Motor Milestones Responders	
Second Primary endpoint	Time to death or permanent ventilation	
Secondary endpoint	Proportion of CHOP INTEND responders (%)	
Secondary endpoint	Overall Survival	
Secondary endpoint	Time to ventilation	Time to ventilation with same characteristics described above
	Secondary endpoint	Proportion of Compound Muscle Action Potential responders (%)
Proportion of patients who have improved CMAP		

	Secondary endpoint	Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration	Time to death or permanent ventilation with the characteristics described above, in patients who had a disease duration below the median at screening
	Secondary endpoint	Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration	Time to death or permanent ventilation with the characteristics described above, in patients who had a disease duration above the median at screening
Database lock	16 December 2016		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Efficacy Set (all subjects with Day 183, Day 302, or Day 394 visit and all subjects with time difference of at least 190 days (183 plus 7 day window) between date of first dose and the clinical cut-off date for the final analysis) [ITT for time to event]		
Descriptive statistics and estimate variability	Treatment group	Control	ISIS 396443
	Number of subject	37 (41 for time to event)	73 (80 for time to event)
	Primary endpoint Proportion of Motor Milestones Responders (%) Logistic regression (Fisher's exact test in the situation of less than 5 responders in either group)	0%	51%
	Primary endpoint Time (wk) to death or permanent ventilation, median (95% CI) Cox proportional hazards model	22.6 (13.6, 31.3)	NA (36.3, NA)

	Secondary endpoint Proportion of CHOP INTEND responders (%) (n, % at latter of Day 183, 302, or 304)	1 (3%)	52 (71%)
	Secondary endpoint Overall Survival, median (95% CI) Cox proportional hazards model	NA (23.1, NA)	NA (NA, NA)
	Secondary endpoint Time to ventilation, median (95% CI) Cox proportional hazards model	NA (22.6, NA)	NA (40.3, NA)
	Secondary endpoint Proportion of Compound Muscle Action Potential responders (%)	5%	36%
	Secondary endpoint Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration, median (95% CI) Cox proportional hazards model	25.4 (13.1, 40.3)	NA (NA, NA)
	Secondary endpoint Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration, median (95% CI) Cox proportional hazards model	19.0 (11.3, 27.1)	27.4 (12.0, NA)
Effect estimate per comparison	Primary endpoint: Proportion of Motor Milestones Responders	Comparison groups	ISIS 396443 vs. control
		Difference (95%) in percentages (ISIS 396443 - control)	50.58

		(95% CI)	(31.81, 66.48)
		P-value (Fisher's exact test)	<0.0001
Primary endpoint: Time to death or permanent ventilation	Comparison groups	ISIS 396443 vs. control	
	Cox proportional hazards model	0.53	
	(95% CI)	(0.3156, 0.8902)	
	P-value (Fisher's exact test)	0.0046	
Secondary endpoint Proportion of CHOP INTEND responders (%)	Comparison groups	ISIS 396443 vs. control	
	Difference (95%) in percentages (ISIS 396443 - control)	68.53	
	(95% CI)	(51.27, 81.99)	
	P-value	<0.0001	
Secondary endpoint Overall Survival	Comparison groups	ISIS 396443 vs. control	
	Cox proportional hazards model	0.372	
	(95% CI)	(0.1787, 0.7745)	
	P-value	0.0041	
Secondary endpoint Time to ventilation, median (95% CI) Cox proportional hazards model	Comparison groups	ISIS 396443 vs. control	
	Hazard ratio	0.66	
	(95% CI)	(0.322, 1.368)	
	P-value	0.1329	
Secondary endpoint Proportion of Compound Muscle Action Potential responders (%)	Comparison groups	ISIS 396443 vs. control	
	Proportion of responders	30.21	
	(95% CI)	(10.35, 48.09)	
	P-value	0.0004	
Secondary endpoint Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration Cox proportional hazards model	Comparison groups	ISIS 396443 vs. control	
	Hazard ratio	0.240	
	(95% CI)	(0.1002, 0.5753)	
	P-value	0.0003	
Secondary endpoint Time to death or	Comparison groups	ISIS 396443 vs. control	
	Hazard ratio	0.844	
	(95% CI)	(0.4270, 1.6698)	

	permanent ventilation in the subgroups of subjects above the study median disease duration, median (95% CI) Cox proportional hazards model	P-value	0.3953
Analysis description	Secondary analysis		
	There were several sensitivity analysis performed for both primary and secondary endpoints. A consistent effect was observed across sensitivity analyses conducted.		

Study CS4

This is a Phase 3, Randomized, Double-Blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients With Later-Onset Spinal Muscular Atrophy [CHERISH].

The primary efficacy endpoint of the study was the change from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) score at 15 months. Secondary efficacy endpoints of the study were as follows:

- Proportion of subjects who achieve a 3-point or greater increase from baseline in
 - HFMSE score at 15 months
 - Proportion of subjects who achieve any new motor milestone at 15 months
 - Number of motor milestones achieved per subject at 15 months
 - Change from baseline in Upper Limb Module Test at 15 months
 - Proportion of subjects who achieve standing alone at 15 months
 - Proportion of subjects who achieve walking with assistance at 15 months

The total duration of subject participation in the study was approximately 16 months and consisted of a Screening Period (up to 28 days), a Treatment Period (9 months), and a Post-Treatment Follow-Up Period (6 months). Eligible subjects were randomized in a 2:1 ratio to receive either a 12-mg dose of nusinersen or a sham-procedure control, respectively. Randomization was stratified based on the subject's age at Screening (<6 years vs. ≥ 6 years).

Interim results submitted from this ongoing, randomized, controlled, double-blind study of nusinersen in 126 subjects with later-onset SMA show that subjects treated intrathecally with nusinersen achieved sustained and clinically meaningful benefits compared with a control group of subjects who received a sham procedure. These benefits included statistically significant greater gains in motor function as measured by HFMSE, as well as an improvement in upper limb functional ability.

The primary efficacy endpoint was the change from baseline in HFMSE score at 15 months. The HFMSE is a tool used to assess motor function in children with SMA. An improvement of ≥3 points in HFMSE is considered to represent a clinically meaningful improvement. A statistically significant change from baseline in HFMSE score was observed in the nusinersen group (4.0 (95% CI: 2.9-5.1)) compared to the sham control group (-1.9 (95% CI: -3.8-0.0)) ($p=0.0000002$) (Figure 10). A consistent effect was observed across all sensitivity analyses conducted, including an analysis based on observed Month 15 values.

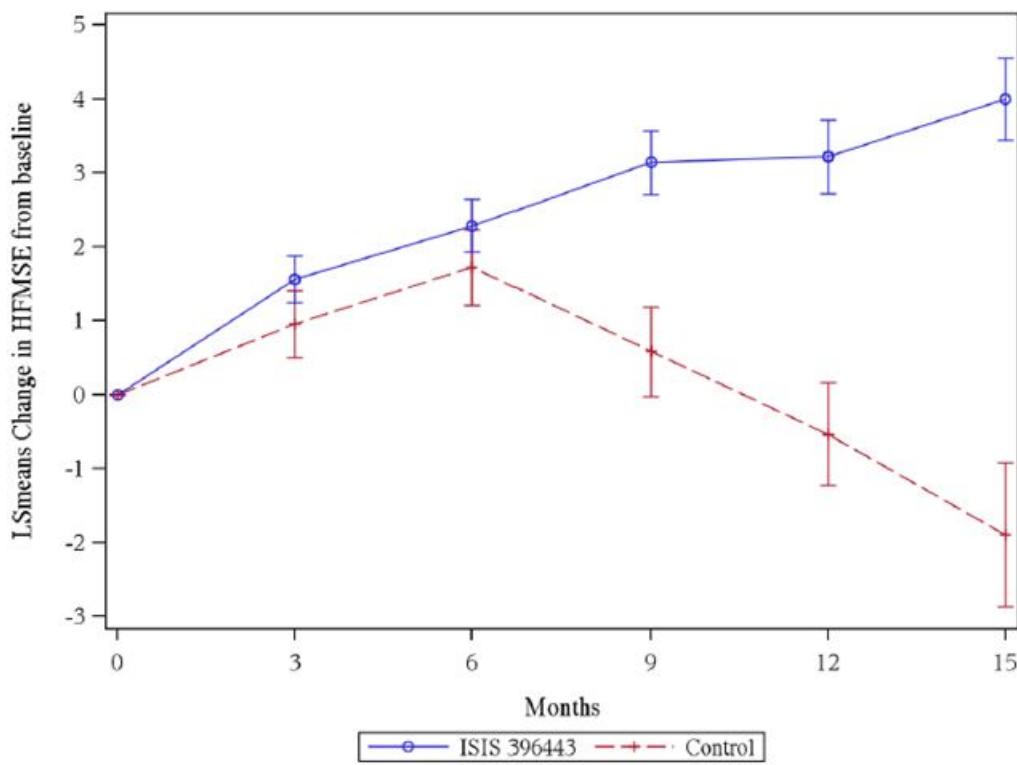


Figure 10 HFMSE: Mean change from baseline (multiple imputation) over time using LSmeans estimates – ITT Set

- A greater improvement in HFMSE scores was seen in the nusinersen group compared to the control group at all timepoints from Month 3 to Month 15. Earlier and greater gains were observed among subjects who were <6 years of age at study entry and subjects with shorter disease duration. Older subjects and subjects with a longer disease duration in the nusinersen group appeared to stabilize or improve in motor function at later timepoints. It may be that in older subjects and in subjects with longer disease duration, the rate of change in motor function is slower so that it takes longer for an improvement to be observed.
- The proportion of subjects who achieved a 3-point or greater increase from baseline in HFMSE score at 15 months in the nusinersen and control groups was 57.3% versus 20.5%, respectively, for a difference of 36.8% in favour of the nusinersen group.
- The proportion of subjects achieving new WHO motor milestones in the nusinersen and control groups was 17.1% and 10.5%, respectively, for a difference of 6.6% in favour of the nusinersen group. At 15 months, none of the 35 subjects in the nusinersen group had lost 1 or more motor milestones as compared to the control group in which 4 of 19 subjects (21%) had lost a motor milestone. In the ≥6 years of age subgroup, no subjects (0 of 3 subjects) in the nusinersen group had lost a motor milestone compared to 2 of 2 subjects (100%) in the control group.
- The number of new motor milestones achieved per subject at Month 15 was slightly higher in the nusinersen group, with a least squares mean difference of 0.3 between the 2 groups.
- There was a greater improvement in Upper Limb Module Test scores from baseline to Month 15 in the nusinersen group (least squares mean change of 3.7) than in the control group (least squares mean change of 0.3), with a least squares mean difference of 3.4 between the 2 groups.
- One subject in the control group achieved standing alone at 15 months and 1 subject in the nusinersen group achieved walking with assistance at 15 months. The most commonly achieved new milestone in the nusinersen group at levels higher than in the control group was hands-and-knees crawling. Gains in HFMSE scores became apparent before gains in WHO motor milestones.

- A consistently higher proportion of subjects in the nusinersen group were rated as much improved or having any improvements compared to the control group at all timepoints in the Investigator and caregiver CGI assessments.
- The unadjusted annualized rates of disease-related AEs and hospitalizations were lower in the nusinersen group than in the control group.

As of the data cut-off date in this ongoing study, nusinersen was well tolerated when administered as multiple IT injections. No specific safety concerns were identified in the overall safety profile of nusinersen.

Supportive studies

The development plan comprised of several supportive studies: in infantile-onset SMA (Study CS3A), later-onset SMA (Type II and Type III) - CS1, CS4, CS10, CS2, and CS12, and in infants with pre-symptomatic SMA (SM201).

Study CS3A

Study CS3A, a Phase 2, open-label study of nusinersen, is being conducted at 4 centres in the United States and Canada.

Enrolment in CS3A was complete at time of assessment: 23 subjects with infantile-onset SMA were screened; 21 were enrolled, and 20 were dosed with nusinersen. Four subjects in Cohort 1 received 6 mg loading doses and 12 mg maintenance doses, and 16 subjects in Cohort 2 received 12 mg loading and maintenance doses. As of the last data cut-off (26 January 2016), 15 of 20 subjects (75%) were alive and continuing in the study. One subject had voluntarily withdrawn from the study, and 4 subjects had died of SMA-related causes.

- The demographics and SMA history of the subjects in Study CS3A were similar to those of the subjects in CS3B and consistent with a Type I SMA population.
 - Most subjects were male (60%) and white (80%)
 - Sixteen of 20 subjects (80%) had symptom onset at <12 weeks of age and were classified as Type IB. Four subjects (20%) were Type IC (symptom onset >12 weeks of age). Subject age ranged from 21 to 154 days (median 56 days) at SMA symptom onset; from 0 to 154 days (median 81 days) at diagnosis of SMA; and from 36 to 210 days (median 155 days) at study enrolment
 - 17 of 20 subjects (85%) had 2 copies of the SMN2 gene (all 4 subjects in Cohort 1 and 13 subjects in Cohort 2); 2 subjects had 3 copies of the SMN2 gene; and 1 subject died before determination of SMN2 gene copy number was completed
- Subjects had received a median of 7 (range 2 to 9) doses at the time of data cut-off. The time on study ranged from 62 to 988 days (median 670 days); 15 subjects (75%) were on study for at least 505 days (72 weeks). Across both cohorts, the total time on study was 32.9 subject-years.
- The ages of the subjects continuing in the study at data cut-off ranged from 24.6 to 39.2 months with a median of 29.6 months

Results of efficacy assessments conducted as of the cut-off date demonstrated continued improvement for over 2 years, which is inconsistent with the natural history of Type I SMA:

- In contrast to the natural history of SMA where there is a failure to achieve motor milestones after symptom onset, sustained and clinically significant improvements in HINE motor milestones were observed in both dose cohorts over time.
 - Motor milestones increased steadily over time from a baseline mean of 2.25 milestones, with mean increases of 0.53, 1.78, 3.76, 4.80, and 9.40 milestones on Days 29, 92, 253, 379, and 694, respectively.
 - 13 of 20 subjects (65%) met the primary endpoint of protocol-defined achievement of new motor milestones.
 - 9 subjects (45%) achieved full head control, 8 subjects (40%) developed the ability to sit independently, 5 subjects (25%) gained the ability to stand with support or independently, and 2 subjects (10%) gained the ability to walk with support or.
- In contrast with the decline associated with Type I SMA [Kolb 2016a], sustained and clinically significant improvements in mean CHOP INTEND total scores were observed in both dose cohorts over time
 - At the time of the last visit for each subject prior to data cut-off, subjects had achieved a mean improvement of 14 points in CHOP INTEND total score
 - 11 of 20 subjects (55%) met the secondary endpoint of an increase in total CHOP INTEND score of ≥ 4 points at the time of data cut-off.
- Sustained improvements of mean CMAP amplitude of the ulnar and peroneal nerve were observed in both dose cohorts over time.
 - Subjects experienced a mean increase of 0.753 mV in ulnar amplitude and 1.85 mV in peroneal amplitude at Day 694.
 - 13 of 20 subjects (65%) had improvement of >0.5 mV in peroneal amplitude as of the last visit prior to the data cut-off date.
- Increases from baseline were observed in all growth parameters measured. However, most subjects were receiving supplemental nutrition by G-tube or other means during the study.
- Fifteen of 20 subjects (75%) were alive and continuing in the study at the time of the data cut-off. Of these 15 subjects, all were >24 months of age, 7 were >30 months of age, and 2 were >36 months of age.
- 13 subjects (65%) were alive, free from permanent ventilation, and continuing in the study at the time of data cut-off. A median time to event-free survival could not be estimated due to an insufficient number of events.
- After the data cut-off, 1 additional subject had died at 3 years of age, and 1 subject met the criteria for permanent ventilation at 3.5 years of age.
- Efficacy results from CS3A showed that subjects who have received nusinersen treatment for over 2 years have achieved clinically meaningful gains in motor milestones, prolonged overall and event-free survival, and improved motor function and motor neuronal health inconsistent with the natural history of Type I SMA.

- The earlier onset and greater magnitude of the improvements in subjects who received the 12-mg loading dose (Cohort 2) compared with those who received the 6-mg loading dose (Cohort 1) are indicative of greater nusinersen exposure from the higher loading dose for subjects in Cohort 2.

Study CS1

Study CS1 was a Phase 1, open-label, single-dose, dose-escalation study to evaluate the safety, tolerability, and PK of a single dose of nusinersen administered IT in subjects with SMA who were 2 to 14 years of age and who were medically stable. The study consisted of 4 dose cohorts who received nusinersen at a dose of 1 mg (n=6); 3 mg (n=6), 6 mg (n=6), and 9 mg (n=10). Subjects in the 1mg cohort of Study CS1 were eligible to continue into Study CS2.

Subjects receiving 3, 6, or 9 mg were eligible to enrol in Study CS10.

- Most subjects (61%) were female and white (82%)
- The mean age of subjects was 6.1 years with a range of 2 to 14 years
- 15 subjects (54%) had Type II SMA and 13 (46%) had Type III SMA
- 25 subjects (89%) had 3 SMN2 copies, 2 subjects (7%) had 4 copies, and 1 subject (4%) had 5 copies
- 18 subjects (64%) were non-ambulatory at baseline and 10 (36%) were ambulatory
- A dose-dependent improvement in HFMSE total score was observed, with a mean increase from baseline of 3.1 points (17.6%) at Day 85 at the highest dose evaluated (9 mg)
- 7 of 10 subjects in the 9-mg dose cohort exhibited a clinically meaningful improvement of ≥ 3 points in the HFMSE

Study CS10

Study CS10 was an open-label study to evaluate the safety, tolerability, and PK of a single dose of nusinersen (6 or 9 mg) administered IT by LP in subjects with SMA who previously participated in CS1. Of the 28 eligible subjects from CS1, 18 enrolled in CS10.

Four subjects received 6 mg of nusinersen and 14 subjects received 9 mg of nusinersen in CS10. Following their participation in CS10, subjects were eligible to enrol in Study CS12.

- Most subjects were female (72%) and white (83%)
- The mean age of subjects was 6.6 years with a range of 2 to 11 years
- 10 subjects (56%) had Type II SMA and 8 subjects (44%) had Type III SMA
- 17 subjects (94%) had 3 SMN2 copies and 1 subject (6%) had 4 copies
- 12 subjects (67%) were non-ambulatory and 6 (33%) were ambulatory

- Dose dependent changes in HFMSE score were observed, with greater increases in subjects who had received 9 mg in CS1 compared to the subjects who received 3 and 6 mg in CS1.
- Significant improvement ($p=0.008$) relative to baseline in HFMSE scores was maintained throughout CS10 for subjects who received 9 mg in CS1

Study CS2

Study CS2 was a Phase 1/2a, open-label, multiple-dose, dose-escalation study designed to assess the safety, tolerability, and PK of nusinersen in 2- to 15-year-old subjects with SMA. Eight subjects were enrolled in each of the 3- and 6-mg dose cohorts, and 9 subjects were enrolled in each of the 9- and 12-mg dose cohorts. Six subjects had previously been treated in Study CS1.

- Overall, 59% of subjects were male and 88% of subjects were white
- Age ranged from 2 to 15 years with a mean of 7.4 years
- 13 subjects (38%) had Type II SMA and 21 (62%) had Type III SMA
- 1 subject (3%) had 2 SMN2 copies, 25 (74%) had 3 copies, and 8 (23%) had 4 copies
- 19 subjects (56%) were non-ambulatory and 15 (44%) were ambulatory
- Time-and dose-dependent improvements in mean total HFMSE score were observed, with the largest improvements seen in the 9- and 12-mg dose cohorts. Improvement was maintained through Day 253 (~6 months after the last dose of study drug).
- Dose- and time-dependent increases in the ULM were observed, particularly in the 9-and 12-mg nusinersen dose cohorts and in subjects with baseline scores within the dynamic range of the scale (≤ 14)
- Substantial increases were observed in distance walked as assessed by the 6MWT
- Electrophysiology measurements assessed by CMAP remained stable, suggesting maintenance of motor neuronal health

Study CS12

Study CS12 is an ongoing Phase 1, open-label, multiple dose study to assess the safety, tolerability, and PK of repeated doses of nusinersen (12 mg) administered as IT injections by LP to subjects with SMA who previously participated in Study CS2 or Study CS10.

A total of 47 subjects were enrolled and treated; 30 subjects were enrolled from Study CS2 and 17 were enrolled from CS10. At the time of data cut-off (07 April 2016), 23 subjects had completed the study, 2 subjects had withdrawn, and 22 were ongoing.

- There were 49% males and 51% females; most subjects were white (92%)
- Age ranged from 3 to 17 years at the time of enrolment with a mean of 8 years
- 22 subjects (47%) had Type II SMA and 25 (53%) had Type III SMA

- 39 subjects (83%) had 3 copies of the SMN2 gene and 8 (17%) had 4 copies
- 26 subjects (55%) were considered non-ambulatory at Baseline and 21 (45%) were considered ambulatory
- Improvement and prevention of worsening of motor function as assessed by HFMSE was observed over time
- Non-ambulatory subjects had stable upper limb function as measured by the ULM
- There was a progressive increase in total distance walked by the 6MWT up to Day 442 (mean increase of 36.56 meters compared to Baseline)
- The mean change from Baseline in the 6MWT was $>2\times$ the standard error of the mean (SEM) at multiple visits, suggesting a likely difference from 0 change
- Thirteen of 22 subjects were able to walk farther than baseline during the study
- 3 subjects who were unable to perform the 6MWT at baseline of CS12 were later able to complete it. One of these subjects (Type II SMA and 3 SMN2 copies) walked without support for the first time in Study CS12. The subject was 12 months of age at symptom onset and 15 months of age at SMA diagnosis. The subject achieved walking with support at the age of 12 months and standing without support at the age of 36 months. On his first attempt on Day 260, the subject walked 51 meters. Distance improved over time and was 150 meters on Days 533 and 624.

Study SM201 (also known as CS5)

Study SM201 is an ongoing Phase 2, open-label, multicentre, single-arm study to assess the efficacy, safety, tolerability, and pharmacokinetics of nusinersen in presymptomatic SMA. The study is being conducted in subjects who were ≤ 6 weeks of age at the time of enrolment with genetic documentation of 5q SMA, 2 or 3 copies of the SMN2 gene, CMAP ≥ 1 mV, and the absence of signs or symptoms of SMA. Up to 25 subjects are planned. Efficacy data available to date indicate that the development and achievement of motor milestones for most subjects has been more consistent with normal development than with the natural history of Type I SMA.

At the time of data cut-off for this filing (08 June 2016), 17 subjects had been enrolled and received at least 1 dose of nusinersen. All subjects are continuing in the study. Thirteen subjects who have received all 4 loading doses or have had the opportunity to complete the Day 64 visit comprise the efficacy set.

- Most subjects are male (65%) and white (53%).
- Age at the first dose ranged from 8 to 42 days with a median of 19 days.
- 12 of 17 subjects (71%) have 2 copies of the SMN2 gene and 5 subjects (29%) have 3 copies.

Efficacy data were available for 13 subjects at Day 64, 10 subjects at Day 183, and 5 subjects at Day 302. Results at the later of these visits demonstrate development that is inconsistent with Type I SMA and the experience of subjects' affected siblings and consistent with age-matched expectations for healthy infants.

- No subjects died or had respiratory intervention (defined as either invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days or tracheostomy).
- One subject received ventilation for ≥ 6 hours/day continuously for ≥ 1 day (4 to 6 hours for 9 continuous days) to treat an SAE of respiratory distress.
- An increase of at least 4 points in the CHOP INTEND total score compared to Baseline was observed for:
 - 7 of 13 subjects (4 with 2 SMN2 copies and 3 with 3 SMN2 copies) at Day 64
 - 8 of 10 subjects (5 with 2 SMN2 copies and 3 with 3 SMN2 copies) at Day 183
 - 3 of 5 subjects with 2 SMN2 copies at Day 302
- A decrease of at least 4 points in CHOP INTEND was observed in 1 subject with 2 SMN2 copies on Day 64, prior to the end of the loading dose period
- All subjects had age-appropriate motor development as measured by the modified Section 2 of the HINE; additional HINE motor milestones compared to Baseline were achieved by:
 - 12 of 13 subjects (9 with 2 SMN2 copies and 3 with 3 SMN2 copies) at Day 64
 - 10 of 10 subjects at Day 183 (7 with 2 SMN2 copies and 3 with 3 SMN2 copies)
 - 5 of 5 subjects with 2 SMN2 copies at Day 302
- 69% of subjects had more categories with improvement (defined as ≥ 2 -motor milestone increase or attainment of the maximum of touching toes in the category of ability to kick, or ≥ 1 -motor milestone increase in any of the categories of head control, rolling, sitting, crawling, standing, or walking) than with worsening in HINE motor milestones at Day 64. 100% of subjects met this criterion at Days 183 and 302.
- 3 subjects with 2 SMN2 copies had a loss of at least 1 motor milestone; however, only 1 subject had a decrease in the total HINE motor milestones achieved.
- Of the 7 subjects at least 7 months of age at the time of data cut-off, 5 subjects (4 with 2 SMN2 copies and 1 with 3 SMN2 copies) were sitting independently (3 or 4 milestones). Of the 5 subjects at least 8 months of age, 1 subject with 2 SMN2 copies was standing unaided (3 milestones). Two other subjects less than 8 months of age were standing with support. (2 milestones) The one subject at least 11 months of age was walking with support (cruising) (2 milestones)
- At least 1 WHO motor milestone was achieved by:
 - 1 (3 SMN2 copies) of 11 subjects at Day 64
 - 7 (4 with 2 SMN2 copies and 3 with 3 SMN2 copies) of 10 subjects at Day 183
 - 4 of 5 subjects with 2 SMN2 copies at Day 302. One subject achieved the WHO motor milestone of sitting without support, while 1 subject, who was able to sit without support at Day 183, achieved the WHO motor milestones of crawling on hands and knees, standing with assistance, and walking with assistance. This subject achieved the WHO motor milestone of standing alone at Day 365.

- All but 1 subject gained weight during the study.
- Four subjects had manifestation of SMA symptoms based on growth failure (defined as weight for age below the fifth percentile [based on WHO growth charts] or a decreased growth velocity resulting in weight for age falling ≥ 2 major percentiles over a 6-month period), including 1 subject who had a percutaneous gastric tube placement. However, many factors unrelated to SMA may contribute to early growth failure in infants. In this regard, the presymptomatic status of the subjects in SM201 confounds the assessment of whether growth failure is a true manifestation of SMA symptom onset. As all of the subjects with growth failure are achieving age-appropriate motor milestones, it is possible that decreased weight velocity may be attributed to non-SMA causes.
- Increases from Baseline in mean ulnar nerve CMAP amplitude were observed at Days 64, 183, and 302, increases of at least 0.5 mV compared to Baseline were observed in:
 - 7 (4 with 2 SMN2 copies and 3 with 3 SMN2 copies) of 11 subjects at Day 64
 - 9 (6 with 2 SMN2 copies and 3 with 3 SMN2 copies) of 10 subjects at Day 183
 - 3 (2 SMN2 copies) of 5 subjects at Day 302
- As of the data cut-off date, information had been collected on 3 siblings. These data indicate that subject development in SM201 is inconsistent with that of their affected siblings. Information on these siblings, as well as additional posthoc sibling data obtained after the data cut-off for 6 subjects is provided in the efficacy narratives.

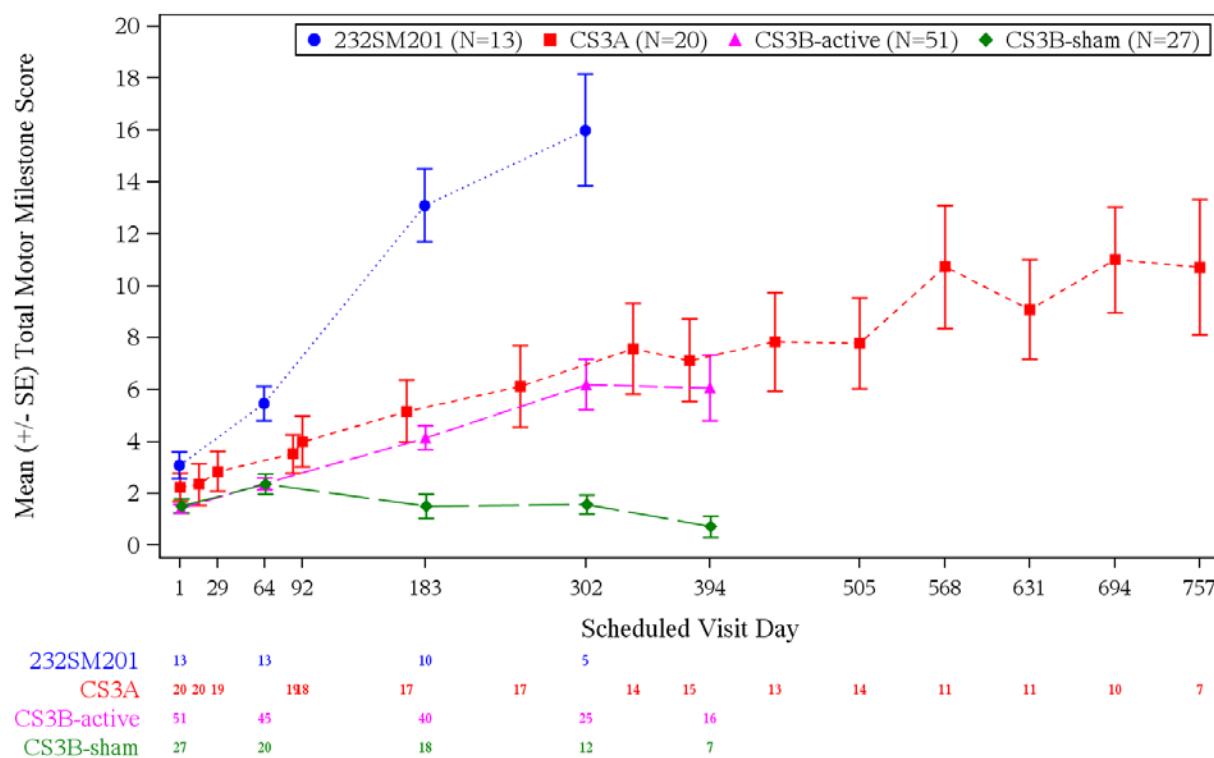
Updated results provided during the review demonstrate continued improvement over time. No subjects have died or required permanent ventilatory support (defined as either invasive or noninvasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days or tracheostomy). From Baseline to last study visit, the majority of subjects in the interim efficacy set had achieved the maximum score for HINE motor milestones in the categories of head control (13 of 18 subjects), kicking (13 of 18 subjects), and sitting (10 of 18 subjects). Additionally, 12 of 18 subjects achieved independent sitting, 3 of 18 subjects achieved independent standing, and 2 of 18 subjects achieved independent walking. Inconsistent with the natural history of Type I SMA, 16 of 18 subjects in the Efficacy Set achieved and maintained improvements in the CHOP INTEND total score. Seven of 18 subjects achieved the highest attainable CHOP INTEND score at the data cut-off date for this interim analysis.

Analysis performed across trials (pooled analyses and meta-analysis)

Due to differences in the study populations and the resulting study designs and endpoints required, efficacy data across all studies could not be integrated and analysed statistically. An overall summary has, however, been provided.

A comparison of motor milestone achievement among the subjects with symptomatic infantile-onset SMA and presymptomatic SMA demonstrates the following:

- Greater improvement in motor milestones for subjects with symptomatic infantile-onset SMA who received nusinersen in CS3B and CS3A relative to subjects in the control group of CS3B.
- A decline in the control group of CS3B consistent with the natural history of Type I SMA.
- Similar improvements in motor milestones over time up to 1 year (Day 394) in CS3B and CS3A.
- Continued benefit in motor milestone achievement over the long term for subjects in Study CS3A.
- Greater milestone development in presymptomatic subjects in SM201, suggesting that initiating nusinersen treatment prior to the onset of symptoms may allow patients to develop normally.



Population used in figure: Nurture - interim efficacy set, CS3A - all dosed subjects, CS3B - interim efficacy set.
For each study, visits with n<5 are not plotted.

Figure 11: Total HINE Motor Milestones by Scheduled Visit Day

The magnitude of motor milestone achievement among nusinersen-treated subjects in Studies CS3B and CS3A was also clinically meaningful. The inability to achieve independent sitting distinguishes Type I SMA from the less severe phenotypes; standing is never observed in patients with Type I SMA, and subjects with Type II SMA do not achieve independent walking.

In contrast to this natural history and the experience of the subjects in the control group of CS3B, subjects with infantile-onset SMA in CS3B and CS3A had achieved the following milestones at the last visit prior to data cut-off:

- Full head control: 16 subjects (22%) in CS3B and 9 subjects (45%) in CS3A

- Independent sitting (either prop, stable sit, or pivot): 6 subjects in CS3B and 8 subjects (40%) in CS3A
- Rolling (prone to supine or supine to prone): 25 subjects (34%) in CS3B and 7 subjects (35%) in CS3A
- Standing (with support or unaided): 1 subject (1%) in CS3B and 5 subjects (25%) in CS3A
- Walking (holding on or unaided): 2 subjects (10%) in CS3A

Among the infants with presymptomatic SMA, results of motor milestone development based on HINE and WHO criteria support that initiating treatment prior to the onset of symptoms in infants with genetically diagnosed SMA has the potential to prevent the impairment of motor function and allow infants to develop normally.

The effect of nusinersen on motor function in later-onset (Type II and Type III) SMA was assessed through the HFMSE (ambulatory and non-ambulatory subjects), the ULM (non-ambulatory subjects), and the 6MWT (ambulatory subjects) in the longitudinal analysis.

Although motor function in later-onset SMA was assessed by different endpoints as there is no single endpoint that may be applied with consistency throughout the spectrum, the results were consistent with those of the measures used in infants and demonstrated clinically meaningful improvement in motor function that was maintained over time, inconsistent with the natural history data.

The overall survival was greater in the nusinersen-treated subjects in studies CS3B and CS3A as compared to the results from the control group of CS3B. At the time of data cut-off, 29 subjects in Study CS3B (16 subjects [43%] in the control group and 13 subjects [18%] in the nusinersen group) and 4 subjects (20%) in CS3A had died. The hazard ratio from a Cox proportional hazards model adjusting for subject disease duration at screening was 0.37 indicating a 63% reduction in the risk of death relative to control with nusinersen treatment. As of the data cut-off for Study CS3A (26 January 2016), 15 subjects (75%), 13 with 2 SMN2 copies, were alive and continuing in the study. All of these subjects were >24 months of age, 7 were >30 months of age, and 2 were >36 months of age.

Consistent with the definition used in the natural history study by Finkel [Finkel 2014], subjects in CS3B and CS3A were considered to have met the criteria for permanent ventilation if they had a tracheostomy or they required at least 16 hours of ventilator support per day continuously for more than 14 (CS3A) or 21 days (CS3B) in the absence of an acute reversible event. Events were reviewed by the study investigators and in CS3B were confirmed by an independent adjudication committee. In the control group of CS3B, 13 subjects (32%) met the criteria for permanent ventilation. Among nusinersen-treated subjects, 18 subjects (23%) in and 3 subjects (%) in CS3A (CSR CS3A, Table 24) met these criteria.

Overall, the summary of main data across all studies confirms the trend of efficacy seen in the interim analysis of the pivotal study.

Clinical studies in special populations

No trial has been performed including adults at study start.

SMA was studied in infants and children. The oldest subject was 19 YO at the time of data cut-off time. This is adequate, since SMA types 1-3 are conditions that can incorporate infants, children and adolescents.

2.5.2. Discussion on clinical efficacy

The totality of data across multiple disease phenotypes of symptomatic and pre-symptomatic SMA provides consistent evidence of the positive effect of nusinersen in patients with SMA. The effects of treatment also appear to be consistent across investigational centres, assessors and multiple measures of disease activity.

Subjects in Studies CS3B and CS3A were identified as having infantile-onset SMA as they were not old enough to have achieved the milestone of independent sitting used to distinguish Type I SMA from less severe phenotypes. Based on the onset of symptoms at <6 months of age and documentation of 5q SMA homozygous gene deletion or mutation, it was considered that these subjects would most likely develop Type I SMA. While SMN2 copy number was not a pre-specified criterion for enrolment in the first study in infantile-onset SMA (CS3A), phenotype testing for SMN2 copy number performed after subjects were enrolled determined that 17 of the 20 subjects in CS3A had 2 SMN2 copies, consistent with the presumptive classification of Type I SMA. SMN2 copy number was only included as an inclusion criterion for studies CS3B and SM201 to improve the homogeneity of the study population. As required by the protocol, all subjects in Study CS3B had symptom onset at <6 months of age and 2 SMN2 copies and were also considered to represent a Type I SMA population.

In the context of the rapidly progressive decline observed in natural history studies of Type I SMA and observations from the control group of CS3B, the demonstrated benefits of early treatment with nusinersen provide strong support for the initiation of treatment as soon as possible after the onset of symptoms or the genetic diagnosis of SMA. Such an approach could have the potential to halt further disease progression that may occur during the interval between the onset of clinical symptoms and genetic confirmation of SMA. Further, as evidenced by the results of SM201 in presymptomatic infants with genetically documented SMA, the initiation of nusinersen treatment before the onset of clinical symptoms has the potential to delay or even prevent the progression of SMA disease and allow infants to develop normally.

Subjects with infantile-onset SMA treated with nusinersen in Studies CS3B and CS3A have achieved clinically meaningful improvements in motor milestones and motor function as compared to those of the subjects in the control group of Study CS3B and are well above the expectations for patients with Type I SMA receiving standard of care in natural history studies. These improvements include attainment of motor milestones such as independent sitting, standing, and walking, which are in stark contrast to the steady loss of motor milestones that is the hallmark of Type I SMA demonstrated by the control group of Study CS3B and natural history data.

Improvement relative to control in motor milestones, CHOP INTEND, and CMAP was observed as early as Day 64 in Study CS3B; however, due to differences in the sensitivity of some assessments, clear separation for some endpoints did not occur until the 6-month visit after the initiation of treatment. This suggests that maximum efficacy of nusinersen may not be reached until completion of the loading dose regimen of 4 doses over 2 months and further emphasises the importance of early treatment for maximum benefit.

In symptomatic subjects with infantile onset SMA, where health status is changing rapidly, CMAP and CHOP INTEND provide sensitive endpoints that can discern small changes.

Conversely, endpoints such as motor milestones, permanent ventilation, and event-free survival that are more distal from the mechanism of action would not be expected to discern a change quite as early as CMAP and CHOP INTEND.

Electrophysiological measures of neuronal innervation of distal muscle groups assessed by CMAP demonstrated improvements in nusinersen-treated subjects that are in direct contrast to the natural history of the disease. In addition, the improvement in CMAP was directly linked with the magnitude of improvement in motor milestones and motor function in Study CS3A.

The ongoing studies in infantile-onset SMA support that treatment with nusinersen has the potential to prolong overall and event-free survival. Time to death or permanent ventilation was significantly prolonged in subjects treated with nusinersen. Overall, there was a 47% reduction in the risk of death or permanent ventilation compared to control. While the median time to death or permanent ventilation in the control group of CS3B was consistent with previous natural history studies (median of 6 months), a median time to death or permanent ventilation could not be estimated in CS3A due to the occurrence of too few events. Subjects in Study CS3A have received long-term treatment with nusinersen for close to 3 years. At the time of the data cut-off, 15 subjects (75%) were alive and remained in the study. Among these subjects, the youngest was 24.6 months of age, and the oldest subject was 39.2 months of age. All 15 subjects in Study CS3A were >2 years of age, which exceeds the life expectancy reported for most infants with 2 SMN2 gene copies and symptom onset at <6 months of age.

Following the data cut-off for CS3A, 1 subject has died and another has met the criteria for permanent ventilation. At the time of this submission, 11 subjects in Study CS3A are alive without permanent ventilation, supporting that nusinersen has the potential to both prolong survival and reduce the comorbidity of SMA. These subjects continue to achieve motor milestones and experience improvement in motor function, and there is no evidence of a lessening of effect over time.

The results from the studies in infantile-onset SMA are corroborated by the study in pre-symptomatic infants with genetically confirmed SMA who are also achieving motor milestones and developing motor function that are in contrast to the experience of their siblings with SMA and the natural history of the disease. Baseline CHOP INTEND and CMAP scores, as well as motor milestone development, for these infants are consistent with those of healthy infants without SMA and support that early treatment, even prior to the onset of clinical symptoms, may be warranted for subjects with genetically diagnosed SMA.

Interim results submitted from study CS4, an ongoing, randomized, controlled, double-blind study of nusinersen in 126 subjects with later-onset SMA show that subjects treated intrathecally with nusinersen achieved sustained and clinically meaningful benefits compared with a control group of subjects who received a sham procedure. These benefits included statistically significant greater gains in motor function as measured by HFMSE, as well as an improvement in upper limb functional ability. This is supported by results from the longitudinal assessment of subjects with later-onset Type II and Type III SMA who first received nusinersen in Study CS2 demonstrate additional milestone attainment and maintenance of effect over time in motor function, upper limb strength, and ambulation, all of which are in contrast to the decline typically seen in these patients following symptom onset. A number of subjects have achieved clinically meaningful improvement in overall motor function and

ambulation. Notably, 1 subject with Type II SMA first gained the ability to walk in Study CS12. These results were also corroborated by the data provided from study CS4 in later-onset patients.

Across the broad population of presymptomatic and symptomatic patients included in the clinical development program, all of the key clinical outcome endpoints, including multiple functional and survival endpoints, move in the same direction of progressive improvement. The consistency among the various key clinical outcome endpoints, each of which provide independent measures central to the pathology of SMA, support significant efficacy in both symptomatic and presymptomatic subjects and across infantile-onset and later-onset SMA.

The evidence for maintenance of efficacy in the long term was not available as a part of this submission and post-authorisation measures have been requested to address this.

2.5.3. Conclusions on the clinical efficacy

The majority of treated infants with infantile-onset SMA achieved improvement, with a great proportion reaching a clinically meaningful and continued improvements in motor milestones (e.g. independent sitting, standing and walking), muscle strength, and motor function that exceed those of the sham control-treated infants in Study CS3B and the natural history of the disease, where a progressive loss of motor function is observed. Data from treated pre-symptomatic infants with genetically confirmed SMA show that they are achieving motor milestones and developing muscle strength and motor function with the nusinersen treatment that are more consistent with those of normal infants than symptomatic infants with SMA. Subjects with later-onset SMA who received nusinersen achieved and maintained motor function across multiple measures and milestones such as the ability to walk that are completely inconsistent with natural history.

The difference in magnitude across endpoints is in alignment with the understanding of the pathology of SMA, where deficiency in SMN protein leads to disease progression from events more proximal to the action of SMN such as declines in motor neuron health as measured by CMAP and CHOP INTEND, through those that are more distal, as measured by motor milestones and event-free survival.

Data from the ongoing studies in infantile-onset SMA support that treatment with nusinersen has the potential to prolong overall and event-free survival. They also support the need for early treatment with nusinersen, since shortly after the loading phase was complete, the rate of ventilation among nusinersen-treated subjects separated from that of the controls.

Taken together, these data demonstrate consistently that nusinersen has produced meaningful benefits across a broad range of SMA phenotypes. The consistency among the various key clinically meaningful endpoints, each of which provide independent measures central to the pathology of SMA, support significant efficacy in both pre-symptomatic and symptomatic subjects and across infantile-onset and later-onset SMA.

The current studies do not provide evidence that the treatment effects persist with indefinite length of treatment, neither in infantile nor in later onset SMA.

The CHMP considers the following measures as key to the B/R ratio of the product and necessary to address issues related to efficacy:

- PAES: In order to evaluate the long term efficacy and safety of Nusinersen in symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 3, open-label extension study (SHINE, CS11).
- PAES: In order to evaluate the long term efficacy and safety of Nusinersen in pre-symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 2, open-label study (NURTURE (SM201)).

Along with the needed data on efficacy and safety to be derived from the above studies, their protocols include PK data collections. These are being used to collect the required PK data in order to enable the company to make future decisions about whether any dose adjustment, or further investigation in to dose adjustment, is required. CSF data are being collected from both these studies and will be used in the comprehensive update to the Pop PK model.

Additionally, the following measures will contribute to the better understanding of the efficacy, safety and clinical applicability of the product:

- EMBRACE (SM202) - Phase 2, randomized, double-blind, sham- procedure controlled study to assess the safety, tolerability, PK, and efficacy in patients who were not eligible to participate in studies CS3b or CS4
- Registries initiative - Collaborations with existing disease registries across the globe to capitalize on the available clinical experts and networks and modifying to be able to collect appropriate information and take in to account availability of medicinal product(s).
- Exploring higher doses - The company is requested to explore whether higher doses of nusinersen could show greater efficacy.

2.6. Clinical safety

Patient exposure

The safety data that form the basis of the marketing application for nusinersen were reported in infants and children in controlled studies as well as open-label studies. Subjects were classified as pre-symptomatic (exhibiting no symptoms of SMA) or symptomatic at the time of enrolment and were further classified depending on the age at diagnosis (<6 and ≥ 6 months of age). Six different pools of subjects (Pools A through F) were created for the integrated safety analysis based on the presence or absence of symptoms and time of first symptom onset. While the age of symptom onset and severity of disease is influenced by SMN2 copy number, the mechanism of action of nusinersen is the same across all patients, regardless of the number of gene copies or age at onset of disease. Therefore, when evaluating the safety of nusinersen, stratification by SMN2 copy number was not performed.

The presentation of data for the integrated safety analysis (Pools A through F) is shown in the Table 7 below.

Table 6 Studies Used for the Integrated Safety Analysis in Subjects With SMA

Description	Study (Duration)	Treatment Groups in Individual Study	Sample Size
Pool A: Open-label, uncontrolled study in infants with presymptomatic SMA	SM201 (868 days/29 months)	ISIS 396443 12 mg	ISIS 396443 [17]
Pool B: Blinded, controlled study in infantile-onset SMA	CS3B (394 days/13 months)	ISIS 396443 12 mg Sham-procedure control	ISIS 396443 12 mg [80] Sham-procedure control [41]
Pool C: Blinded, controlled and open-label, uncontrolled studies in all ISIS 396443-treated infantile-onset SMA	CS3B (394 days/13 months)	ISIS 396443 12 mg	ISIS 396443 [100]
	CS3A (1352 days/45 months)	ISIS 396443 6 mg × 3 then 12 mg × 9 ISIS 396443 12 mg × 12	
Pool D: Blinded, controlled and open-label, uncontrolled studies in all ISIS 396443-treated infants diagnosed with SMA (presymptomatic SMA and infantile-onset SMA) in Pools A and C	SM201 (868 days/29 months)	ISIS 396443 12 mg	ISIS 396443 [117]
	CS3B (394 days/13 months)	ISIS 396443 12 mg	
	CS3A (1352 days/45 months)	ISIS 396443 6 mg × 3 then 12 mg × 9 ISIS 396443 12 mg × 12	
Pool E: Open-label, uncontrolled studies in later-onset SMA	CS1, CS10, CS2, CS12*	Combinations of doses from different studies as highlighted in Figure 2	ISIS 396443 [56]
Pool F: Blinded, controlled and open-label, uncontrolled studies in all ISIS 396443-treated subjects with SMA in Pools A, B, C, D, and E	SM201 (868 days/29 months)	ISIS 396443 12 mg	ISIS 396443 [173]
	CS3B (394 days/13 months)	ISIS 396443 12 mg	
	CS3A (1352 days/45 months)	ISIS 396443 6 mg × 3 then 12 mg × 9 ISIS 396443 12 mg × 12	
	CS1, CS10, CS2, CS12	Combinations of doses from different studies	

*The safety profile of the unique subjects in CS1 and CS2 from the parent and extension studies were combined.

In the data being reported, the overall exposure to nusinersen was 246.08 subject-years in 173 subjects:

- Infantile-Onset SMA: Study CS3B
 - Study CS3B was stopped prematurely due to the efficacy observed in the nusinersen-treated group compared to the sham-control group during an interim analysis. Safety data are presented with a date of 21 November 2016 for the last patient last visit and represent the final data for Study CS3B. Median time on study was 280.0 and 187.0 days for the nusinersen-treated and sham-control groups, respectively. The total number of subject-years on study was 83.43 (58.04 subject-years in the nusinersen-treated group and 25.39 subject-years in the sham-control group) [
- Infants With Presymptomatic SMA: Study SM201

- A total of 25 subjects were screened, of whom 20 subjects were enrolled and treated. Nineteen subjects (95%) received 3, 4, 5, 6, or 7 doses, and 1 subject (5%) had 1 dose; the median number of doses was 6.0
- For subjects with later-onset SMA, of the 126 subjects who received treatment, 54 subjects (43%) completed the study (42% of subjects in the nusinersen-treated group and 45% of subjects in the sham-control group) and 114 subjects (90%) had completed treatment (89% in the nusinersen-treated group and 93% in the sham-control control group). No subjects discontinued treatment or withdrew from the study. As of the data cutoff date, 49 out of 84 subjects (58%) in the nusinersen group and 23 out of 42 subjects (55%) in the control group were continuing in the study. Time on study ranged from 170 to 470 days (approximately 6 to 16 months), with a median of 416 days (approximately 14 months). Total subject-years on study were 134.06.

Of the 260 patients who received Spinraza up to a maximum of 4 years, 154 patients received treatment for at least 1 year.

Additionally, approximately 170 subjects are participating in other ongoing blinded studies (CS4, SM202 and CS11 [blinded during the loading phase]).

Only limited data (e.g., SAEs, deaths) from subjects participating in some blinded studies (CS4, CS11, and SM202) have been included to protect study integrity as these studies are still ongoing and therefore remain blinded.

Adverse events

The safety of nusinersen has been analysed using integrated presentations of data from studies in infants and children with SMA. A total of 1433 adverse events (AEs) were reported in 92 subjects (92%) in Study CS3A and CS3B combined, 94 AEs were reported in 13 subjects (76%) in Study SM201, and 682 AEs were reported in 56 subjects (100%) in the later-onset SMA studies.

The commonly reported AEs in infants and children treated with nusinersen in the clinical studies were either consistent with events occurring in the natural history of SMA, consistent with common conditions in the general population, consistent with common age-appropriate events, or consistent with events observed in the context of lumbar puncture.

Subjects who were pre-symptomatic for SMA had fewer AEs reported compared with symptomatic infants, which is consistent with a healthier baseline condition at the time of enrolment.

Infants Diagnosed with SMA

A total of 100 subjects with symptomatic infantile-onset SMA were treated with nusinersen in Studies CS3B and CS3A.

In Study CS3B, adverse events (AEs) were reported in 96% of subjects who received nusinersen treatment and 98% of subjects who received sham (control) treatment. A lower percentage of

subjects in the nusinersen group had a severe or moderate event (nusinersen vs. control: 88% vs. 95%), a severe event (56% vs. 80%), or an SAE (76% vs. 95%). No SAEs were considered by the Investigator to be related or possibly related to the study treatment. A lower percentage of nusinersen-treated subjects discontinued treatment due to an AE (16% vs. 39%). All discontinuations, in both groups, were due to fatal SAEs.

The most commonly reported AEs occurred in the system organ classes (SOCs) of infections and infestations, and respiratory, thoracic and mediastinal disorders. The most commonly reported AEs in 20% or more of subjects (nusinersen versus control) were respiratory and/or infectious in nature: upper respiratory tract infection (nusinersen vs. control: 30% vs. 22%), respiratory distress (26% vs. 29%), pneumonia (29% vs. 17%), respiratory failure (25% vs. 39%), atelectasis (23% vs. 29%), acute respiratory failure (14% vs. 24%), viral upper respiratory tract infection (10% vs. 17%), oxygen saturation decreased (13% vs. 24%) and cough (11% vs. 20%). Other commonly reported events include pyrexia (56% vs. 59%), constipation (35% vs. 22%), vomiting (18% vs. 20%), gastroesophageal reflux disease (13% vs. 20%), and dysphagia (11% vs. 20%). The nature of these events in the nusinersen-treated arm was generally consistent with those reported in the sham-control arm, and in line with what is expected for subjects with infantile-onset SMA. Overall, there was no safety concern emerging from close monitoring following dosing. There was no notable difference in the overall incidence of AEs between the loading dose and maintenance dose periods. When measured by 90-day intervals, the incidence of AEs and SAEs showed a small decrease over time. There was no new type of AEs appearing with longer exposure. The results from the open-label study CS3A were similar.

Based on preclinical findings of hippocampal vacuoles, a medical review was performed for AEs suggestive of epilepsy, which might indicate hippocampal pathology in human subjects. There was no epilepsy reported. There was 1 event of seizure reported in an nusinersen-treated subject, in the context of brain injury.

In Study SM201 (CS5, pre-symptomatic subjects):

A total of 16 out of 20 subjects (80%) experienced at least 1 AE, and the most common AEs were upper respiratory tract infection, pyrexia, and nasopharyngitis.

Most subjects experienced AEs that are considered either mild (5 subjects [25%]) or moderate (9 subjects [45%]) in severity, and only 2 subjects (10%) with 3 events experienced severe AEs; 3 subjects (15%) experienced AEs considered by the Investigator to be possibly related to the study treatment, which were muscular weakness and weight bearing difficulty in 1 subject; hyperreflexia and tachycardia in 1 subject; and pyrexia, ALT and AST increased with eosinophil count, lymphocyte count, and WBC count increased in 1 subject. Five subjects (25%) experienced AEs considered by the Investigator to be related to the LP procedure, which were post LP discomfort and subdural haematoma in 1 subject; post LP syndrome, spinal cord haematoma, and hypertension in 1 subject; extradural haematoma, weight bearing difficulty, tachycardia, and muscular weakness in 1 subject; epidural haemorrhage, spinal subarachnoid haemorrhage, hyperreflexia, and tachycardia in 1 subject; and post procedural swelling in 1 subject.

No deaths were reported, and no subjects discontinued study treatment or withdrew from the study.

SAEs of bronchitis, choking, and pneumonia were reported by 1 subject; pneumonia was reported by 1 subject; urinary tract infection was reported by 1 subject; failure to thrive was reported by 1 subject; pyrexia was reported by 1 subject; and abdominal distension, respiratory distress, dehydration, rhinovirus infection, and post LP syndrome were reported in 1 subject. No subjects

experienced SAEs that led to discontinuation of study treatment or withdrawal from the study. Overall, the events reported with an incidence of more than 10% in both infantile-onset SMA studies were similar in type and frequency. The commonly reported AEs were either generally consistent with those expected in a population with infantile-onset SMA, consistent with common conditions occurring in the general population, or consistent with age-appropriate events in these studies.

Subjects with Later Onset SMA

Fifty-six subjects with later-onset SMA, aged 2 to 15 years at time of first dose, were treated with nusinersen in Studies CS1, CS2, CS10 and CS12.

Study CS4

Of the 126 subjects who received treatment, 54 subjects (43%) completed the study (42% of subjects in the nusinersen-treated group and 45% of subjects in the sham-control group) and 114 subjects (90%) had completed treatment (89% in the nusinersen-treated group and 93% in the sham-control control group). No subjects discontinued treatment or withdrew from the study. As of the data cutoff date, 49 out of 84 subjects (58%) in the nusinersen group and 23 out of 42 subjects (55%) in the control group were continuing in the study. The median number of doses received was 4 (minimum, maximum: 3, 4), and 116 subjects (92%) had received 4 doses or underwent sham procedure. Time on study ranged from 170 to 470 days (approximately 6 to 16 months), with a median of 416 days (approximately 14 months). Total subject-years on study were 134.06.

Treatment-emergent adverse events (TEAEs) were reported in 93% of subjects who received nusinersen treatment and 100% of subjects who received sham (control) treatment. A lower percentage of subjects in the nusinersen group had a severe or moderate event (nusinersen vs. control: 42% vs. 48%), a severe event (5% vs. 7%), or an SAE (14% vs. 26%). No SAEs were considered by the Investigator to be related or possibly related to the study treatment. No subjects in either treatment group discontinued treatment due to an AE.

Events reported in more than 20% of subjects in either arm were upper respiratory tract infection (27% nusinersen vs. 38% sham-control), nasopharyngitis (20% vs. 36%), cough (24% vs 21%), pyrexia (39% vs 36%), vomiting (25% vs 10%), back pain (25% vs 0%), and headache (27% vs 7%). The majority of the AEs were considered to be either related to SMA disease, common events in the general population, or events related to the lumbar puncture procedure, consistent with the observations in the open-label trials. Twenty-five subjects (30%) in the nusinersen group vs. 3 subjects (7%) in the sham-control group had a possibly-related or related AE in the opinion of the investigator. Fourteen out of the 25 subjects in the nusinersen group with a possibly-related or related AE experienced an event likely associated with the lumbar puncture procedure, such as headache, back pain, post lumbar puncture syndrome, vomiting or procedural nausea, all of which were mild or moderate in severity. The AE of procedural nausea is the only event in those 25 subjects that was considered related to study drug in the opinion of the Investigator. 14% of subjects in the nusinersen group vs. 26% of subjects in the sham control group. The most common SAE was pneumonia in both groups (2% in the nusinersen group vs. 12% in the sham-control group).

There were no deaths or TEAEs with a fatal outcome.

Overall, the nature of the AEs reported in the later-onset SMA studies were either consistent with what is expected for the Type II and Type III SMA population, consistent with common conditions in the general population, or consistent with events observed in the context of the lumbar puncture procedure. The subjects in these later-onset studies were older and therefore had better verbal communication skills than subjects in the infantile-onset studies; thus explaining a higher incidence of reported lumbar puncture-related events in comparison to infants

Analysis of Adverse Events Over Time

Infants Diagnosed with SMA

An analysis of AEs over time by 90-day intervals and by loading and maintenance phase was performed for subjects in Studies CS3B and CS3A, both separately and combined; these analyses were not performed for Study SM201 due to the small number of subjects who were followed for a relatively short time on study. An analysis of events reported during the 24 and 72 hours post-lumbar puncture procedure was performed for subjects in all three studies. This analysis was specifically performed to examine lumbar puncture related complications as most lumbar puncture related events occur within a 72-hour timeframe. Certain events commonly seen in the context of a lumbar puncture such as headache and back pain could be underreported in infants as compared to children due to the difference in verbal communication skills.

In Study CS3B, the incidence of AEs was generally consistent over time. No new types of events were identified with longer drug exposure. In Study CS3A, when assessed at 90-day intervals, the incidence of AEs tended to decrease over time. This may reflect subjects in Study CS3A being on study longer and experiencing continued improvement.

In both Study CS3B and Study CS3A, there were no notable differences in the types of AEs reported during the loading and maintenance dosing periods. The analysis of events reported during the 24 and 72 hours post lumbar puncture procedure in Studies CS3B, CS3A and SM201 revealed no safety concerns.

Subjects with Later-Onset SMA

An analysis of events reported over time by 90-day intervals and by loading and maintenance phase was not performed for subjects in the later-onset SMA studies, as these subjects experienced long gaps in time between studies. An analysis of events reported during the 24 and 72 hours post lumbar puncture procedure was performed. No safety concerns emerged from close monitoring following the lumbar puncture procedure, and only events expected in the context of lumbar puncture were reported.

The SmPC guideline requires that specific aspects of the treatment related to the use of the medicinal product or its effects should be mentioned and that all adverse reactions (and only adverse drug reactions) be listed in section 4.8. Since this product is for intrathecal use, adverse reactions linked with this route of administration should be communicated as they are an intrinsic part of the use and safety of the medicine. The fact that they are linked to the route of administration required special attention and discrimination in SmPC and information characterising specific adverse reactions which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice (including frequency, time of onset and reversibility).

Analysis of Adverse Events by Severity

In Studies CS3B and CS3A, most events were mild or moderate in severity, and the few severe events were respiratory in nature (e.g. respiratory failure and respiratory distress). The incidence of severe events was lower in the nusinersen-treated group (nusinersen vs. control: 56% vs. 80%). Many of the most commonly reported events were rated severe in intensity: respiratory failure (18% vs. 37%), acute respiratory failure (14% vs. 22%), respiratory distress (15% vs. 20%), pneumonia (13% vs. 12%), and atelectasis (8% vs. 10%). In Study SM201, no severe AEs were reported.

In subjects with later-onset SMA, most events were mild or moderate in severity, and the only severe event reported by more than 1 subject was viral pneumonia in 2 subjects.

Adverse Events by Relationship to Study Treatment

Infants Diagnosed with SMA

In Study CS3B, no AEs were considered by the Investigators to be related to study treatment. Only a few events were considered to be possibly related, and the incidence of these events was slightly lower in nusinersen-treated subjects versus controls: (11% vs. 15%). These possibly related AEs were evaluated on an individual basis and causality to nusinersen was excluded. For medical review, events classified by the Investigator as “possible” or “related” were considered to be related to the study treatment. No AEs were considered by the Investigators to be related to the study treatment (Table 5). Very few events were considered to be possibly related to the study treatment (nusinersen vs. control: 10 events in 9 subjects vs. 7 events in 6 subjects) [Table 9]. The incidence of AEs thought by the Investigator to be possibly related to treatment was lower in the nusinersen-treated group (nusinersen vs. control: 11% vs. 15%)

In Study CS3A, 2 AEs, both mild in severity, were considered by the Investigator as related to study treatment. These included a transient neutropenia in 1 subject and vomiting in 1 subject. Both of these AEs resolved.

In Study SM201, no AEs were considered by the Investigator to be related to study treatment. Three subjects (18%) experienced AEs that were considered by the Investigator to be possibly related to study drug. These events included muscular weakness and weight bearing difficulty in 1 subject, hyperreflexia and tachycardia in 1 subject, and ALT and AST increased and pyrexia, ALT and AST increased with eosinophil count, lymphocyte count, and WBC count increased in 1 subject. Study SM201 was also designed to be able to capture a distinction in relatedness to the lumbar puncture procedure. Five subjects (29%) experienced AEs considered by the Investigator to be related to the lumbar puncture procedure. These included post lumbar puncture syndrome and spinal cord hematoma in 1 subject, epidural hemorrhage and spinal subarachnoid hemorrhage in 1 subject, extradural hematoma and weight bearing difficulty in 1 subject, postprocedural swelling in 1 subject, and subdural hematoma in 1 subject. All of these were associated with failed lumbar puncture attempts (sometimes multiple failed attempts), and resolved via standard of care.

Subjects with Later-Onset SMA

In subjects with later-onset SMA, 7 AEs in 6 subjects were assessed as possibly related to study treatment. These included headache in 2 subjects, and CSF White Blood Cell (WBC) count increased, heart rate increased, palpitations, paresthesia and post lumbar puncture syndrome in 1 subject each.

These events appear to be more likely related to the LP procedure. More serious complications associated with lumbar puncture such as serious infections (e.g. meningitis), have not been observed in the nusinersen clinical studies as of the cut-off date.

There is no information provided by the Applicant on cognition, learning abilities or attention for infants / children / adolescents with SMA treated with nusinersen.

Serious adverse events and deaths

Deaths

As of the cutoff date for the original submission, a total of 29 deaths were reported in the CS3B study. While no deaths were reported in subjects with pre-symptomatic SMA and later-onset SMA, there were several deaths reported in subjects with infantile-onset SMA, where death can be considered an expected outcome in this severe form of the disease. In Study CS3B, a total of 29 subjects died including 13 subjects in the nusinersen-treated arm and 16 subjects in the sham-control arm. The mortality rate in nusinersen-treated subjects was less than that in sham-control subjects (15% versus 32%). The applicant provided data from the final analysis of CS3B, which supports the efficacy data from the interim analysis. As of the cutoff date for the final analysis, 31 subjects (39%) in the nusinersen group and 28 subjects (68%) in the control group had died or required permanent ventilation. The separation was clear, between the 3 and 6 months, when the loading doses have been finished.

Deaths reported in the infant population were consistent with the typical causes of death in the setting of this rapidly progressive and fatal form of SMA, both for nusinersen-treated and sham-control subjects. However, the fatality rate for SIS 396443-treated subjects was less than half the fatality rate of sham-control subjects (nusinersen vs. control: 16% vs. 39%).

Of the 16 sham-control subjects, 7 subjects died from respiratory failure, 2 from respiratory distress and 1 from acute respiratory failure. A further 3 subjects died from cardiorespiratory arrest, 2 from hypoxic condition and a single subject died of unknown causes.

In Study CS3A, a total of 4 subjects died; 2 subjects died due to respiratory failure, 1 due to accidental asphyxia and 1 due to metapneumovirus infection.

The causes of death in both infantile-onset SMA studies were mostly respiratory in nature and were consistent with the causes of death typically observed in infants with Type I SMA. None were considered related to study treatment.

One additional death occurred after the cut-off date for the integrated safety analysis and involved a 3 year old girl in Study CS3A who developed a mucous plug which led to cardiac arrest and irreversible hypoxic ischemic injury; life support was withdrawn.

Since the nature of the event is consistent with other events observed in the context of SMA, the overall safety assessment remains unchanged.

Death in subjects with SMA is not unexpected. Across all deaths reported in subjects in the nusinersen clinical development program, none were considered related to treatment and all occurred in subjects with the most severe SMA phenotype.

Post-mortem examination was done in a limited number of cases. There is no evidence of hippocampal pathology although this is noted as a concern in the non clinical studies; furthermore no case of hypoxic injury was related to seizure (reflective of hippocampal lesion).

Serious Adverse Events

No SUSARs have been reported during the nusinersen clinical development program. The majority of SAEs reported were events expected in the context of SMA disease or events observed in the context of lumbar puncture.

Infants Diagnosed with SMA

In Study CS3B, 61 subjects (76%) in the ISIS 396643 group and 39 subjects (95%) in the control group experienced at least 1 SAE. The most common SAEs were respiratory distress (nusinersen vs. control: 26% vs. 20%), respiratory failure (25% vs. 39%), pneumonia (24% vs. 12%), acute respiratory failure (14% vs. 22%), atelectasis (18% vs. 10%), pneumonia aspiration (10% vs. 12%), rhinovirus infection (9% vs. 5%), pneumonia viral (8% vs. 5%), and cardio-respiratory arrest (6% vs. 12%).

In Study CS3A, a total of 16 subjects experienced at least 1 SAE. These included respiratory distress (30%), respiratory failure (25%), acute respiratory failure (20%), pneumonia (20%), rhinovirus infection (20%) bronchiolitis (15%), metapneumovirus infection (10%), apnoea, (10%) atelectasis (10%, pneumonia aspiration (10%) (10%), pneumonia viral (10%) and viral infection (10%). All other SAEs were reported in a single subject each (5%) and included asphyxia, aspiration, hypoventilation, hypoxia, pneumomediastinum, corona virus infection, enterovirus infection, lower respiratory virus infection viral, parainfluenzae virus infection, pneumonia bacterial, pneumonia pseudomonas aeruginosa, respiratory syncytial virus bronchiolitis, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection, bradycardia, cardiac arrest, cardiorespiratory arrest, cyanosis, pneumopericardium, failure to thrive, hyponatremia, vomiting, synovitis and convulsion.

In Study SM201, a total of 5 subjects (29%) reported an SAE. These SAEs included bronchitis, pneumonia, failure to thrive, and urinary tract infection reported in 1 subject each and post lumbar puncture syndrome, abdominal distension, and respiratory distress all reported in a single subject.

The types of SAEs reported in subjects in the infantile-onset studies were consistent with events reported in the context of Type I SMA.

Subjects with Later-Onset SMA

In subjects with later-onset SMA in the open-label studies, 14 SAEs were reported, which included respiratory failure, acute respiratory failure, dyspnea, atelectasis, pneumonia, metapneumovirus infection, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia viral, gastroenteritis, post lumbar puncture syndrome, and drug hypersensitivity (to fentanyl). All SAEs were reported in one subject each, with the exception of post lumbar puncture syndrome and pneumonia viral which were reported in 2 subjects. In the controlled study CS4, twelve subjects (14%) in the nusinersen group and 11 subjects (26%) in the control group experienced at least 1 SAE. The most common SAEs were pneumonia (nusinersen vs. control: 2% vs. 12%), pneumonia viral (2% vs. 0%), and respiratory distress (2% vs. 5%). No SAE was reported by more than 2 subjects in the nusinersen group.

The types of SAEs seen in subjects with later-onset SMA were consistent with events reported in the context of Type II or Type III SMA.

Other Serious Adverse Events in Subjects in Other Populations

Overall, 75 SAEs were reported in 31 subjects in Studies CS4, CS11, and SM202 as of the data cut-off date for the original filing. The majority of the SAEs were respiratory in nature.

Adverse Events Leading to Discontinuation

In Studies CS3B and CS3A, all AEs that led to discontinuation were events with a fatal outcome. No AEs leading to discontinuation have occurred in infants with pre-symptomatic SMA or in subjects with later-onset SMA.

Adverse Drug Reactions

A comprehensive approach was undertaken to identify potential adverse drug reactions (ADR) for nusinersen, which took into consideration differences in AE incidence from a randomized, controlled study, as well as Investigator relatedness, lumbar puncture procedure relatedness, and a thorough medical review of the events in the context of the natural history of the disease. In addition, medical review of AEs from all open-label studies was performed.

AEs with $\geq 5\%$ higher incidence in nusinersen-treated vs sham-controlled subjects in Study CS3B were identified (the 5% higher incidence threshold was chosen based on the 2:1 subject randomization and the size of the study). Events reaching the threshold were assessed for risk factors/confounders or alternative explanations to account for the observed higher incidence.

In addition, for Study CS3B and the other open-label studies, this assessment was complemented by medical review of additional AEs (as listed below) to identify any other potential ADRs:

- Events that may be related to preclinical findings – assessed for plausibility as ADRs
- Events assessed by the Investigator as related or possibly related to study drug
- Events possibly related to the lumbar puncture procedure (in infants includes assessment of AEs occurring within 72 hours of drug administration)

After thorough medical review of AEs was performed by the Sponsor, none were considered related to nusinersen, and the majority of the events were considered to be related to either SMA disease, common events in the general population, age-appropriate events, or events related to the lumbar puncture procedure.

Therefore, no ADRs were identified for nusinersen.

Data presentation in prescribing information (proposed in initial filing):

No ADRs for nusinersen were identified. However, to adequately provide information to physicians that is useful in making treatment decisions and monitoring and advising patients, the prescribing information will include a table of common AEs occurring in at least 20% of nusinersen-treated vs sham-controlled subjects even though these events are not considered drug-related. Events with $\geq 5\%$ higher incidence in nusinersen-treated vs sham-controlled subjects or in the text below as follows:

**Table 7 Summary of Adverse Events by System Organ Class and Preferred Term
Occurring in at Least 20% of Patients Treated with nusinersen or Sham in Study
CS3B.**

MedDRA System Organ Class	MedDRA preferred term	ISIS 396443 N=80 (100%)	Sham N=41 (100%)	ISIS 396443 Frequency category*	
				Very Common (≥1/10)	Common (≥1/100 - <1/10)
Respiratory, thoracic and mediastinal disorders	Respiratory distress^	19 (24%)	14 (34%)	Very Common	
	Respiratory failure^	17 (21%)	14 (34%)	Very Common	
	Atelectasis^	15 (19%)	9 (22%)	Very Common	
	Acute respiratory failure^	11 (14%)	8 (20%)	Very Common	
	Cough^	6 (8%)	8 (20%)		Common
Infections and infestations	Upper respiratory tract infection^	20 (25%)	9 (22%)	Very Common	
	Pneumonia^	17 (21%)	6 (15%)	Very Common	
	Viral upper respiratory tract infection	10 (13%)	8 (20%)	Very Common	
Gastrointestinal disorders	Constipation^	24 (30%)	9 (22%)	Very Common	
	Vomiting^	12 (15%)	8 (20%)	Very Common	
	Dysphagia	9 (11%)	8 (20%)	Very Common	
General disorders and administration site conditions	Pyrexia^	39 (49%)	22 (54%)	Very Common	
Investigations	Oxygen saturation decreased	8 (10%)	9 (22 %)	Very Common	

In addition to the events indicated in the Table above, the most common AEs reported in study CS3A ($\geq 20\%$ of nusinersen treated patients, n=20) were nasal congestion (35%), increased upper airways secretion (25%), chronic respiratory failure (20%), hypoxia (20%), nasopharyngitis (30%), otitis media (30%), rhinovirus infection (30%), respiratory tract infection (25%), viral infection (20%), gastro-esophageal reflux disease (30%), diarrhoea (25%), teething (20%), joint contracture (40%), scoliosis (35%), kyphosis (20%), rash (25%), dermatitis diaper (20%), and pain (20%).

In Study SM201 the adverse event reported in more than 20% of the nusinersen treated pre-symptomatic patients (n=17) was upper respiratory tract infection (35%).

In the integrated analysis of 4 open-label studies (Study CS1, CS2, CS10, and CS12, n=56) in later-onset SMA the most common AEs reported in more than 20% of the nusinersen treated patients (regardless of causality) were upper respiratory tract infection (48%), nasopharyngitis (29%), vomiting (21%), pyrexia (29%), post lumbar-puncture syndrome (41%), back-pain (41%), scoliosis (27%), and headache (50%).

Adverse reactions related to lumbar puncture procedure reported in CS4 (later onset SMA) with an

incidence at least 5% higher in patients treated with Spinraza than sham-control

MedDRA System Organ Class	MedDRA preferred term	Spinraza Frequency Category, n=84
Nervous system disorders	Headache*	Very Common
Gastrointestinal disorders	Vomiting*	Common
Musculoskeletal and connective tissue disorders	Back pain*	Very Common

*Adverse events considered related to the lumbar puncture procedure. These events can be considered manifestations of post-lumbar puncture syndrome.

Safety Areas of Special Interest

No safety areas of special interest were identified based on consideration of the mechanism of action of nusinersen, data from nonclinical studies, therapeutic class effects (e.g. severe thrombocytopenia), and underlying conditions in SMA that might be affected by treatment with nusinersen.

SMA201: Number of Successful and Failed Lumbar Punctures

Of 20 subjects, the LP procedure was successful in 19 subjects (95%); of those 19 subjects, LP was successful on the first attempt in 13 subjects (65%), after the second attempt in 4 subjects (20%), after the third attempt in 1 subject (5%), and after >3 attempts in 1 subject (5%; Table 20). Five attempts were made for the subject with whom the LP procedure was not successful on the first attempted LP day; LP was successful with ultrasound guidance after 3 attempts on the second attempted LP day.

Laboratory findings

There were no patterns or trends observed in abnormalities of CSF safety laboratory values or blood chemistry, hematology or urinalysis parameters. There were no adverse changes in vital signs, or physical examination findings that were considered related to treatment with nusinersen.

. A warning regarding a class effect on platelets and renal function has been added to the SmPC.

Safety in special populations

The highest age which has been exposed to nusinersen is 19 years old. Therefore all adverse events have occurred in patients up to 19YO.

Intrinsic Factors

Age Groups – Integrated

The age subgroups were <90 (27 subjects) and ≥ 90 days of age (90 subjects), for a total of 117 subjects treated with nusinersen (Pool D).

The number and percentage of subjects who experienced at least 1 AE were 22 subjects (81%) in the <90 days of age subgroup and 83 subjects (92%) in the ≥ 90 days of age subgroup. Overall, the incidence of AEs by SOC was higher in the ≥ 90 days of age subgroup than the <90 days of age

subgroup, with the exception of AEs in the SOC of blood and lymphatic system disorders, which was $\geq 10\%$ higher in the <90 days of age subgroup. The overall lower incidence of AEs in the <90 days of age subgroup is likely influenced by the presence of the pre-symptomatic subjects who were contributing to this cohort. At baseline, these subjects are healthier than subjects who are symptomatic with infantile-onset SMA. Indeed when pre-symptomatic subjects are removed from the <90 days of age cohort, these differences become less apparent between the 2 age groups. Some respiratory infections became more common in the <90 days of age cohort, consistent with young symptomatic subjects having a more severe disease.

The age subgroups included children <6 years of age (28 subjects) and children ≥ 6 years of age (28 subjects), for a total of 56 subjects treated with nusinersen (Pool E). The number (percentage) of subjects who experienced at least 1 AE were 28 subjects (100%) in the <6 years of age subgroup and 28 subjects (100%) in the ≥ 6 years of age subgroup. The AE incidence was generally similar between the 2 age subgroups. The most common SOCs were similar between the <6 years of age subgroup and the ≥ 6 years of age subgroup, e.g., infections and infestations (82% versus 75%, respectively) and musculoskeletal and connective tissue disorders (75% versus 71%, respectively). However, LP-related events were more commonly reported in the older age group (e.g., post lumbar puncture syndrome 21% in the <6 years of age subgroup versus 61% in the ≥ 6 years of age subgroup).

Of note very little data are available in subjects 18 years of age and above; also scoliosis, hypoxemia or low or high SMN2 copy number were exclusion criteria for study CS3B.

Sex

Of the 117 infants, 60 were male and 57 were female. There was no difference in AE incidence between the subgroups, and the most common SOCs were the same, e.g., infections and infestations and respiratory, thoracic, and mediastinal disorders, consistent with the underlying SMA disease.

Of the 56 later onset subjects, 26 were male and 30 were female. There was no difference in AE incidence between the subgroups, and the most common SOCs were the same, e.g., infections and infestations and musculoskeletal and connective tissue disorders.

Race

Of the 113 infant subjects who reported race, 93 were White and 20 were non-White. There was no difference in AE incidence between the subgroups, and the most common SOCs were the same, e.g., infections and infestations; respiratory, thoracic and mediastinal disorders; and gastrointestinal disorders.

The overall incidence of later-onset subjects with at least 1 AE was the same between the 2 racial subgroups (100%). The non-White subgroup had relatively few subjects ($n = 7$) compared with the White subgroup ($n = 49$), thereby limiting meaningful comparisons between the 2 subgroups.

Body Weight

Of the 117 infants, 29, 28, 28, and 32 subjects were in the weight quartile subgroups of <5.42, 5.42 to <6.31, 6.31 to <7, and ≥ 7 kg, respectively. The overall incidence of subjects with at least 1 AE was the same between the 4 weight quartile subgroups. The number of subjects experiencing specific events within these weight quartile subgroups was very small. The most common SOCs (incidence $\geq 10\%$) for all 4 subgroups were infections and infestations; gastrointestinal disorders; general

disorders and administrative site conditions; and respiratory, thoracic and mediastinal disorders. Overall, body weight appeared to have no impact on the incidence of AEs.

Of the 56 later onset subjects, 14 subjects each were in the weight quartile subgroups of <13.4, 13.4 to <19.1, 19.1 to <32.8, and ≥ 32.8 kg. The overall incidence of subjects with at least 1 AE was the same between the 4 weight quartile subgroups (100%). The most common SOCs (incidence ≥ 10%) for all 4 subgroups were infections and infestations; musculoskeletal and connective tissue disorders; injury, poisoning, and procedural complications; general disorders and administrative site conditions; nervous system disorders; gastrointestinal disorders; respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders.

Subjects With Hepatic Insufficiency or Severe Renal Failure

Patients with hepatic insufficiency or severe renal impairment were not studied in the nusinersen clinical development program. There has been no literature published indicating that infants and children with SMA are prone to hepatic disease or renal failure. A small study of riluzole in subjects with SMA reported that there was no evidence of liver or renal failure during the study. There were no adverse events of kidney failure or liver failure reported in the nusinersen clinical program. No clinically significant changes in kidney laboratory parameters were observed in the nusinersen clinical studies. While some subjects in the nusinersen clinical studies had increases in liver function tests at some timepoint during their participation in the studies, no sustained increases were observed despite continuous drug exposure, making these changes not likely to be due to nusinersen. Given the known PK of nusinersen and the 2'-MOE ASO class, the natural history of the target population, and the results of the clinical and nonclinical studies to date, hepatic and renal effects are not anticipated and specific hepatic or renal impairment studies were not conducted.

Extrinsic Factors

The geographic regions included North America, Europe, and Asia-Pacific. Subjects with later-onset SMA included in the integrated analysis were enrolled at sites in North America. In total, 126 subjects were enrolled in North America, 33 in Europe, and 14 in Asia-Pacific (Pool F).

For all subjects treated with nusinersen (Pool F), the SOC of skin and subcutaneous tissue disorder had a higher incidence in North America (54 subjects [43%]) than in Europe (3 subjects [9%]), or Asia-Pacific (1 subject [7%]). The PTs of rash (13 subjects [10%]), dermatitis diaper (12 subjects [10%]), and dermatitis contact (6 subjects [5%]) in North America appear to be the difference. Only 2 subjects from Europe and Asia-Pacific reported rash or dermatitis diaper.

Overall, these data are not suggestive of clinically meaningful differences in AE incidences across the geographic regions.

Immunological events

The immunogenic response to nusinersen (ADA) in plasma was determined in subjects from all 7 clinical studies in the original filing.

All clinical immunogenicity samples evaluated in Studies CS1, CS2, CS10, and SM201 were negative with respect to presence of ADA. A low incidence of ADA response was observed in Studies CS12, CS3A, and CS3B with 2 out of 47 subjects (4.3%) and 1 out of 20 (5%), and 6 out of 128 (5.1%), respectively, being classified as ADA positive. One subject from Study CS3B had ADA positive samples

on predose Day 1, and two were from the sham treatment arm, thus not considered related to nusinersen as the subjects had not been exposed to nusinersen at the time of sampling. Three of the 4 ADA-positive subjects were considered to have a transient response (1 positive sample, with all samples before and after being negative), and 1 subject in Study CS12 was considered to have a persistent response, based on 4 samples evaluated from predose to Day 351 of treatment. The reported titer values (without including the 50x minimum required dilution) for the 4 ADA-positive subjects were very low ranging from 1 to 16.

ADA-positive plasma samples seemed to have a sporadic and inconsistent effect on plasma concentrations, but showed no effect on CSF concentrations compared with the ADA-negative samples at the same time and dose level. ADA-positive plasma samples seemed to have a sporadic and inconsistent effect on plasma concentrations, but showed no effect on CSF concentrations compared with the ADA-negative samples at the same time and dose level.

Electrocardiograms:

No thorough QT/QTc study was performed and only ECG data from the clinical development program are available.

In the final analysis of Study CS3B, there were 2 subjects in the nusinersen-treated group who had a QTc value above 500 msec and a change from baseline of >60 msec, (1.6%) and neither subject reported any cardiovascular events during the study. Both subjects had a QTc >450 msec on ECG on only one occasion. In Study CS4, there was one subject with a single QTc value above 500 msec. There were no subjects who had a QTc value above 500 msec and a change from baseline of >60 msec in Study CS4. In addition, there were no reports of torsade de pointes or sudden death in Studies CS3B or CS4, and in both studies, fewer cardiac disorders were reported in the nusinersen-treated group (nusinersen versus control: 23% versus 32% in Study CS3B and 5% versus 7% in Study CS4). These changes are not considered to be clinically relevant.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions are not expected with nusinersen. Nusinersen is metabolized via nucleases and not by the cytochrome P450 (CYP450) system. In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism and indicated that the likelihood for interactions with nusinersen due to competition for plasma protein binding, or competition with or inhibition of transporters is low.

No clinical studies of interactions of nusinersen with other medicines have been performed. Most concomitant medications in the clinical studies were used to treat typical complications of SMA or were used as sedation during the LP procedure. There was no noticeable potentiation of other common side effects to concomitant medication. There were also no AEs observed suggestive of any potential drug-drug interaction with nusinersen.

Use in Pregnancy and Lactation

In toxicity studies in animals, no effects on reproductive organs, male or female fertility, or embryo-fetal development were observed. There are no data from clinical studies on the use of nusinersen during pregnancy or during lactation in humans.

Overdose

No overdose was reported across the clinical studies of nusinersen, and the Sponsor has no knowledge of the occurrence of an overdose of nusinersen in humans. No AEs that might point towards an accidental overdose have been reported.

One potential type of overdose would be an acute type in which significantly more nusinersen than intended is mistakenly administered. This would lead to a higher concentration of nusinersen in CSF (both maximum observed concentration and area under the concentration time curve) than planned. Based on the juvenile monkey toxicity studies following IT bolus administration of doses \geq 3 mg per dose, which were not designed to study overdose, acute transient lower limb reflex changes during the immediate period after dosing are a possible outcome of an overdose. Clinical signs and symptoms should be monitored and appropriate supportive care and necessary countermeasures should be undertaken if clinical evidence suggests this has occurred.

Another potential type of overdose would be more frequent administration of nusinersen than recommended. This was not observed in the clinical studies of nusinersen.

There is no known intervention to reverse an overdose of nusinersen if it were to occur. However, overdose of nusinersen is very unlikely as the drug will be prepared and administered by a healthcare professional in a medical facility. Dosing instructions and frequency of dosing will be clearly stated in the prescriber information. Furthermore, the pharmacological action of nusinersen is restoration of full-length SMN protein via modifying splicing, which is a native occurring protein, without known deleterious effects.

Drug Abuse

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

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

Withdrawal and Rebound

No studies were designed to assess the potential for nusinersen to produce withdrawal or rebound effects. Due to the life threatening nature of infantile onset SMA, infants were dosed throughout the studies, and no gaps in dosing were observed. One infant who was voluntarily withdrawn from Study CS3A appeared to be stable and showed no signs of withdrawal or rebound as per Investigator follow up. However, it is expected that after discontinuation of nusinersen, the natural progression of SMA ultimately would occur.

In the later-onset SMA studies, there were gaps between the studies that enrolled children; e.g., the gap between the last dose in Study CS1 and the first dose in Study CS10 ranged from 206 to 399 days. No withdrawal or acute rebound was observed.

Discontinuation due to adverse events

Adverse Events Leading to Study Treatment Discontinuation in Infants and later onset Diagnosed With SMA

In Study CS3B and Study CS3A, all events leading to treatment discontinuation were a result of death that occurred before the next scheduled dose of nusinersen (Interim CSR CS3A. No event led to treatment discontinuation in Study SM201.

No AEs leading to study treatment discontinuation have been reported as of the data cut-off date. No AEs leading to study treatment discontinuation have been reported in Studies CS4, SM202, and CS11 of the safety data cut-off date.

2.6.1. Discussion on clinical safety

The current marketing application is intended to support the use of nusinersen for the treatment of SMA. SMA is a devastating neurodegenerative disease and the most common genetic cause of infant mortality and morbidity. There is no treatment for SMA currently available. SMA is an orphan disease. In the clinical studies used as the basis for the safety evaluation, nusinersen has been administered to 173 infants and children with SMA, encompassing different clinical phenotypes of disease.

This includes infants with pre-symptomatic disease and infants and children with symptomatic disease (infantile-onset and later-onset SMA), which reflects clinical Types I, II and III SMA. Safety data from these cohorts were included in an integrated safety assessment, which also includes a direct comparison of nusinersen-treated subjects with sham-controlled subjects from a blinded, randomized, controlled clinical study of infantile-onset SMA. An additional 170 infants and children with SMA are participating in ongoing, blinded clinical studies of nusinersen, and aggregate SAE listings from these subjects were also provided. The clinical development program provides long-term exposure to nusinersen in infants and children, with 154 subjects having been on study for \geq 360 days. The overall nusinersen exposure across the different clinical studies allows for an adequate assessment of safety in the context of this disease.

Nusinersen is a 2'MOE ASO delivered by the IT route. Other ASOs delivered by the SC or IV route that are on the market or in late-phase development are administered at higher doses and frequencies, thus leading to higher systemic exposures and associated toxicities. To date, there is no evidence in the nusinersen nonclinical and clinical safety data to suggest a signal for these toxicities that were reported in other SC and IV ASOs (e.g. severe thrombocytopenia, renal disorders). Notwithstanding, a class effect warning will be present in the SmPC, as this risk cannot be absolutely excluded.

Across the clinical development program, common adverse events in symptomatic subjects with infantile-onset SMA who received nusinersen were consistent with either events commonly observed in the context of SMA disease, with common events observed in the general population, with common age-appropriate events, or with events commonly observed in the context of lumbar puncture. In symptomatic infants and children with SMA, across different dosing regimens, the most common

adverse events reported were respiratory in nature, within the SOCs of infections and infestations and respiratory disorders, and all reported events were consistent with underlying SMA disease. Nevertheless, there may be a slight higher frequency of infections, higher than would be expected with the motor improvement that has been observed. Lumbar puncture-related events, such as headache and post lumbar puncture syndrome, were reported more commonly in children than in infants in the nusinersen clinical studies, and this most likely reflects the higher verbal communication skills present in children appropriate for their age. To assess for the presence of possible LP-related events in infants who are not able to verbally communicate, an analysis of AEs reported in the 24- and 72-hour periods after dosing was performed. This analysis showed an increase in reports of vomiting (a known complication of the LP procedure) in the 72-hour period post LP in nusinersen-treated subjects than in the sham-controlled subjects; yet, vomiting overall is a common adverse event reported in both groups throughout the clinical studies. No serious infectious complications of the LP procedure, such as meningitis, although some intrathecal haemorrhages have been described during the clinical studies of nusinersen.

The Applicant provided detailed information on the different schedules and doses for each patient across studies, to facilitate assessment on the frequency, severity and time to occurrence of adverse events.

No patient was withdrawn from the study due to failure of administration or to LP related adverse events. With the number of LPs performed in each patient, it is not unlikely that a significant number of patients will develop an adverse event related to LP. The Applicant also provided data regarding the number of LP related events in the scoliosis group as compared to the non scoliotic, particularly in SMAII and III, after request from CHMP.

The applicant has provided a justification for the occurrence of haemorrhagic events at LP, which were related to several attempts in study SM201, and not in any other. The applicant proposes to perform LPs under imaging guidance. Also, the increased frequency of PLPS in nusinersen was justified with the fact that events accumulate as patients survive and keep being treated. Moreover, the applicant has compared the frequency of PLPS in nusinersen patients to the ones treated with repeated LPs for chemotherapy administration, and the frequency of events is overlapping. Considering that administration of nusinersen and chemotherapy do require drainage of an equivalent amount of CSF to prevent increased CSF pressure, and that sometimes imbalance in draining and injection does occur, this approach can be acceptable.

There was no difference on the rate of hospitalisation between nusinersen and the control arm in study CS3B. To the question "*Has any AE in nusinersen arm been more likely to require hospital admission than AEs in the control arm?*", the applicant has justified the more frequent admissions to hospital on the nusinersen group with the fact that this group had a slightly poorer condition at baseline than the control group. The duration of stay at the hospital is different though, with 8.9 days for nusinersen treated vs 13.9 in the control group. There is also no significant difference between the type of adverse events or severity between groups.

There were no deaths reported in the pre-symptomatic infants and in the later-onset SMA subjects. Deaths were reported in the infantile-onset SMA studies, both for nusinersen-treated and sham-controlled subjects. The fatality rate of the nusinersen-treated subjects was half that of the sham-controlled subjects. Causes of death in both cohorts were consistent with causes of death typically observed in the setting of this rapidly progressive and fatal form of infantile-onset SMA.

A detailed review was performed to identify adverse drug reactions. This included a comparison of AE incidence rates between nusinersen-treated and sham-controlled subjects in Study CS3B. This was complemented by a medical review of additional AEs in Study CS3B and the other open-label studies, including a review of events that were assessed as related or possibly related by the Investigator, a review of plausible events based on preclinical data, and a review of possible LP-related events. No adverse drug reactions were identified. In addition, no new types of events were identified that occurred with longer exposure to nusinersen or with the addition of data from a randomised clinical trial in later-onset patients..

Infants who were treated with nusinersen before presenting with symptoms of SMA had fewer AEs and SAEs (13 subjects [76%] and 5 subjects [29%, respectively) compared with infants who already were symptomatic at the time of SMA diagnosis (92 subjects [92%] and 72 subjects [72%, respectively). This most likely reflects a healthier baseline condition in the pre-symptomatic infants at the time of enrollment in the study, and this appears to be maintained throughout their participation in the study, with the unprecedented development of normal motor milestones.

The applicant justified the more frequent respiratory infections on nusinersen with the fact that nusinersen treated subjects were in worse clinical condition at baseline, and more commonly had baseline risk factors such as prior history of pneumonia, paradoxical breathing at baseline, and swallowing and feeding difficulties, as noted in their medical histories. Also, the duration of observation time in the trial was twice as long for the nusinersen group compared with the sham-control group (37.7 versus 17.9 years) making it more likely to pick an infection as AE. Finally in study CS4 respiratory infections were less observed in the nusinersen treated than in the control group.

Lastly, review of the available laboratory data for nusinersen demonstrated no abnormal pattern or trend in hematology or clinical chemistry data. No adverse pattern or trend was observed in vital signs, ECGs or on physical examinations. Subjects who received ISIS 398443 showed a gain in motor milestones, and an improvement in their neurological exams.

The applicant submitted an update of the various studies that were ongoing at the time of the original submission.

Of note patients in study CS4 received less doses than in studies CS3B and SM201.

The main adverse events related to respiratory function and infections, which is consistent with the nature of events observed in the context of Spinal Muscular Atrophy. The main adverse reactions are complications of the lumbar puncture and such complications should be clearly addressed in the SmPC.

In Study SM201 (pre-symptomatic patients) 14 of the 20 patients experienced a shift to high in eosinophil count, 12 subjects experienced a shift that was mild (500 to 1500 eosinophils/ μ L); shifts >1500 eosinophils/ μ L were single events in 2 subjects. Seven of the 14 subjects recovered. Increases in Creatinine kinase were mainly transient and associated with confounders. There was no signal with regards to shifts to high from baseline for eosinophil values in studies CS3B (nusinersen: 26% vs. Control 40%) and CS4 (7/84 and 6/42 respectively).

In study CS3B a higher percentage of nusinersen subjects experienced nervous system disorders (11% vs. 5%). No one event contributed to the higher incidence.

No case of vasculitis or necrosis was reported in studies SM201 or CS4. Suspected vasculitis was reported in one subject (2 events) receiving nusinersen in Study CS3B but alternative diagnosis was provided, and the patient continued to be exposed to ISIS396443. No relationship to the treatment was noted.

In general no patient discontinued treatment or withdrew from the study as a result of an AE.

The main issue relates to post LP symptoms and no clear frequency has been given by the applicant across the clinical development of ISIS396443. Temporal association was clearly seen as soon as 6 hour after the procedure and were still reported after 7 days in Study CS4.

Changes to the SmPC have been implemented, such as the abovementioned warning regarding class effect with other ASO and phosphorothioate linkers regarding potential effect on kidney function and platelet count/coagulation. A warning was also added in section 4.4 regarding the need to check platelet count/coagulation prior to LP in case of risk factors such as symptomatic bleeding or serious infection and for renal function if clinically indicated.

Anti-Drug-Antibodies were found in 7 of the 148 patients who had negative baseline values; this is reflected in the SmPC and the wording is adequate.

2.6.2. Conclusions on the clinical safety

The safety profile of nusinersen was characterized in subjects with infantile-onset SMA in a randomized controlled study and an open-label study; pre-symptomatic infants with SMA in an open-label study, and children with later-onset SMA in a randomized study and open-label studies. Review of the available data demonstrated no safety concerns due to nusinersen exposure. The majority of AEs and SAEs reported in subjects exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA. Pre-symptomatic infants treated with nusinersen experienced fewer adverse events compared with symptomatic infants which is most likely due to their healthier baseline condition, which they maintained throughout participation in the study. In addition, the fatality rate in nusinersen-treated subjects with infantile-onset SMA was about half that of sham-controlled subjects.

nusinersen has demonstrated a favourable safety and efficacy pattern in the treatment of infantile-onset SMA from a randomized controlled clinical study, Study CS3B. This was supported by favourable safety and efficacy data from the interim analysis of a randomized controlled clinical study, CS4 in later-onset subjects, open-label studies in pre-symptomatic subjects, and subjects with infantile-onset and later-onset SMA, where the attainment of motor milestones in subjects receiving treatment differed from that seen in the natural history of SMA.

Based on the totality of the data, it can be agreed that nusinersen has a positive benefit/risk profile for treating SMA. Long-term safety data will be obtained from the planned and ongoing studies.

2.7. Risk Management Plan

Table 13 - Summary of the Safety concerns

Important identified risks	None
Important potential risks	Thrombocytopenia and coagulation abnormalities Renal toxicity
Missing information	Safety profile in patients >18 years of age Safety profile in patients with severe and progressive scoliosis Safety profile in patients receiving repetitive lumbar punctures (LPs) 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 (e.g., Type 0 and Type IV SMA)

Pharmacovigilance plan

Table 14 – Table of Ongoing and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
<u>Study SM202 (EMBRACE)</u> <u>Category 3</u>	This is a Phase 2, randomized, double-blind, sham- procedure controlled study to assess the safety, tolerability, PK, 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, PK and efficacy data for patients with infantile and later onset SMA assessed for up to ~43 months. Cardiac safety.	Ongoing	2019
MDA US Neuromuscular Disease Registry	Prospective longitudinal registry in a research agreement with the Muscular Dystrophy Association.	Missing information: safety profile in patients with low or	Ongoing	Synopsis of available data and

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
<u>Category 3</u>	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.	higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years		data fields in the MDA dataset: Within 1 month after EC decision
International SMA Consortium (ISMAC) natural history study <u>Category 3</u>	Longitudinal natural history study with the 3 regional centres that comprise the ISMAC (SMA Reach UK, Italian SMA Network, and Dr. Richard Finkel at Nemours Children's Health System). Outputs expected to include baseline characteristics of treated patients and longitudinal data on nusinersen treatment patterns, motor function, respiratory function, hospitalisations, and comorbidities.	Missing information: safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs
TREAT-NMD Alliance registries <u>Category 3</u>	Longitudinal natural history studies in a research agreement with the TREAT-NMD Alliance to expand current registries to include nusinersen treatment information. The Global SMA Patient Registry consists of 26 national patient registries representing 29 countries (20 countries in Europe), collecting data from genetically confirmed patients across the spectrum of SMA. Data are self-reported and/or provided by healthcare professionals. More than 5000 SMA patients worldwide have been enrolled in TREAT-NMD-associated registries.	Missing information: safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs

Risk minimisation measures

Table 15 – Summary table of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
None	N/A	N/A
Important potential risks		
Thrombocytopenia and coagulation abnormalities	Wording in SmPC section 4.4	None
Renal toxicity	Wording in SmPC section 4.4	None
Missing information		
Safety profile in patients >18 years	None	None
Safety profile in patients with severe and progressive scoliosis	None	None
Safety profile in patients receiving repetitive lumbar punctures (LPs)	None	None
Safety profile in patients with long-term exposure to nusinersen	None	None
Safety profile in pregnant or breastfeeding women	Wording in SmPC section 4.6	None
Safety profile in patients with low or higher SMN2 copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	None	None

Conclusion

The CHMP and PRAC considered that the risk management plan version is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

In order to support the claim that ISIS 396443/Nusinersen is a new active substance the applicant states to have performed a search on the available chemical literature, patent databases, and databases such as SciFinder (Chemical Abstracts). No approved drug substance in the EU matching the chemical structure of ISIS 396443/Nusinersen were found.

The applicant also compared the molecular structure and full-length sequence of ISIS 396443/Nusinersen with that of two other oligonucleotides that have been authorised previously in the EU, fomiversen and pegaptanib. In neither case a structural similarity was found with ISIS 396443/Nusinersen. It is thus acceptable that ISIS 396443/Nusinersen does not contain an active principal molecular features and thus a therapeutic moiety also found in other drug substance already authorised in the EU. Facing this, the claim of NAS for ISIS 396443/Nusinersen is acceptable.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.10.2. Labelling exemptions

A request of translation exemption of the labelling (outer carton and immediate label) as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable for the immediate label, but unacceptable for the outer carton by the QRD Group for the following reasons:

The QRD Group accepted to have the immediate label in English only based on the estimates of the prevalence of the disease, and the low forecast of production expected. However, the QRD Group requested the applicant to explore the possibility of multilingual outer cartons.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spinraza (nusinersen) is included in the additional monitoring list as it is a new active substance (NAS).

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Nusinersen is intended for the treatment of SMA. SMA is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk.

SMA diagnosis is suspected when a patient presents with flaccid muscle weakness. Genetic diagnosis is the most common form of diagnosis, which allows for premorbid diagnosis in siblings where one previously affected member has been identified.

SMA is a serious, debilitating, and life-threatening disease. With a global incidence of 8.5 to 10.3 per 100,000 live births, it is the most common genetic cause of infant mortality, and a major cause of childhood morbidity due to weakness.

3.1.2. Available therapies and unmet medical need

SMA is a progressively disabling and fatal disease that has a devastating effect upon patients, their families and caregivers. There is currently no available therapy, and patients are limited to supportive therapy which can include respiratory, nutritional and orthopaedic support; none of which can stop or even slow disease progression.

The aim of the therapy with Nusinersen is to allow for the production of a functional SMN protein, thus preventing degeneration of spinal motor neurons and the consequent muscle weakness. This could theoretically allow for the achievement of normal development milestones in children who have not developed clinical signs, and prevent worsening and possibly restore some function in already disabled children.

3.1.3. Main and supportive clinical studies

Study CS3B is a completed Phase 3, multicentre, randomized, double-Blind, sham-procedure controlled study to assess the clinical efficacy and safety of Spinraza in 121 patients with infantile-onset SMA \leq 7 months of age.

Study CS4 is an ongoing Phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of Spinraza in 126 patients with later-onset SMA and a median age at screening of 3 years.

The development plan comprised several additional, supportive studies in symptomatic and pre-symptomatic SMA patients.

Study CS3A is an ongoing, Phase 2, open-label study in 20 patients with infantile-onset SMA.

Study CS1 was a Phase 1, open-label, single-dose, dose-escalation (1-9 mg) study to evaluate the safety, tolerability, and PK of a single dose of Spinraza in subjects with later-onset SMA who were 2 to 14 years of age and who were medically stable.

Study CS10 was an open-label study to evaluate the safety, tolerability, and PK of a single dose of Spinraza (6 or 9 mg) administered IT by LP in subjects with SMA who previously participated in CS1. Of the 28 eligible subjects from CS1, 18 enrolled in CS10.

Study CS2 was a Phase 1/2a, open-label, multiple-dose, dose-escalation study designed to assess the safety, tolerability, and PK of Spinraza in 2- to 15-year-old subjects with later-onset SMA.

Study CS12 is a Phase 1, open-label, multiple dose study to assess the safety, tolerability, and PK of repeated doses of Spinraza 12 mg providing 3 year-long treatment data in subjects with SMA who previously participated in Study CS2 or Study CS10.

Finally, study SM201 is an ongoing Phase 2, open-label, multicentre, single-arm study to assess the efficacy, safety, tolerability, and pharmacokinetics of Spinraza in pre-symptomatic SMA. The study is being conducted in subjects who were ≤6 weeks of age at the time of enrolment with genetic documentation of 5q SMA, 2 or 3 copies of the SMN2 gene, CMAP ≥1 mV, and the absence of signs or symptoms of SMA.

3.2. Favourable effects

In the pivotal study CS3B in infantile-onset patients, a statistically significantly greater percentage of subjects achieved the pre-defined motor milestone response in the Spinraza group (51%), one of the primary endpoints, compared to the control group (0%; p<0.0001).

In addition, time to death or permanent ventilation, the other primary endpoint, was statistically significantly prolonged in subjects treated with Spinraza (HR=0.53 [95%CI: 0.32-0.89]; p=0.0046) compared to controls. This was even more prolonged in the subjects treated with Spinraza who were below the median for disease duration at baseline (HR=0.21 [95%CI: 0.08-0.53]; p=0.0003), suggesting that early treatment with Spinraza may confer a strong benefit for event-free survival.

A statistically significantly greater percentage of subjects achieved a CHOP INTEND response in the Spinraza group (71%) compared to the control group (3%; p<0.0001). Several of the infants treated with Spinraza had improvements of 10 points or more on the CHOP INTEND total score. Sixteen (22%) achieved full head control, six (8%) achieved independent sitting and one achieved standing with support. With the exception of one subject, all subjects in the control group showed no change or worsened.

These results are supported by the ongoing study CS3A, where patients with infantile-onset SMA who have received Spinraza for over 2 years achieved clinically meaningful gains in motor milestones, prolonged overall and event-free survival, and improved motor function and motor neuronal health inconsistent with the natural history.

In the interim analysis conducted in the ongoing randomized, sham-procedure controlled, double-blind CS4 study with later-onset SMA, a statistically significant change from baseline in HFMSE score at 15 months, the primary endpoint, was observed in the Spinraza group (+4.0 [95% CI: 2.9-5.1]) compared to the sham control group (-1.9 [95% CI: -3.8-0.0]); p=0.0000002). An improvement was also observed in upper limb functional ability.

In the pre-symptomatic setting, the results available from the ongoing Phase 2, open-label, multicentre, single-arm Study SM201 indicate that the development and achievement of motor milestones for most subjects has been more consistent with normal development than with the natural history of Type I SMA.

3.3. Uncertainties and limitations about favourable effects

While multiple phenotypes of the disease have been comprehensively studied in the development programme, patients with very severe, inborn symptoms (previously categorized as Type 0), and patients with a mild, adult onset course (previously categorized as type IV SMA) were not included in it.

Another limitation of the current data set resides in the lack of long term data. Therefore, it is not known whether the effect size could change as the disease progresses and patients grow up/grow older.

The development has limitations in terms of the most appropriate dose to be used for the different patients, both according to their disease severity and according to their changed disease progression. As it is expected that this drug may increase the survival of a significant part of the SMA population, these patients will reach milestones in their physical development that may necessitate a dose adjustment according to their increased body height or other relevant parameters. Also, it has not been significantly ascertained that the proposed therapeutic dose is the optimal one in terms of potential benefit to be gained, and that a higher dose cannot bring additional benefits. The imposed post-authorisation measures are aimed, among other things, at gathering sufficient data to enable future decisions about the necessity of dose adjustment.

Lastly, there is an uncertainty related to the individual decision to be made to treat each SMA patient taking into account their symptoms' severity and duration, individual disease progression and the expected benefit to be derived from the drug.

3.4. Unfavourable effects

The safety assessment of Spinraza was based on data from two Phase 3 clinical studies in infants (CS3B) and children (CS4) with SMA, together with open-label studies including pre-symptomatic infants genetically diagnosed with SMA and infants and children with SMA. Of the 260 patients who received Spinraza up to a maximum of 4 years, 154 patients received treatment for at least 1 year.

Review of the available data demonstrated no specific safety concerns that can be attributed to nusinersen exposure. The majority of AEs and SAEs reported in subjects exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA. Pre-symptomatic infants treated with nusinersen experienced fewer adverse events compared with symptomatic infants which is most likely due to their healthier baseline condition, which they

maintained throughout participation in the study. In addition, the fatality rate in nusinersen-treated subjects with infantile-onset SMA was about half that of sham-controlled subjects.

Nusinersen has demonstrated a favourable safety pattern in the treatment of SMA judging from the available data from the randomized controlled clinical studies. This was supported by favourable safety data from open-label studies in pre-symptomatic subjects, and subjects with infantile-onset and later-onset SMA.

3.5. Uncertainties and limitations about unfavourable effects

There is a risk of adverse reactions occurring as part of the lumbar puncture procedure. Potential difficulties with this route of administration may be seen in very young patients and those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration of Spinraza, can be considered at the physician's discretion.

Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides. If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of Spinraza.

Renal toxicity has been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.

3.6. Effects Table

Table 8 Effects Table for nusinersen in the treatment of SMA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Proportion of Motor Milestones Responders	A subject is considered to have responded if the number of motor milestone categories in which there was an improvement from baseline was greater than the number that showed worsening.	%	ISIS 396443 IT 12 mg weight adjusted	Sham LP 51 0	The evidence is robust ($p<0.0001$), also considering that improvement is not expected in natural history of disease. However there were many patients which have not achieved improvement.	Study CS3B

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Time to death or permanent ventilation	Time to death or permanent ventilation (if a tracheostomy was performed or at least 16 hours of ventilator support per day continuously for more than 21 days was required in the absence of an acute reversible event)	%	47 reduction in the risk of death or permanent ventilation compared to control		Time to death or permanent ventilation was prolonged in subjects treated with ISIS 396443 in the pivotal trial	Study CS3B
Proportion of CHOP INTEND responders	Proportion of patients who are responders according to CHOP-INTEND - a specific SMA scale used to assess function	(%)	71	3	a statistically significantly ($p<0.0001$) greater percentage of subjects achieved a CHOP INTEND response in the ISIS 396443 group	Study CS3B

Unfavourable Effects

Deaths		Number of deaths (%)	13 (16%)	16 (39%)	Deaths were considered related to SMA progression or frailty, none as an AE	Study CS3B
Pyrexia	Frequency of adverse event	% of AEs	56	59	Reported AEs were generally consistent with those expected in a population with infantile-onset SMA, consistent with common conditions occurring in the general population, or consistent with age-appropriate events in these studies	Study CS3B
Upper resp. tract infection			30	22		Study CS3B
Respiratory distress			26	29		Study CS3B
Respiratory failure			14	24		Study CS3B
Risks related to the LP					There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. headache, back pain, vomiting)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Class-related (AON) risks					<p>Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides.</p> <p>Renal toxicity has been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides.</p>	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

SMA is a degenerative neuromuscular disorder where severe unmet medical need exists. Patients with the most severe forms never achieve the ability to sit independently and, without major supportive care, die before the age of 2 years. Patients with the milder forms of disease may survive longer, but have progressive disability.

Maintaining function and slowing down disease progression is a priority for patients. A majority of the subjects with infantile-onset SMA treated with Spinraza in Studies CS3B and CS3A achieved clinically meaningful improvements in motor milestones and motor function. These improvements include attainment of motor milestones such as independent sitting, standing, and walking, which are in stark contrast to the steady loss of motor milestones that is the hallmark of infantile-onset SMA as demonstrated by the control group of Study CS3B and natural history data.

An even larger treatment effect was seen in patients with shorter disease duration at baseline which, in the context of the rapidly progressive decline observed in natural history studies of infantile-onset SMA makes the case for the initiation of treatment as soon as possible after the onset of symptoms. This is supported by the available results from the ongoing SM201 study where pre-symptomatic children treated with Spinraza achieved milestones unexpected in infantile-onset SMA and more consistent with normal development.

The interim results from the ongoing study CS4 show that subjects with later-onset SMA treated with Spinraza also achieved sustained and clinically meaningful benefits compared with controls. The mean improvement in the HFMSE score from baseline at month 15 in patients treated with Spinraza exceeded the 3 points which is typically considered to represent a clinically meaningful, while a mean -

0.19 decline was observed in the control group. The results from the longitudinal assessment of subjects with later-onset SMA in study CS12 demonstrate additional milestone attainment and maintenance of effect over time in motor function, upper limb strength, and ambulation, all of which are in contrast with the decline typically seen in these patients following symptom onset.

The majority of AEs and SAEs reported in subjects exposed to Spinraza were consistent with the nature and frequency of events typically occurring in the context of SMA. There are some class-related risks that have to be taken into consideration together with the risks stemming from the application procedure (LP), but no specific major risks were attributed to the product itself.

3.7.2. Balance of benefits and risks

While not all patients responded to treatment with Spinraza, the efficacy observed across multiple disease phenotypes of symptomatic and pre-symptomatic SMA patients as well as across trials and endpoints is evident, in stark contrast with the control groups and natural history data, and outweigh the risks essentially associated with the intrathecal administration.

Clinical trial data are not available in patients with very severe, inborn symptoms and in patients with a mild, adult onset course. However, these patients are part of the continuum in phenotypes of one genetically defined but clinically heterogeneous disease. Based on the efficacy shown in the other, most prevalent phenotypes and the established mechanism of action of Spinraza, the therapeutic indication recommended by the CHMP includes all 5q⁻13.2 SMA patients.

The decision to treat should be based on an individualised expert evaluation of the expected benefits balanced against the potential risks for that individual. In addition, the need for continuation of therapy should be reviewed regularly on an individual basis, especially as long-term data are not available at this point.

In order to obtain additional data key to the benefit-risk of Spinraza, the CHMP recommended that conditions are included in the Marketing Authorisation, creating an obligation for the MAH to complete and present the results of two ongoing studies in symptomatic and pre-symptomatic SMA patients, respectively. These results are expected to evaluate the long-term efficacy and safety of the product, and the need to consider dose adjustment with the course of the disease being changed by the positive effects of the drug.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Spinraza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Spinraza is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 3, open-label extension study (SHINE, CS11).	Submission of study results: August 2023.
Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in pre-symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 2, open-label study (NURTURE (SM201)).	Submission of study results: April 2023.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that nusinersen a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.