**Review Report**

August 22, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for partial change approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Spinraza Intrathecal injection 12 mg |
| **Non-proprietary Name** | Nusinersen Sodium (JAN*) |
| **Applicant** | Biogen Japan Ltd. |
| **Date of Application** | July 5, 2017 |
| **Dosage Form/Strength** | Injection: Each vial (5 mL) contains 12.63 mg of Nusinersen Sodium (equivalent to 12 mg of nusinersen). |
| **Application Classification** | Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage |
| **Items Warranting Special Mention** | Orphan drug (Drug Designation No. 392 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 1124-6 dated November 24, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) |
| **Reviewing Office** | Office of New Drug III |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy of the product in the treatment of spinal muscular atrophy, and the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

| | |
|---|---|
| **Indication** | ~~Infantile~~ Spinal muscular atrophy<br>(Strike-through denotes deletion.) |
| **Dosage and Administration** | Infantile spinal muscular atrophy<br>The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 4 doses at Weeks 0, 2, 4 and 9 followed by dosing every 4 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes. |

Non-infantile spinal muscular atrophy

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 3 doses at Weeks 0, 4 and 12 followed by dosing every 6 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

| Age on the day of dosing | Dose | Injection volume |
|---|---|---|
| 0-90 days | 9.6 mg | 4 mL |
| 91-180 days | 10.3 mg | 4.3 mL |
| 181-365 days | 10.8 mg | 4.5 mL |
| 366-730 days | 11.3 mg | 4.7 mL |
| ≥731 days | 12 mg | 5 mL |

(Underline denotes additions.)

**Conditions of Approval**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Due to the very limited number of patients studied in Japan, the applicant is required to conduct a use-results survey, covering all patients treated with the product, during the re-examination period, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

**Attachment**

# Review Report (1)

July 28, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Spinraza Intrathecal injection 12 mg |
| **Non-proprietary Name** | Nusinersen Sodium |
| **Applicant** | Biogen Japan Ltd. |
| **Date of Application** | July 5, 2017 |
| **Dosage Form/Strength** | Solution for injection: Each vial (5 mL) contains 12.63 mg of Nusinersen Sodium (12 mg of nusinersen). |
| **Proposed Indication** | ~~Infantile~~ Spinal muscular atrophy |

(Strike-through denotes deletion.)

**Proposed Dosage and Administration**

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 4 doses at Weeks 0, 2, 4 and 9 followed by dosing every 4 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

| Age on the day of dosing | Dose | Injection volume |
|---|---|---|
| 0-90 days | 9.6 mg | 4 mL |
| 91-180 days | 10.3 mg | 4.3 mL |
| 181-365 days | 10.8 mg | 4.5 mL |
| 366-730 days | 11.3 mg | 4.7 mL |
| ≥731 days | 12 mg | 5 mL |

(No changes)

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| ASO | Antisense Oligonucleotide |
| AST | Aspartate Aminotransferase |
| AUC | Area Under Concentration-time Curve |
| BMI | Body Mass Index |
| BUN | Blood Urea Nitrogen |
| CHOP INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| $C_{max}$ | Maximum Concentration |
| CSF | Cerebrospinal Fluid |
| CTD | Common Technical Document |
| CYP | Cytochrome P450 |
| FDA | Food and Drug Administration |
| HFMS | Hammersmith Functional Motor Scale |
| HFMSE | Hammersmith Functional Motor Scale - Expanded |
| HINE | Hammersmith Infant Neurological Examination |
| HLGT | High Level Group Term |
| Hyb-ECL | Hybridization Electrochemiluminescence |
| ITT | Intention-to-Treat |
| LC-MS/MS | Liquid Chromatography-tandem Mass Spectrometry |
| MedDRA | Medical Dictionary for Regulatory Activities |
| 2'-MOE | 2'-*O*-(2-methoxyethyl) |
| mRNA | Messenger Ribonucleic Acid |
| (n-1) mer | Nusinersen (18 mer) minus 1 nucleotide |
| OC | Observed Case |
| PD | Pharmacodynamics |
| PPK | Population Pharmacokinetics |
| PT | Preferred Term |
| QTc | Corrected QT |
| QTcF | Fridericia-corrected QT |
| SMA | Spinal Muscular Atrophy |
| SMN | Survival Motor Neuron |
| *SMN1* | Survival Motor Neuron 1 |
| *SMN2* | Survival Motor Neuron 2 |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |
| $t_{max}$ | Time to Reach Maximum Concentration |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| The product | Spinraza Intrathecal injection 12 mg |
| Nusinersen | Nusinersen Sodium |

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. SMA is caused by a deletion of the *SMN1* gene or loss-of-function mutations in the *SMN1* gene, etc. that lead to survival motor neuron (SMN) protein deficiency. SMA has been categorized into 5 types: Types 0, I, II, III, and IV. The severity of symptoms significantly varies depending on phenotypes; while infants with SMA die shortly after birth (Type 0), patients with SMA manifesting after 20 to 30 years of age experience mild to moderate muscle weakness, but have a normal life expectancy (Type IV) (*Lancet Neurol*. 2012; 11: 443-52, *J Child Neurol*. 2007; 22: 1027-49). Type I SMA is the most common form of SMA, which accounts for approximately 58% of all SMA patients. Types II and III SMA represent approximately 29% and 13% of SMA patients, respectively (*Eur J Hum Genet.* 2004; 12: 1015-23). Although the incidences of Types 0 and IV are considered to be low, there are a few specific reports on the incidence. In Japan, SMA is a designated intractable disease. The estimated prevalence of SMA is 0.5 to 1.0 per 100,000 in Japan (*Journal of Tokyo Women's Medical University.* 2007; 83: E52-7). SMA patients are eligible for specific medical care for designated intractable diseases. A total of 894 specific medical care recipient certificates were issued for SMA patients in the fiscal year 2014 (http://www.nanbyou.or.jp/entry/1356).

Nusinersen is a 2'-MOE modified ASO consisting of 18 nucleotide residues discovered by ISIS Pharmaceuticals, Inc. (the US) (a predecessor of Ionis Pharmaceuticals, Inc.). It binds to the *SMN2* pre-mRNA to modulate splicing of the SMN2 gene that produces defective SMN protein, resulting in an increase in normal SMN protein expression. The development of nusinersen began overseas in [redacted] and then Biogen Inc. (the US) acquired global development rights. Nusinersen was approved in December 2016 in the US and in May 2017 in the EU.

In Japan, ISIS Pharmaceuticals, Inc. (a predecessor of Ionis Pharmaceuticals, Inc.) initiated a clinical study involving mainly Type I SMA patients in August 2014. The applicant acquired development rights after the initiation of the clinical studies, and received marketing approval of nusinersen for the indication of "infantile spinal muscular atrophy" on July 3, 2017. On the other hand, clinical studies involving mainly Types II and III SMA patients began in November 2014, and the efficacy and safety of nusinersen in the treatment of mainly Types II and III SMA as well as infantile SMA (the previously approved indication) have been demonstrated. Thus, claiming that the efficacy and safety of nusinersen in all SMA patients have been demonstrated, the applicant has filed a partial change application for nusinersen.[1)] As of November 24, 2016, nusinersen was designated as an orphan drug with the intended indication of "spinal muscular atrophy" (Drug Designation No. 392 of 2016 [*28 yaku*]).

In Japan, adenosine triphosphate disodium hydrate for injection has been approved for the indications of

1) Although a marketing application for nusinersen as a drug with a new active ingredient was submitted on [redacted], for the same indication as that in the present application, this application was withdrawn after approval of nusinersen for infantile SMA. A partial change application for nusinersen as a drug with a new indication was submitted on July 5 of the same year, using similar data. "Expedited Review and Inspection for Drug" (PSEHB/PED Notification No. [redacted] dated [redacted]) was issued, and the marketing application submitted on [redacted] was subject to expedited review.

"progressive spinal muscular atrophy and its similar diseases."

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application is intended for the approval of a new indication,[2)] and "data relating to quality" have not been submitted.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for the approval of a new indication,[2)] "non-clinical pharmacological data" have not been submitted because nusinersen has been approved for the indication of "infantile spinal muscular atrophy" and is expected to show efficacy via similar pharmacological effects in patients with any type of SMA.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application is intended for the approval of a new indication,[2)] and "non-clinical pharmacokinetic data" have not been submitted.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for the approval of a new indication,[2)] and "toxicity data" have not been submitted.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

"Biopharmaceutic data" have not been submitted.

Nusinersen concentrations in human plasma and CSF were determined by Hyb-ECL (lower limit of quantitation [LLOQ], 0.05 ng/mL).[3)]

### 6.2 Clinical pharmacology

The applicant submitted the results from a multi-regional phase III study in Japanese and non-Japanese SMA patients (CTD 5.3.5.1-1, Study CS4) as evaluation data. Unless otherwise specified, doses are expressed in terms of nusinersen and concentrations are expressed in terms of nusinersen sodium. The $t_{max}$ is expressed as the median and other pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

#### 6.2.1 Study in SMA patients (CTD 5.3.5.1-1, Study CS4 [[redacted] 20[redacted] Data Cutoff])

2) As described in Section 7.R.7, dosage and administration may be changed, taking also account of comments from the Expert Discussion. However, PMDA considers that even if the application classification is changed to "drug with a new indication" and "drug with a new dosage," the data that need to be submitted for each section remain unchanged.

3) Human CSF and plasma were spiked with nusinersen 0.15 to 7.5 ng/mL and then further spiked with its metabolite [(n-1) mer (3'- or 5'-deletion)] (5% or 20% of nusinersen). Then nusinersen concentrations were determined by Hyb-ECL. The percent increase relative to the theoretical concentration was 6.6% to 42.6%, indicating that the spiked metabolite interfered with the assay and that nusinersen concentrations were overestimated. When metabolite concentrations in plasma and CSF samples after administration of nusinersen were determined by LC-MS/MS, no metabolites were detected in CSF, and up to 5.8% of (n-1) mer (relative abundance) as the primary metabolite was detected in plasma (initial application documents, CTD 5.3.1.4-8).

Japanese and non-Japanese SMA patients (2-9 years of age, 84 patients included in pharmacokinetic assessment) received 12 mg intrathecal (IT) doses of nusinersen on Days 1, 29, 85, and 274. On Day 1, the plasma $C_{max}$ of nusinersen was 350 ± 181 ng/mL, the $t_{max}$ was 3.90 hours, and the $AUC_{0\text{-}24h}$ was 3523 ± 1288 ng·h/mL. Nusinersen trough concentrations in plasma and CSF over time are shown in Table 1.

In 5 Japanese patients with SMA participating in this study, the plasma $C_{max}$ of nusinersen on Day 1 was 527 ± 288 ng/mL and the $t_{max}$ was 3.97 hours. In 2 Japanese patients with available data, the $AUC_{0\text{-}24h}$ values were 2873 and 7458 ng·h/mL, respectively. Nusinersen trough concentrations in CSF on Days 29 and 85 were 3.08 ± 1.36 and 4.85 ± 1.24, respectively, and nusinersen trough concentration in CSF on Day 274 in 1 patient with available data was 4.34 ng/mL. Thus, the applicant discussed that there were no major ethnic differences in the pharmacokinetics of nusinersen.

Table 1. Nusinersen trough concentrations in plasma and CSF over time
following multiple IT doses of 12 mg of nusinersen in Japanese and non-Japanese SMA patients

| Time point | Plasma | | CSF | |
|---|---|---|---|---|
| | No. of evaluable subjects | Trough concentration (ng/mL)[a)] | No. of evaluable subjects | Trough concentration (ng/mL)[b)] |
| Day 29 | 84 | 0.70 ± 0.34 | 81 | 3.11 ± 1.32 |
| Day 85 | 83 | 0.93 ± 0.54 | 81 | 4.62 ± 2.09 |
| Day 274 | 72 | 0.34 ± 0.15 | 74 | 4.66 ± 2.03 |

Mean ± SD

a) Data on markedly high plasma nusinersen concentrations (1 subject on Day 85 [2177 ng/mL]; 5 subjects on Day 274 [4.22, 7.81, 17.5, 23.1, and 32.8 ng/mL]) were excluded from analysis.

b) Data on markedly high CSF nusinersen concentrations (3 subjects on Day 29 [23.8, 52.4, and 2031 ng/mL]; 3 subjects on Day 85 [1541, 6059, and 45,770 ng/mL]; 3 subjects on Day 274 [68.7, 805, and 9453 ng/mL]) were excluded from analysis.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Effect of age on pharmacokinetics

Given that age-based dosing, taking account of CSF volume, has been selected for patients <2 years of age, PMDA asked the applicant to explain the effect of age on the pharmacokinetics of nusinersen and then the appropriateness of not proposing age-based dosing for patients ≥2 years of age.

The applicant's explanation:

Nusinersen is administered intrathecally, and it has been reported that no major volumetric changes of CSF occur in humans ≥2 years of age (*Cereb Cortex*. 2001; 11:335-42). Based on the parameters obtained from PPK analysis[4)] using data from clinical studies in patients with infantile SMA and patients with Type II or III SMA, nusinersen trough concentrations in CSF over time were simulated. The results of simulation showed that CSF nusinersen concentrations were similar across all age groups. Thus, age is unlikely to have a significant impact on the pharmacokinetics of nusinersen in patients ≥2 years of age.

In a multi-regional phase III study in patients 2 to 9 years of age receiving 12 mg (a fixed dose) of nusinersen (CTD 5.3.5.1-1, Study CS4), patients were stratified by median age on Day 1 (<4.14 years or ≥4.14 years). The plasma pharmacokinetic parameters of nusinersen and nusinersen trough concentrations in CSF after the first dose by age group are shown in Table 2. There was no trend towards differences in plasma and CSF exposures between younger and older patients.

4) Initial application documents, CTD 5.3.3.5-2, CPP-17-001-BIIB058 analysis

Table 2. Plasma pharmacokinetic parameters of nusinersen and nusinersen trough concentrations in CSF after the first dose by age group in Study CS4

| | Plasma concentration (Day 1) | | | | CSF concentration (Day 29) | |
|---|---|---|---|---|---|---|
| | No. of evaluable subjects | $C_{max}$ (ng/mL) | $t_{max}$ (h)[a)] | $AUC_{0\text{-}24h}$ (ng·h/mL) | No. of evaluable subjects | Concentration (ng/mL) |
| <4.14 years | 42 | 362.7 ± 182.8 | 3.93 | 3599.8 ± 1204.7[b)] | 40 | 2.98 ± 1.12 |
| ≥4.14 years | 42 | 336.9 ± 180.0 | 3.81 | 3456.1 ± 1379.0[c)] | 41 | 3.25 ± 1.50 |

Mean ± SD
a) Median, b) n = 21, c) n = 24

Based on the above, there were no age-related differences in the pharmacokinetics of nusinersen in patients ≥2 years of age, and age-based dosing is not necessary.

PMDA accepted the above explanation.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results from a multi-regional phase III study in SMA patients (CTD 5.3.5.1-1, Study CS4) as efficacy and safety evaluation data.

### 7.1 Multi-regional phase III study (CTD 5.3.5.1-1, Study CS4 [ongoing since November 2014 (Data Cutoff, [redacted] 20[redacted])])

A sham-procedure controlled, randomized, double-blind, parallel-group study was conducted in 10 countries (the US, Canada, Spain, Italy, Germany, France, Sweden, China, South Korea, Japan) to assess the efficacy and safety of nusinersen in SMA patients 2 to 12 years of age who had onset of clinical signs and symptoms consistent with SMA at >6 months of age[5)] (target sample size, 117 subjects[6)]; 39 in the sham-procedure control group[7)] and 78 in the nusinersen group) [for pharmacokinetics, see Section 6.2]. Although a treatment period (9 months) and a post-treatment follow-up period (6 months) were included in the study, a decision to stop the study due to early demonstration of efficacy was made based on the results of an interim analysis.[8)]

Subjects were to undergo a sham procedure or receive 12-mg doses of nusinersen on Days 1, 29, 85, and 274. Patients who completed the study and wished to continue treatment with nusinersen and patients receiving study drug at the time of the decision to stop the study due to early demonstration of efficacy were allowed to participate in an extension study (initial application documents, reference data, CTD 5.3.5.4-3, Study CS11). In Study CS11, subjects assigned to the nusinersen group in Study CS4 were to receive 12-mg IT doses of nusinersen every 6 months following the last dose in Study CS4, and subjects assigned to the sham-procedure control group in Study CS4 were to receive 12-mg IT doses of nusinersen on Days 1, 29, and 85 followed by doses every 6 months.

5) Patients who met the following criteria were eligible.
· Genetic documentation of homozygous *SMN1* deletion or mutation or compound heterozygote
· Be able to sit independently, but has never had the ability to walk independently
· HFMSE score of ≥10 and ≤54
6) A feasibility survey was conducted among physicians treating SMA patients in Japan. Taking account of the estimated number of patients meeting the eligibility criteria and the expected enrollment period, it was forecasted that approximately 8 Japanese patients can be enrolled. A total of 8 Japanese patients were enrolled in the study.
7) The same study drug administration procedure as in the nusinersen group was to be performed. The lumbar puncture needle broke the skin but no IT injection of drug solution was to occur.
8) An interim analysis was to be conducted, once all subjects completed the Month 6 assessment and at least 39 subjects completed the Month 15 assessment. A final analysis was performed based on data at the time of the decision to stop the study due to early efficacy.

All of 126 randomized subjects (42 in the sham-procedure control group and 84 in the nusinersen group) were included in the ITT Set and in the Safety Set. There were no withdrawals.

The primary endpoint for the study was the change from baseline in the Hammersmith Functional Motor Scale - Expanded (HFMSE) score[9] at 15 months in the ITT Set. The results of the interim analysis is shown in Table 3. There was a statistically significant difference between the nusinersen and sham-procedure control groups ($P = 0.0000002$,[10] based on an ANCOVA model including treatment as a factor and age and baseline value as covariates).[11]

Table 3. Change from baseline in HFMSE score at 15 months in Study CS4 (ITT Set, multiple imputation method)

| | HFMSE score | | Change[a,b] | Treatment difference [95% confidence interval (CI)][b] | *P*-value[b,c] |
|---|---|---|---|---|---|
| | Baseline | 15 months | | | |
| Sham-procedure control | 19.9 ± 7.23 (42) | 19.9 ± 8.13 (19) | -1.9 ± 0.97 | 5.9 [3.7, 8.1] | 0.0000002 |
| Nusinersen | 22.4 ± 8.33 (84) | 24.9 ± 10.64 (35) | 4.0 ± 0.56 | | |

Mean ± SD (No. of evaluable subjects)
a) Adjusted mean ± standard error (SE)
b) Based on an ANCOVA model including treatment as a factor and age and baseline value as covariates
c) Significance level of 0.025 at interim analysis

The incidences of adverse events (including clinical laboratory abnormalities) were 100% (42 of 42 subjects) in the sham-procedure control group and 93% (78 of 84 subjects) in the nusinersen group, but no deaths were reported. Other serious adverse events occurred in 11 subjects in the sham-procedure control group (pneumonia [4 subjects]; faecaloma, parainfluenzae virus infection, pneumonia adenoviral, and respiratory distress; respiratory failure, bronchitis, and pneumonia; constipation, dehydration, and faecaloma; influenza and upper respiratory tract infection; influenza and respiratory distress; gastroenteritis and dehydration; and respiratory syncytial virus infection, 1 subject each) and 12 subjects in the nusinersen group (pneumonia viral [2 subjects]; respiratory distress, bacteraemia, and pneumonia; metapneumovirus infection and respiratory distress; parainfluenzae virus infection; post lumbar puncture syndrome; pneumonia moraxella; abdominal distension; bronchitis; gastroenteritis; pain; and pneumonia [1 subject each]), and a causal relationship to study drug could not be ruled out for post lumbar puncture syndrome and gastroenteritis observed in the nusinersen group.

The incidences of adverse events for which a causal relationship to study drug could not be ruled out were 31% (13 of 42 subjects) in the sham-procedure control group and 45% (38 of 84 subjects) in the nusinersen group. The main adverse events included headache (1 subject vs. 15 subjects [sham-procedure control vs. nusinersen]), pyrexia (4 subjects vs. 14 subjects), back pain (0 subjects vs. 10 subjects), vomiting (0 subjects

9) The HFMSE consists of measures of motor function in children with SMA. Motor function in the seated, supine, prone positions, etc. is scored from 0 (low function) to 2 (high function).
10) Significance level of 0.025 at interim analysis. Significance level at final analysis was to be determined by resampling.
11) After the initiation of the study, the method for analysis of the primary endpoint was changed as follows:
(1) Initial protocol (dated September 26, 2014. Amendment 1): An MMRM analysis (an unstructured variance-covariance matrix) with fixed effects for treatment, time, time-by-treatment interaction, and age, a random effect for subject, and a covariate for baseline value (significance level of 0.01 at interim analysis; significance level of 0.04 at final analysis)
(2) Final protocol (dated June 30, 2016. Amendment 2, revised after discussion with FDA); Analysis using an ANCOVA model including treatment as a factor and age and baseline value as covariates (significance level of 0.02 at interim analysis; significance level at final analysis was to be determined by resampling)
(3) Statistical analysis plan (dated October 12, 2016. Due to a high unmet medical need for treatment of SMA, significance level at interim analysis was increased.): Analysis using an ANCOVA model including treatment as a factor and age and baseline value as covariates (significance level of 0.025 at interim analysis; significance level at final analysis was to be determined by resampling)
Each analysis also demonstrated a statistically significant difference between the nusinersen and sham-procedure control groups [(1) $P = 0.0000013$; (2) $P = 0.0000002$].

vs. 9 subjects), post lumbar puncture syndrome (0 subjects vs. 3 subjects), upper respiratory tract infection (1 subject vs. 2 subjects).

There were no clinically relevant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate). The observed ECG findings were left ventricular hypertrophy (2 subjects), electrocardiogram T wave abnormal (1 subject), and electrocardiogram Q wave abnormal (1 subject) in the sham-procedure control group.

The applicant's explanation:
The above data demonstrated the efficacy of nusinersen in SMA patients 2 to 12 years of age who had symptom onset at >6 months of age. Although a certain number of serious adverse events occurred, there were no major differences in the nature or incidence of adverse events between the nusinersen and sham-procedure control groups, and there should be no major safety issues.

**7.R Outline of the review conducted by PMDA**

**7.R.1 Clinical positioning of nusinersen**

PMDA asked the applicant to explain the clinical positioning of nusinersen.

The applicant's explanation:
As the standard of care in SMA, the International Expert Consensus released in 2007 (*J Child Neurol*. 2007; 22: 1027-49) and the clinical practice manual in Japan (Clinical Practice Manual for Spinal Muscular Atrophy. Kinpodo; 2012) list supportive measures such as respiratory therapy, rehabilitation, nutritional support, and surgical therapy for the care of patients with non-infantile SMA, but not drug therapies that alter disease progression. Although adenosine triphosphate disodium hydrate for injection has been approved for the indications of "improvement of the symptoms of progressive spinal muscular atrophy and its similar diseases" in Japan, the above Expert Consensus does not recommend its use. Medical experts in Japan also commented that adenosine triphosphate disodium hydrate for injection is not actively used for the treatment of SMA in clinical practice. At present, no effective treatment for non-infantile SMA has been established worldwide.

In a multi-regional phase III study in mainly Type II or III SMA patients (CTD 5.3.5.1-1, Study CS4), patients treated with nusinersen achieved improved motor function compared to sham-procedure controls. Given the mechanism of action of nusinersen, the efficacy of nusinersen is expected in patients with any type of SMA [see Section 7.R.6]. Thus, nusinersen will offer a new treatment option for patients with non-infantile SMA.

PMDA accepts the above, and considers that nusinersen will offer a new treatment option for patients with non-infantile SMA.

**7.R.2 Evaluation based on multi-regional study**

**7.R.2.1 Intrinsic and extrinsic ethnic factors**

PMDA asked the applicant to explain how intrinsic and extrinsic ethnic factors that influence the efficacy and safety of nusinersen were taken into consideration when conducting a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4).

The applicant's explanation:

- The pharmacokinetics of nusinersen in Japanese patients were unknown at the time of planning Study CS4. However, ethnic differences in the pharmacokinetics of nusinersen are unlikely to be seen because (i) it was considered that there are no ethnic differences in the activities of 3' and 5' exonucleases, the major metabolizing enzymes for nusinersen, and (ii) nusinersen is not a substrate for CYPs etc. and is therefore not affected by ethnic differences in metabolizing enzyme activities.
- There are no racial or ethnic differences in the genetic cause of SMA (*Genet Test Mol Biomarkers*. 2012; 16: 123-9), and Japanese SMA patients are similar to SMA patients in other countries, from a pathological point of view (*Brain Dev*. 2011; 33: 321-31). There are no reports that there are racial, ethnic, or regional differences in the prevalence or incidence of SMA.
- Diagnosis and standard of care of SMA have been based on the Expert Consensus released in Japan and globally in 2007 (*J Child Neurol*. 2007; 22:1027-49).
- Appropriate measures were taken to allow a unified efficacy evaluation: In order to allow a unified assessment by HFMSE score, the primary endpoint for Study CS4, relevant physical therapists were required to attend assessment training regularly, and a series of assessments for each patient were required to be performed by the same physical therapist wherever possible.

The above information indicated that the impacts of intrinsic and extrinsic ethnic factors on the efficacy and safety evaluation of nusinersen were small. The applicant therefore decided to conduct a phase III study as a multi-regional study and to allow the participation of Japanese subjects in this study. The applicant considered such decision was appropriate.

**7.R.2.2 Differences in efficacy and safety among regions in Study CS4**

PMDA asked the applicant to explain interregional differences in the efficacy and safety of nusinersen in Study CS4.

The applicant's explanation:

Due to the very limited number of Japanese patients, it was considered appropriate to assess ethnic differences between the East Asian population including Japanese patients and other ethnic patient populations or the overall population. In the ITT Set of Study CS4, patient characteristics were compared among regions (North America/Europe/East Asia [including Japan]). East Asian patients in the nusinersen group tended to have higher age (median [years]) at baseline (3.0 in North America, 3.5 in Europe, 6.0 in East Asia) and a longer disease duration (median [months]) (37.9 in North America, 37.4 in Europe, 62.0 in East Asia), and there were no clinically meaningful differences in other demographic or baseline characteristics among the regions. Because (i) a trend towards a greater treatment difference in the subgroup of patients with a shorter disease

duration was suggested (Table 7) and (ii) East Asian patients had no 15-month data, it was difficult to assess differences in the efficacy of nusinersen between East Asian patients and the overall population. However, the results in North American or European patients were similar to those in the overall population (Table 4).

Table 4. Change from baseline in HFMSE score at 15 months by region in Study CS4 (ITT, OC)

| | Change in HFMSE score | | Treatment difference [95% CI][a)] |
|---|---|---|---|
| | Sham-procedure control | Nusinersen | |
| Overall population | -2.2 ± 1.00 (19) | 4.6 ± 0.73 (35) | 6.8 [4.3, 9.3] |
| North America | -2.4 ± 1.16 (15) | 4.4 ± 0.82 (30) | 6.8 [3.9, 9.7] |
| Europe | -2.1 ± 1.47 (4) | 5.7 ±1.32 (5) | 7.7 [2.6, 12.8] |
| East Asia[b)] | - | - | - |

Adjusted mean ± SE (No. of evaluable subjects)
-: Not calculable due to lack of 15-month data
a) Based on an ANCOVA model including treatment as a factor and age and baseline value as covariates
b) China, Korea, Japan

Many of Japanese patients had higher age at baseline and a longer disease duration. The results of subgroup analyses of the overall population (Table 7) suggest that efficacy may be reduced in Japanese patients. The changes from baseline in HFMSE score over time in individual Japanese patients are presented (Table 5). A change from baseline of -1 to 3 was observed in 5 Japanese patients who completed the Month 6 assessment as of the Data Cutoff, and a change from baseline of 5 was observed in 1 Japanese patient who completed the Month 9 assessment as of the Data Cutoff. Only the limited number of Japanese patients were assessed, and unlike in the overall population, the sham-procedure control group showed a trend towards improvement. However, there was no trend towards substantial differences compared to the changes in the nusinersen group in the overall population (adjusted mean ± SE [95% CI]; 2.3 ± 0.36 [1.6, 3.0] at 6 months, 3.1 ± 0.43 [2.3, 4.0] at 9 months). Thus, the efficacy of nusinersen in Japanese patients is unlikely to be substantially inferior to that in non-Japanese patients.

Table 5. Changes from baseline in HFMSE score over time in the overall population and individual Japanese patients in Study CS4

| | | 3 months | 6 months | 9 months | 12 months | 15 months |
|---|---|---|---|---|---|---|
| Overall population[a)] | Sham-procedure control (N = 42) | 1.0 ± 0.45 | 1.7 ± 0.51 | 0.6 ± 0.61 | -0.5 ± 0.70 | -1.9 ± 0.97 |
| | Nusinersen (N = 84) | 1.6 ± 0.32 | 2.3 ± 0.36 | 3.1 ± 0.43 | 3.2 ± 0.49 | 4.0 ± 0.56 |
| Japanese patients[b)] | Sham-procedure control | 3 | 5 | - | - | - |
| | | 7 | 8 | 8 | 7 | - |
| | | 8 | 4 | 5 | - | - |
| | Nusinersen | 3 | 2 | - | - | - |
| | | 2 | 3 | 5 | - | - |
| | | 1 | 2 | - | - | - |
| | | -1 | 3 | - | - | - |
| | | -5 | -1 | - | - | - |

- : Not measured.
a) Adjusted mean ± SE based on an ANCOVA model including treatment as a factor and age and baseline value as covariates (Missing values were imputed using multiple imputation method)
b) Changes from baseline in individual patients

The occurrence of adverse events by region in Study CS4 is shown in Table 6. There were no clear differences in the observed events among the regions.

Table 6. Occurrence of adverse events by region in Study CS4

| | North America | | Europe | | East Asia[a)] | | Japan | |
|---|---|---|---|---|---|---|---|---|
| | S group | Nusinersen | S group | Nusinersen | S group | Nusinersen | S group | Nusinersen |
| N | 23 | 47 | 14 | 28 | 5 | 9 | 3 | 5 |
| All adverse events | 23 (100) | 46 (97.9) | 14 (100) | 25 (89.3) | 5 (100) | 7 (77.8) | 3 (100) | 3 (60.0) |
| Serious adverse events | 7 (30.4) | 8 (17.0) | 2 (14.3) | 2 (7.1) | 2 (40.0) | 2 (22.2) | 2 (66.7) | 1 (20.0) |
| Main adverse events | | | | | | | | |
| Pyrexia | 9 (39.1) | 22 (46.8) | 4 (28.6) | 10 (35.7) | 2 (40.0) | 1 (11.1) | 1 (33.3) | 1 (20.0) |
| Upper respiratory tract infection | 13 (56.5) | 18 (38.3) | 1 (7.1) | 2 (7.1) | 2 (40.0) | 3 (33.3) | 0 | 0 |
| Headache | 2 (8.7) | 18 (38.3) | 1 (7.1) | 4 (14.3) | 0 | 1 (11.1) | 0 | 1 (20.0) |
| Vomiting | 3 (13.0) | 17 (36.2) | 1 (7.1) | 3 (10.7) | 0 | 1 (11.1) | 0 | 1 (20.0) |
| Back pain | 0 | 15 (31.9) | 0 | 6 (21.4) | 0 | 0 | 0 | 0 |
| Cough | 5 (21.7) | 14 (29.8) | 2 (14.3) | 4 (14.3) | 2 (40.0) | 2 (22.2) | 1 (33.3) | 2 (40.0) |
| Gastroenteritis viral | 4 (17.4) | 8 (17.0) | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 7 (30.4) | 6 (12.8) | 6 (42.9) | 9 (32.1) | 2 (40.0) | 2 (22.2) | 2 (66.7) | 2 (40.0) |
| Diarrhoea | 1 (4.3) | 6 (12.8) | 1 (7.1) | 1 (3.6) | 1 (20.0) | 1 (11.1) | 1 (33.3) | 0 |
| Upper respiratory tract congestion | 2 (8.7) | 5 (10.6) | 0 | 0 | 0 | 0 | 0 | 0 |
| Rhinorrhoea | 4 (17.4) | 4 (8.5) | 2 (14.3) | 0 | 1 (20.0) | 1 (11.1) | 1 (33.3) | 1 (20.0) |
| Epistaxis | 0 | 4 (8.5) | 0 | 0 | 0 | 2 (22.2) | 0 | 1 (20.0) |
| Gastroenteritis | 4 (17.4) | 3 (6.4) | 3 (21.4) | 3 (10.7) | 0 | 0 | 0 | 0 |
| Bronchitis | 1 (4.3) | 3 (6.4) | 2 (14.3) | 4 (14.3) | 1 (20.0) | 1 (11.1) | 0 | 1 (20.0) |
| Influenza | 1 (4.3) | 3 (6.4) | 2 (14.3) | 4 (14.3) | 0 | 1 (11.1) | 0 | 1 (20.0) |

n (incidence [%])
S group: sham-procedure control group
a) China, Korea, Japan

The above findings are summarized below. Since there were slight interregional differences in patient characteristics in Study CS4, it was difficult to conclude on differences in efficacy between the East Asian population and the overall population. Meanwhile, there seemed no major differences in efficacy between the North America and European populations and between Japanese patients and the overall population, nor were there any major interregional differences in safety.

PMDA's view:

Given that there should be no major differences in intrinsic or extrinsic ethnic factors associated with SMA, there were no major problems with the conduct of Study CS4 as a multi-regional study. Because (i) there were differences in patient characteristics and (ii) the number of patients was limited, the consistency of efficacy results between the East Asian population/the Japanese subgroup and the overall population could not be examined based on between-group comparison. However, the efficacy and safety of nusinersen in Japanese patients can be evaluated based on the results from Study CS4, for the following reasons: (1) there were no major differences in the change in HFMSE score over time in the nusinersen group between the Japanese subgroup and the overall population, (2) no major interregional differences in safety were observed, and (3) SMA is a rare disease. The efficacy of nusinersen in Japanese patients is expected based on the results of the study. Since the number of Japanese patients who participated in the clinical study is very small at present, the applicant should continue to collect information on the safety and efficacy of nusinersen via post-marketing surveillance. A final decision on the above will be made, taking account of comments from the Expert Discussion.

**7.R.3 Efficacy of nusinersen**

**7.R.3.1 Appropriateness of primary endpoint for multi-regional phase III study (CTD 5.3.5.1-1, Study CS4)**

PMDA asked the applicant to explain the appropriateness of selecting HFMSE score as the primary endpoint for a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4).

The applicant's explanation:
Since patients with Type II or III SMA (the main population for Study CS4) have a better survival prognosis as compared with patients with infantile SMA, selecting a motor function endpoint, instead of a time to an event (e.g., death, permanent ventilation) endpoint, as the primary endpoint, was considered appropriate. The HFMSE, which was selected as the primary endpoint for Study CS4, was developed as an expanded version of the HFMS (developed as a scale consisting of 20 items to assess motor ability and clinical progression in Type II or III SMA patients with limited ambulation) (*Eur J Paediatr Neurol*. 2003; 7: 155-9) that adds 13 items for the assessment of ambulatory SMA patients. Moreover, the HFMSE was highly correlated with another motor function scale (Gross Motor Function Measure[12)]), showed excellent reliability (*Neuromuscul Disord.* 2007; 17: 693-7), and was appropriately validated for use in SMA patients (*BMC Neurol.* 2017; 17: 39). Thus, selection of the HFMSE as the primary endpoint for Study CS4 should be appropriate.

PMDA's view:
The above explanation is acceptable. There were no major problems with selecting HFMSE score as the primary endpoint for Study CS4. Because patients with SMA consistent with Type II or III have a better survival prognosis as compared with patients with infantile SMA, nusinersen is expected to be used over a longer period of time. Clinical studies in mainly Type I SMA patients (initial application documents, CTD 5.3.5.1-1, Study CS3B and Reference data CTD 5.3.5.4-3, Study CS11) suggested that patients treated with nusinersen can acquire motor milestones but subsequently lose them with the progression of SMA symptoms. Thus, the applicant should continue to collect information on the efficacy of nusinersen administered over a longer period of time via post-marketing surveillance.

**7.R.3.2 Factors affecting the efficacy of nusinersen**
PMDA asked the applicant to explain the factors affecting the efficacy of nusinersen.

The applicant's explanation:
The results of subgroup analyses of the change from baseline in HFMSE score at 15 months according to patient characteristics are presented (Table 7). Although the difference in the change in HFMSE score between the nusinersen and sham-procedure control groups tended to be smaller in the subgroup of patients with onset at higher age, the subgroup of patients with higher age at baseline, the subgroup of patients with a disease duration of ≥25 months, and the subgroup of patients with scoliosis, there was a trend towards improvement in the nusinersen group compared to the sham-procedure control group across all subgroups. No subgroups showed substantially reduced efficacy of nusinersen. The impact of *SMN2* copy number could not be examined due to the limited number of patients with *SMN2* copy number other than 3.

12) A measure developed to evaluate changes in the gross motor function of children with cerebral palsy. It consists of 88 items that have been categorized into 5 dimensions of gross motor function: lying and rolling; sitting; crawling and kneeling; standing; and walking, running, and jumping (*Neuromuscul Disord*. 2006; 16: 374-80). It is used also for clinical assessment of SMA (*Neuromuscul Disord*. 2007; 17: 693-7).

Table 7. Change from baseline in HFMSE score at 15 months by patient characteristics in Study CS4 (ITT Set, OC)

| | | Change in HFMSE score[a)] | | Treatment difference [95% CI][a)] |
|---|---|---|---|---|
| | | Sham-procedure control | Nusinersen | |
| Overall population | | -2.2 ± 1.00 (19) | 4.6 ± 0.73 (35) | 6.8 [4.3, 9.3] |
| Gender | Male | -3.2 ± 1.56 (10) | 4.7 ± 1.23 (16) | 8.0 [3.8, 12.1] |
| | Female | -0.2 ± 1.63 (9) | 4.0 ± 1.12 (19) | 4.1 [0.1, 8.2] |
| Age of onset | ≤10 months | -2.8 ± 1.47 (9) | 4.5 ± 1.00 (19) | 7.2 [3.5, 10.9] |
| | >10 months | -1.0 ± 1.77 (10) | 4.2 ± 1.40 (16) | 5.2 [0.6, 9.9] |
| Age at screening | ≤3 years | -1.6 ± 1.39 (13) | 6.5 ± 1.21 (17) | 8.1 [4.3, 11.9] |
| | >3 years | -1.6 ± 1.87 (6) | 2.1 ± 1.03 (18) | 3.7 [-0.9, 8.3] |
| *SMN2* copy number | 2 | -11.6 (1) [c)] | 2, 11 (2) [c)] | 20.4 |
| | 3 | -0.9 ± 1.12 (17) | 4.1 ± 0.81 (33) | 5.0 [2.2, 7.7] |
| | 4 | -10 (1) [c)] | - (0) [b)] | - |
| Disease duration | <25 months | -1.7 ± 1.88 (10) | 8.1 ± 1.88 (10) | 9.8 [3.8, 15.8] |
| | ≥25 months and <44 months | 0.6 ± 1.72 (6) | 3.2 ± 1.05 (15) | 2.6 [-1.8, 6.9] |
| | ≥44 months | -7.7 ± 1.61 (3) | 2.5 ± 0.75 (10) | 10.2 [5.9, 14.6] |
| Baseline HFMSE score | ≤19 | -0.9 ± 1.41 (8) | 3.3 ± 0.89 (20) | 4.3 [0.8, 7.7] |
| | >19 | -2.1 ± 1.68 (11) | 5.4 ± 1.44 (15) | 7.4 [2.9, 12.0] |
| SMA type[13)] | Consistent with Type II | -2.2 ± 1.42 (12) | 4.1 ± 0.91 (29) | 6.3 [2.9, 9.7] |
| | Consistent with Type III | -1.0 ± 1.97 (7) | 5.3 ± 2.13 (6) | 6.3 [-0.2, 12.8] |
| Scoliosis | Yes | 1.2 ± 1.52 (6) | 2.4 ± 1.00 (14) | 1.3 [-2.6, 5.1] |
| | No | -3.1 ± 1.42 (13) | 5.5 ± 1.11 (21) | 8.6 [4.9, 12.3] |

Adjusted mean ± SE (No. of evaluable subjects)
-: Not calculable
a) Overall population and disease duration: based on an ANCOVA model including treatment as a factor and age and baseline value as covariates
Other factors: based on an ANCOVA model including treatment as a factor and baseline value as a covariate
b) HFMSE score measured at 15 months was not available.
c) Measured value in each subject

PMDA's view:

The above explanation is acceptable. However, Study CS4 assessed the efficacy of nusinersen in very few patients with *SMN2* copy number other than 3, and the number of evaluable subjects was limited for other patient characteristics as well. Thus, the applicant should continue to collect information on the impact of *SMN2* copy number and other factors on the efficacy of nusinersen via post-marketing surveillance.

### 7.R.4 Safety of nusinersen

#### 7.R.4.1 Differences in safety compared with the previously approved indication

PMDA asked the applicant to explain differences in the safety profile of nusinersen between a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4) and a clinical study in the previously approved indication of infantile SMA.

The applicant's explanation:

Main adverse events occurring in Study CS4 (interim analysis) and a clinical study in infantile SMA patients (Initial application documents, CTD 5.3.5.1-2, Study CS3B [final analysis][14)]) are shown in Table 8. Although headache, vomiting, and back pain occurred more frequently in nusinersen-treated subjects in Study CS4, these events were considered related to lumbar puncture or associated analgesia/sedation. These safety data suggested no risk specific to patients included in Study CS4.

13) Classified based on the following definitions:
Consistent with Type III: Subjects who (1) previously achieved the milestone of "ambulation with support" or "independent ambulation (≥15 feet)" before baseline, (2) have *SMN2* copy number = 4, or (3) have achieved the motor milestone of "ambulation with support" at baseline
Consistent with Type II: Subjects who do not meet the above definition of Type III in the ITT Set

14) A sham-procedure-controlled, randomized, double-blind, parallel-group study to assess the efficacy, safety, and pharmacokinetics of nusinersen in mainly Type I SMA patients (≤7 months of age at screening, a deletion or mutation of the *SMN1* gene, 2 copies of the *SMN2* gene). Assessment was based on the results of the interim analysis for the initial application for nusinersen.

Table 8. Main adverse events in Studies CS4 and CS3B

| | Study CS4 | | Study CS3B | |
|---|---|---|---|---|
| | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| N | 42 | 84 | 41 | 80 |
| Adverse events | 42 (100) | 78 (92.9) | 40 (97.6) | 77 (96.3) |
| Main adverse events | | | | |
| Pyrexia | 15 (35.7) | 33 (39.3) | 24 (58.5) | 45 (56.3) |
| Upper respiratory tract infection | 16 (38.1) | 23 (27.4) | 9 (22.0) | 24 (30.0) |
| Headache | 3 (7.1) | 23 (27.4) | 0 | 0 |
| Vomiting | 4 (9.5) | 21 (25.0) | 8 (19.5) | 14 (17.5) |
| Back pain | 0 | 21 (25.0) | 0 | 1 (1.3) |
| Cough | 9 (21.4) | 20 (23.8) | 8 (19.5) | 9 (11.3) |
| Nasopharyngitis | 15 (35.7) | 17 (20.2) | 4 (9.8) | 15 (18.8) |
| Diarrhoea | 3 (7.1) | 8 (9.5) | 7 (17.1) | 11 (13.8) |
| Constipation | 5 (11.9) | 4 (4.8) | 9 (22.0) | 28 (35.0) |
| Pneumonia | 7 (16.7) | 4 (4.8) | 7 (17.1) | 23 (28.8) |
| Rash | 2 (4.8) | 3 (3.6) | 4 (9.8) | 9 (11.3) |
| Respiratory tract infection | 1 (2.4) | 3 (3.6) | 2 (4.9) | 9 (11.3) |
| Nasal congestion | 2 (4.8) | 3 (3.6) | 5 (12.2) | 8 (10.0) |
| Viral infection | 2 (4.8) | 3 (3.6) | 3 (7.3) | 8 (10.0) |
| Respiratory distress | 2 (4.8) | 2 (2.4) | 12 (29.3) | 21 (26.3) |
| Bronchiolitis | 0 | 2 (2.4) | 3 (7.3) | 8 (10.0) |
| Viral upper respiratory tract infection | 2 (4.8) | 2 (2.4) | 7 (17.1) | 8 (10.0) |
| Oxygen saturation decreased | 0 | 1 (1.2) | 10 (24.4) | 10 (12.5) |
| Respiratory failure | 1 (2.4) | 0 | 16 (39.0) | 20 (25.0) |
| Atelectasis | 0 | 0 | 12 (29.3) | 18 (22.5) |
| Teething | 0 | 0 | 3 (7.3) | 14 (17.5) |
| Acute respiratory failure | 0 | 0 | 10 (24.4) | 11 (13.8) |
| Gastrooesophageal reflux disease | 1 (2.4) | 0 | 8 (19.5) | 10 (12.5) |
| Rhinovirus infection | 0 | 0 | 6 (14.6) | 10 (12.5) |
| Dysphagia | 0 | 0 | 9 (22.0) | 9 (11.3) |
| Pneumonia aspiration | 0 | 0 | 7 (17.1) | 9 (11.3) |

n (Incidence [%])

Then the applicant explained the occurrence of lumbar puncture-related adverse events, CNS adverse events, renal impairment, and hepatic impairment, effect on the blood coagulation system, and QT/QTc interval prolongation as adverse events of special interest associated with nusinersen. The detailed explanation is presented in the following sections.

### 7.R.4.1.1 Lumbar puncture-related adverse events

The applicant's explanation:

The occurrence of lumbar puncture-related adverse events[15)] in Studies CS4 (interim analysis) and CS3B (final analysis) is shown in Table 9. The incidence of lumbar puncture-related adverse events in the nusinersen group was higher in Study CS4 compared to Study CS3B. The incidence in the nusinersen group was higher in Study CS4 because infants included in Study CS3B had not developed verbal communication skills and were possibly unable to verbally report the typical symptoms of lumbar puncture such as headache and back pain. Although the reason for a higher incidence of vomiting in the nusinersen group in Study CS4 is unknown, lumbar puncture-related adverse events reported in Study CS4 were all mild or moderate in severity. Post lumbar puncture syndrome (1 subject) only was reported as a serious adverse event, which resolved 4 days later. There were no events leading to treatment discontinuation.

15) Events coded to the following MedDRA PTs:
back pain, cerebrospinal fluid leakage, epidural haemorrhage, extradural haematoma, headache, injection site haematoma, injection site haemorrhage, injection site pain, nausea, post lumbar puncture syndrome, post procedural complication, post procedural contusion, post procedural discomfort, post procedural swelling, procedural complication, procedural headache, procedural nausea, procedural pain, procedural site reaction, puncture site pain, spinal cord haematoma, spinal subarachnoid haemorrhage, subdural haematoma, vomiting, procedural dizziness, brain herniation, lumbar puncture abnormal, traumatic lumbar puncture

Table 9. Lumbar puncture-related adverse events in Studies CS4 and CS3B

| | Study CS4 | | Study CS3B | |
|---|---|---|---|---|
| | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| N | 42 | 84 | 41 | 80 |
| Lumbar puncture-related adverse events | 7 (16.7) | 40 (47.6) | 9 (22.0) | 17 (21.3) |
| Main adverse events | | | | |
| Headache | 3 (7.1) | 23 (27.4) | 0 | 0 |
| Vomiting | 4 (9.5) | 21 (25.0) | 8 (19.5) | 14 (17.5) |
| Nausea | 2 (4.8) | 2 (2.4) | 0 | 0 |
| Back pain | 0 | 21 (25.0) | 0 | 1 (1.3) |
| Post lumbar puncture syndrome | 0 | 3 (3.6) | 0 | 0 |
| Procedural pain | 1 (2.4) | 2 (2.4) | 0 | 2 (2.5) |
| Procedural nausea | 0 | 1 (1.2) | 0 | 0 |

n (Incidence [%])

Based on the above, no further precautions about lumbar puncture-related adverse events associated with nusinersen in the package insert are required because relevant events have been listed in the other adverse reactions section of the package insert.

### 7.R.4.1.2 CNS adverse events

The applicant's explanation:

The occurrence of CNS adverse events[16)] in Studies CS4 (interim analysis) and CS3B (final analysis) is shown in Table 10. The incidence of CNS adverse events in the nusinersen group was higher in Study CS4 compared to Study CS3B, and most of the events were headache, which were considered to be lumbar puncture-related adverse events. Because there were no CNS adverse events of concern other than lumbar puncture-related adverse events [see Section 7.R.4.1.1] in Study CS4, no further precautions in the package insert should be required.

Table 10. CNS adverse events in Studies CS4 and CS3B

| | Study CS4 | | Study CS3B | |
|---|---|---|---|---|
| | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| N | 42 | 84 | 41 | 80 |
| CNS adverse events | 8 (19.0) | 32 (38.1) | 15 (36.6) | 22 (27.5) |
| Main adverse events | | | | |
| Headache | 3 (7.1) | 23 (27.4) | 0 | 0 |
| Muscle contractions involuntary | 2 (4.8) | 3 (3.6) | 0 | 1 (1.3) |
| Post lumbar puncture syndrome | 0 | 3 (3.6) | 0 | 0 |
| Dysphonia | 0 | 2 (2.4) | 0 | 0 |
| Insomnia | 0 | 2 (2.4) | 0 | 0 |
| Sleep apnoea syndrome | 0 | 1 (1.2) | 4 (9.8) | 0 |
| Failure to thrive | 1 (2.4) | 0 | 2 (4.9) | 3 (3.8) |
| Irritability | 0 | 0 | 1 (2.4) | 3 (3.8) |
| Agitation | 0 | 0 | 2 (4.9) | 2 (2.5) |
| Nystagmus | 0 | 0 | 1 (2.4) | 2 (2.5) |
| Anxiety | 0 | 0 | 0 | 2 (2.5) |

n (Incidence [%])

16) Events coded to the MedDRA SOCs "Nervous system disorders" and "Psychiatric disorders"

**7.R.4.1.3 Renal impairment**

The applicant's explanation:

Abnormal changes in laboratory values for renal function (urine protein, BUN, creatinine, cystatin C) observed in Studies CS4 (interim analysis) and CS3B (final analysis) were assessed. As a result, 33.3% (14 of 42) of subjects in the sham-procedure control group and 50.0% (42 of 84) of subjects in the nusinersen group in Study CS4 and 17.1% (7 of 41) of subjects in the sham-procedure control group and 32.5% (26 of 80) of subjects in the nusinersen group in Study CS3B had abnormally high/positive urine protein after study drug administration. There were no abnormal changes in other laboratory values for renal function. The incidences of renal impairment-related adverse events[17)] were 2.4% in the sham-procedure control group (1 of 42 subjects; white blood cells urine positive) and 1.2% in the nusinersen group (1 of 84 subjects; urine analysis abnormal) in Study CS4 (interim analysis) and 2.4% (1 of 41 subjects) in the sham-procedure control group and 12.5% (10 of 80 subjects) in the nusinersen group in Study CS3B (final analysis). There was no trend towards a higher incidence in Study CS4 compared to Study CS3B.

As described above, Study CS4 detected no risk of new apparent renal impairment, and a precaution about renal impairment associated with nusinersen has been provided in the package insert. Therefore, no further precautions in the package insert are required.

**7.R.4.1.4 Hepatic impairment**

The applicant's explanation:

The proportions of patients who had abnormally high ALT after study drug administration were 7.1% (3 of 42 subjects) in the sham-procedure control group and 2.4% (2 of 84 subjects) in the nusinersen group in Study CS4 (interim analysis) and 9.8% (4 of 41 subjects) in the sham-procedure control group and 12.5% (10 of 80 subjects) in the nusinersen group in Study CS3B (final analysis). The proportions of patients who had abnormally high AST were 2.4% (1 of 42 subjects) in the sham-procedure control group and 2.4% (2 of 84 subjects) in the nusinersen group in Study CS4 and 2.4% (1 of 41 subjects) in the sham-procedure control group and 6.3% (5 of 80 subjects) in the nusinersen group in Study CS3B. The results were similar between Studies CS4 and CS3B. The incidences of hepatic impairment-related adverse events[18)] were 2.4% (1 of 42 subjects) in the sham-procedure control group and 0% (0 of 84 subjects) in the nusinersen group in Study CS4 (interim analysis) and 2.4% (1 of 41 subjects) in the sham-procedure control group and 3.8% (3 of 80 subjects) in the nusinersen group in Study CS3B (final analysis). There was no trend towards a higher incidence in Study CS4 compared to Study CS3B.

As described above, Study CS4 detected no risk of new apparent hepatic impairment, and a precaution about hepatic impairment associated with nusinersen has been provided in the package insert. Therefore, no further precautions in the package insert are required.

17) Events coded to the MedDRA SOC "Renal and urinary disorders" and HLGT "Renal and urinary tract investigations and urinalyses"
18) Events in the MedDRA SMQ "Drug related hepatic disorders - comprehensive search"

### 7.R.4.1.5 Effect on blood coagulation system

The applicant's explanation:

The proportions of patients who had abnormally low platelet count after study drug administration were 25.6% (10 of 39 subjects) in the sham-procedure control group and 19.7% (15 of 76 subjects) in the nusinersen group in Study CS4 (interim analysis) and 0% (0 of 33 subjects) in the sham-procedure control group and 12.9% (9 of 70 subjects) in the nusinersen group in Study CS3B (final analysis). There was no trend towards a higher incidence in the nusinersen group in Study CS4 (interim analysis).

The occurrence of coagulation-related adverse events[19)] in Studies CS4 (interim analysis) and CS3B (final analysis) is shown in Table 11. Epistaxis occurred frequently in the nusinersen group in Study CS4. Coagulation-related adverse events observed in Study CS4 were all mild or moderate in severity. There were no serious adverse events or events leading to treatment discontinuation. A causal relationship to nusinersen was denied except for 1 case of epistaxis.

Table 11. Coagulation-related adverse events in Studies CS4 and CS3B

| | Study CS4 | | Study CS3B | |
|---|---|---|---|---|
| | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| N | 42 | 84 | 41 | 80 |
| Coagulation-related adverse events | 0 | 7 (8.3) | 7 (17.1) | 5 (6.3) |
| Main adverse events | | | | |
| Epistaxis | 0 | 6 (7.1) | 0 | 0 |
| Vessel puncture site bruise | 0 | 1 (1.2) | 2 (4.9) | 0 |
| Haemorrhage subcutaneous | 0 | 1 (1.2) | 0 | 0 |
| Haematochezia | 0 | 0 | 0 | 2 (2.5) |
| Ecchymosis | 0 | 0 | 0 | 2 (2.5) |

n (Incidence [%])

As described above, there was no new apparent effect on the blood coagulation system in Study CS4, and a precaution about the effect of nusinersen on the blood coagulation system has been provided in the package insert. Therefore, no further precautions in the package insert are required.

### 7.R.4.1.6 QT/QTc interval prolongation

The applicant's explanation:

The results of categorical analysis of QTcF interval data in Studies CS4 (interim analysis) and CS3B (final analysis) are shown in Table 12. In both studies, more patients in the nusinersen group had an absolute QTcF value >500 ms or a change from baseline of >60 ms. Study CS4 did not suggest greater risk than Study CS3B.

19) Events in the MedDRA SMQs "Embolic and thrombotic events" and "Haemorrhages"

Table 12. Results of categorical analysis of QTcF interval data in Studies CS4 and CS3B

| | | Study CS4 | | Study CS3B | |
|---|---|---|---|---|---|
| | | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| N | | 41 | 81 | 41 | 80 |
| Maximum QTcF interval through the last time point (ms) | >450 | 0 | 4 (4.9) | 13 (31.7) | 24 (30.0) |
| | >480 | 0 | 3 (3.7) | 2 (4.9) | 7 (8.8) |
| | >500 | 0 | 1(1.2) | 0 | 3 (3.8) |
| Change from baseline in QTcF interval (ms) | >30 | 7 (17.1) | 22 (27.2) | 12 (29.3) | 17 (21.3) |
| | >60 | 0 | 6 (7.4) | 4 (9.8) | 5 (6.3) |

n (Incidence [%])

No adverse events related to QT/QTc interval prolongation and proarrhythmia[20)] were reported in Study CS4. In Study CS3B, the incidences of adverse events related to QT/QTc interval prolongation and proarrhythmia were 17.1% (7 of 41 subjects) in the sham-procedure control group and 10.0% (8 of 80 subjects) in the nusinersen group. Study CS4 did not suggest greater risk than Study CS3B.

Based on the above, no new precautions in the package insert are required at present. On the other hand, Study CS4 or CS3B was not intended to assess the risk of QT/QTc interval prolongation, and interpretation of the study results had limitations. However, increased number of patients in the nusinersen group had QTcF interval prolongation in both studies. ECG will be assessed in as many patients as possible at an appropriate time point after administration of nusinersen and information on the risk of QT/QTc interval prolongation will be collected via post-marketing surveillance.

PMDA's view:

The incidences of some lumbar puncture-related adverse events such as headache and back pain in the nusinersen group were higher in Study CS4 compared to Study CS3B, but the applicant's explanation (infants included in Study CS3B had not developed verbal communication skills, and were possibly unable to verbally report the typical symptoms of lumbar puncture such as headache and back pain) is understandable. Although the incidence of vomiting in the nusinersen group was higher in Study CS4 compared to Study CS3B, all events were mild or moderate in severity. No additional precautions are required at present. The applicant should appropriately communicate information on the risk of QT/QTc interval prolongation observed in clinical studies to healthcare professionals in clinical practice. No additional precautions about other adverse events are required at present. However, the applicant should continue to collect information on the occurrence of lumbar puncture-related adverse events, CNS adverse events, renal impairment, and hepatic impairment, effect on the blood coagulation system, and adverse events related to QT/QTc interval prolongation and proarrhythmia via post-marketing surveillance.

### 7.R.4.2 Effect on growth

PMDA asked the applicant to explain the effect of nusinersen on growth.

20) Events in the MedDRA SMQ "Torsade de pointes/QT prolongation [narrow]" and PTs sudden death, ventricular fibrillation, ventricular flutter, syncope, and epilepsy

The applicant's explanation:

Weight-for-age percentile based on WHO Child Growth Standards[21)] over time in a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4) (interim analysis) is shown in Table 13. A population that attended the Day 365 or 456 assessment consisted of patients who were enrolled in the study earlier, and incidental differences in weight-for-age percentile at baseline were observed in this patient population (the mean weight-for-age percentiles at baseline were 29.4 in the sham-procedure control group [n = 28] and 19.3 in the nusinersen group [n = 52] among patients who attended the Day 365 assessment and 31.6 in the sham-procedure control group [n = 19] and 13.7 in the nusinersen group [n = 35] among patients who attended the Day 456 assessment), which resulted in higher weight-for-age percentiles in the sham-procedure control group and lower weight-for-age percentiles in the nusinersen group at later time points. The change from baseline in percentile at each time point increased over time in both groups, and the possibility that nusinersen affected growth should be low.

Table 13. Weight-for-age percentile based on WHO Child Growth Standards over time in Study CS4

| Time point | Weight-for-age percentile | | Change from baseline at each time point | |
|---|---|---|---|---|
| | Sham-procedure control | Nusinersen | Sham-procedure control | Nusinersen |
| Baseline | 26.9 ± 25.5 (42) | 22.7 ± 28.6 (84) | - | - |
| Day 29 | 26.4 ± 27.2 (42) | 21.6 ± 27.2 (84) | -0.5 ± 6.8 (42) | -1.1 ± 11.1 (84) |
| Day 85 | 28.0 ± 29.3 (42) | 22.2 ± 27.7 (84) | 1.0 ± 8.8 (42) | -0.5 ± 12.0 (84) |
| Day 92 | 28.1 ± 28.8 (41) | 22.1 ± 27.6 (83) | 0.5 ± 8.7 (41) | -0.9 ±11.9 (83) |
| Day 169 | 26.9 ± 29.6 (41) | 23.8 ± 29.0 (84) | -0.6 ± 17.1 (41) | 1.1 ±15.6 (84) |
| Day 274 | 28.3 ± 30.5 (40) | 24.0 ± 28.9 (75) | 1.1 ± 14.2 (40) | 1.1 ± 17.1 (75) |
| Day 365 | 32.4 ± 34.3 (28) | 22.0 ± 28.7 (52) | 3.0 ± 18.1 (28) | 2.6 ± 12.0 (52) |
| Day 456 | 38.9 ± 37.0 (19) | 18.7 ± 24.6 (35) | 7.2 ± 20.9 (19) | 5.0 ± 13.0 (35) |

Mean ± SD for percentile (No. of evaluable subjects)

PMDA's view:

Although the change from baseline in weight-for-age percentile based on WHO Child Growth Standards was smaller in the nusinersen group than in the sham-procedure control group, especially on Day 456 in Study CS4 (interim analysis), it is difficult to conclude based on these data that nusinersen causes a reduction in growth, for the following reasons: (i) there were differences in baseline value between the nusinersen and sham-procedure control groups and (ii) a limited number of patients attended the Day 456 assessment. However, given that a multi-regional phase III study in patients with infantile SMA (Initial application documents, CTD 5.3.5.1-1, Study CS3B) also showed a trend towards smaller increases in height-for-age and weight-for-age percentiles in the nusinersen group than in the sham-procedure control group, nusinersen may affect growth. Hence, the applicant should appropriately communicate information on the effect of nusinersen on growth observed in clinical studies to healthcare professionals in clinical practice and then collect information on the effect of nusinersen on growth via post-marketing surveillance.

**7.R.5 Anti-nusinersen antibodies**

PMDA asked the applicant to explain the incidence of anti-nusinersen antibodies during treatment with nusinersen and the efficacy and safety of nusinersen in patients with anti-nusinersen antibodies.

21) World Health Organization (WHO) Child Growth Standards (WHO 2006)

The applicant's explanation:
Since immunogenicity had not been evaluated at the time of the interim analysis of a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4), immunogenicity data at the final analysis were evaluated. No patients in the sham-procedure control group tested positive for anti-nusinersen antibodies, and 7.1% (6 of 84) of patients in the nusinersen group tested positive, including 3 patients who had a persistent response.

Efficacy data were evaluated. Five of the 6 patients with anti-nusinersen antibodies in the nusinersen group attended the Month 15 assessment as of the Data Cutoff, and the mean change from baseline in HFMSE score (mean ± SD) in these patients was 1.6 ± 3.44, which tended to be lower than the change (adjusted mean ± SE, 4.0 ± 0.56) in the nusinersen group in the overall population at the interim analysis. This was considered due to a longer disease duration in these patients: Of these 5 patients, 1 patient had a disease duration of <25 months, 2 patients had a disease duration of ≥25 months and <44 months, and 2 patients had a disease duration of ≥44 months. Thus, there was no trend towards reduced efficacy in patients positive for anti-nusinersen antibodies.

The main adverse events reported in the 6 patients positive for anti-nusinersen antibodies were nasopharyngitis (50% [3 of 6 subjects]), pneumonia, influenza, upper respiratory tract infection, and headache (33.3% each [2 of 6 subjects]), which were similar to adverse events observed in the overall population in Study CS4. Bacteraemia and salivary hypersecretion occurred in patients positive for anti-nusinersen antibodies only, but their relationship to anti-nusinersen antibodies was denied. Thus, a safety issue is unlikely to arise in patients positive for anti-nusinersen antibodies.

Based on the above, the possibility that the presence of anti-nusinersen antibodies affects the efficacy and safety of nusinersen has not been suggested at present, and there should be no major problem with not measuring anti-nusinersen antibodies during treatment with nusinersen.

PMDA accepted the above.

**7.R.6 Indication**
SMA patients 2 to 12 years of age at screening[5)] were eligible for a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4), which demonstrated the efficacy and safety of nusinersen. PMDA asked the applicant to explain the appropriateness of the indication.

The applicant's explanation:
SMA patients are classified into 4 types (I-IV) based mainly on the highest motor milestone achieved (Table 14), and Type 0 SMA is a rare type in which neonates are born with weakness or clinical signs of death.[22)] The appropriateness of the proposed indication is described below.

22) *Pediatr Clin North Am.* 2015; 62: 743-66, *Nat Rev Neurol.* 2015; 11: 351-9, *Neuromuscul Disord*. 2015; 25: 593-602, *Semin Spine Surg*. 2012; 24:164-8, *Eur J Hum Genet*. 2004; 12: 1015-23, and *Neuromuscul Disord*. 2015; 25: 979-89.

Table 14. Subtypes of SMA

| SMA type | | Age at onset (diagnosis) | Life expectancy | Highest motor milestone achieved | *SMN2* copy number | % of SMA cases |
|---|---|---|---|---|---|---|
| 0 | | Fetal (at birth) | Approximately 1 week | None | 1 | - |
| I | I A | Fetal (2 weeks) | Approximately 1-2 weeks | Milestones rarely achieved | 1 or 2 | 58% |
| | I B | Infancy (3 months) | <2 years of age without respiratory support | Head control never achieved | 2 or 3 | |
| | I C | Infancy (3-6 months) | | Head control achieved, but never rolls or sits independently | | |
| II | | Infancy (6-18 months) | >2 years; 70% alive at 25 years | Attain independent sitting when placed. May stand, but unable to walk | 3 in most patients | 29% |
| III | III A | Early childhood (18-36 months) | Normal | Able to sit independently, stand, and walk with difficulties. Majority lose ambulation before or around puberty | 3 or 4 | 13% |
| | III B | Late childhood to school-age/adolescence (3-10 years, generally ≤18 years) | | | | |
| IV | | Adulthood (>35 years) | | Normal. Increased motor impairment after onset. | ≥ 4 | - |

- Since patients with onset at >6 months of age were eligible for Study CS4, the main population seemed to be patients with Types II to IV SMA. Exact classification into Type II, III, or IV is based on the highest motor milestone achieved. Patients enrolled in Study CS4 were aged 2 to 9 years, and some of them were in the process of developing motor function. For these reasons, the exact type of SMA cannot be identified. However, when SMA was classified retrospectively based on each subject's age of onset and *SMN2* copy number, 67% (28 of 42) of subjects in the sham-procedure control group had SMA consistent with Type II, 33% (14 of 42) of subjects in the sham-procedure control group had SMA consistent with Type III, 76% (64 of 84) of subjects in the nusinersen group had SMA consistent with Type II, and 24% (20 of 84) of subjects in the nusinersen group had SMA consistent with Type III.[13)] Since Study CS4 demonstrated the efficacy and safety of nusinersen in these subjects [see Section 7.1], it should be appropriate to include patients with Type II or III SMA in the indication.

- The applicant's view on the efficacy and safety of nusinersen in a patient population not enrolled in Study CS4 and the appropriateness of including such patients in the indication:
  - In many patients with SMA, degeneration of the motor neurons in the anterior horn of the spinal cord is a result of reduced levels of the SMN protein caused by a deletion of the *SMN1* gene located on chromosome 5q or loss-of-function mutations in the *SMN1* gene (*Cell*. 1995; 80: 155-65, *Am J Med Genet Part A*. 2004; 130A: 307-10). In 4% to 5% of all patients with SMA, genes other than *SMN1* on chromosome 5q are responsible for the SMA phenotype (*Am J Hum Genet.* 1999; 64: 1340-56), and patients with SMA related to abnormalities in the *IGHMBP2* gene, *DYNC1H1* gene, etc. have been reported as *SMN1*-unlinked SMA patients (*Pediatr Clin North Am*. 2015; 62: 743-66), but association with SMA type is unknown.
  - Nusinersen increases the amount of normal SMN protein produced by the *SMN2* gene by modulating the *SMN2* pre-mRNA splicing pattern (see Section 3.R.1 in the Review Report (1) for the initial application). The efficacy of nusinersen is expected in patients with any type of SMA (1) caused by genetic defects in the *SMN1* gene and (2) *SMN2* copy number = ≥1, in view of the mechanism of action. On the other hand, regarding safety, patients enrolled in Study CS4 had 3 or 4 copies of the *SMN2* gene. There may be patients with ≥5 copies of the *SMN2* gene, especially among patients with Type IV SMA. The function of SMN protein in the body is unclear at present. There are no safety information in the

case where the level of increased SMN protein expression in patients treated with nusinersen far exceeds the expression level in healthy humans. Taking account of these points, the package insert should contain the information on the patient populations in which the efficacy and safety of nusinersen have been demonstrated in clinical studies.

- Although it is difficult to identify the number of patients with Type IV SMA in Japan, patients with Type IV SMA caused by a deletion or mutation of the *SMN1* gene confirmed by genetic testing are considered to account for <1% of all SMA patients.[23)] When this figure is extrapolated to the number of recipient certificates issued for treatment of designated intractable disease in Japan (874 patients), <10 patients with Type IV SMA are candidates for treatment with nusinersen in Japan. Given that nusinersen has been approved for all types of SMA in the US and Europe, that it is difficult to conduct a Japanese clinical study in patients with Type IV SMA who were not enrolled in Study CS4, and that the degeneration of motor neurons and muscular atrophy progress irreversibly in SMA patients, the appropriate indication should be "spinal muscular atrophy" (all types of SMA) also in Japan, and post-marketing surveillance should confirm that there are no safety or efficacy problems.

PMDA's view:

There are no major problems with including patients with Type II or III SMA in whom the efficacy and safety of nusinersen have been demonstrated in Study CS4, in the indication.

Based on the mechanism of action of nusinersen, a certain level of pharmacological effects are expected in Type IV SMA patients as well as in patients with other types of SMA. However, whether a clinically meaningful improvement in symptoms is observed is unclear at present, and also regarding safety, there may be effects of an excessive SMN protein expression exceeding the level of expression in healthy humans. Given that it is difficult to conduct a clinical study in patients with Type IV SMA and that the degeneration of motor neurons and muscular atrophy progress irreversibly in SMA patients, as with the indication in the US and Europe, the indication of "spinal muscular atrophy" (all types of SMA) is acceptable. The package insert should contain the information on the patient populations in which the efficacy and safety of nusinersen have been demonstrated in clinical studies. In addition, the applicant should collect information on the impact of SMA type on the safety and efficacy of nusinersen (especially, safety and efficacy in patients with Type IV SMA) via post-marketing surveillance.

A final decision on the above will be made, taking account of comments from the Expert Discussion.

### 7.R.7 Dosage and administration

#### 7.R.7.1 Rationale for dosing regimen employed in multi-regional phase III study

PMDA asked the applicant to explain the rationale for dosing regimen employed in the multi-regional phase III study (CTD 5.3.5.1-1, Study CS4).

23) Based on a survey of 258 patients clinically diagnosed with SMA (Health and Labour Sciences Research, Rare/Intractable Disease Project, Research on collection of biomaterials from patients with childhood-onset spinal muscular atrophy, FY 2009 Annual Report, 2010), the percentage of patients clinically diagnosed with Type IV SMA was 8.5% (22 of 258 patients), and 9.1% (2 of 22) of these patients had a deletion or mutation of the *SMN1* gene confirmed by genetic testing for whom nusinersen is indicated. Thus, patients with Type IV SMA for whom nusinersen is indicated were considered to account for 0.8% (2 of 258) of all SMA patients surveyed.

The applicant's explanation:

- A pharmacology study in SMN2 mice[24] (initial application documents, reference data, CTD 4.2.1.1-4) indicated that nusinersen concentrations of 1 to 10 μg/g in spinal cord tissue are needed to produce pharmacologic effects of nusinersen.
- There were no sufficient human pharmacokinetic data at the time of planning Study CS4. A 2-compartment model was developed using toxicokinetic data from a 14-week intermittent dose IT toxicity study in juvenile monkeys (initial application documents, CTD 4.2.3.2-1), and then nusinersen concentrations in spinal cord tissue over time were simulated using CSF half-life values in a phase I study in mainly Type II or III SMA patients (≥2 years of age) (initial application documents, CTD 5.3.4.2-2, Study CS2).[25] As a result, the mean tissue concentrations in the lumbar, thoracic, and cervical spinal cord regions were all predicted to be above 5 μg/g in children ≥2 years of age receiving 3 doses of 12 mg of nusinersen (on Days 1, 29, and 85) followed by maintenance doses every 6 months.
- Based on the above, 12 mg doses of nusinersen on Days 1, 29, and 85 followed by dosing every 6 months for Study CS4 was considered appropriate.
- The dosage and administration for the previously approved indication of infantile SMA was selected, considering that infantile SMA is the most severe phenotype and needs more frequent dosing.

**7.R.7.2 Appropriateness of proposed dosage and administration**

PMDA asked the applicant to explain the appropriateness of changing the dosing regimen for non-infantile SMA from the one selected for Study CS4 to the same dosing regimen as that for infantile SMA: loading doses at Weeks 2, 4, and 9 followed by dosing every 4 months.

The applicant's explanation:

Non-infantile SMA progresses slowly compared to infantile SMA, and patients with non-infantile SMA are unlikely to require a ventilator or die in the short-term. The applicant considered the study should be design so as to allow patients with non-infantile SMA to maintain the appropriate nusinersen concentration in spinal cord tissue and to minimize the frequencies of visits and lumbar punctures. Based on considerations in Section 7.R.7.1, a dosing regimen different from that used in Study CS3B was selected for Study CS4. However, taking account of the following points, the applicant considered that the same dosing regimen as that for infantile SMA should be selected.

- Since the proportion of patients who achieved an improvement in HFMSE score[26] was 57.3% in Study CS4, it was considered necessary to select a dosing regimen that is expected to provide higher efficacy in non-infantile SMA patients (Reference: the proportion of responders was 41.2% in a multi-regional phase III study in patients with infantile SMA [initial application documents, CTD 5.3.5.1-1, Study CS3B]).

24) Mice in which endogenous *Smn* has been removed and human *SMN2* has been randomly integrated into the mouse genome
25) Doses were converted to human equivalent doses (× 10) based on the nominal volume difference in CSF between monkeys (15 mL, *Radiology*. 1985; 157: 373-7) and humans ≥2 years of age (150 mL, *Cereb Cortex*. 2001; 11: 335-42), and then simulations were conducted.
26) Subjects who achieved a ≥3-point increase from baseline in HFMSE score

- Based on predicted nusinersen CSF exposures ($AUC_{0\text{-}6month}$ and $AUC_{0\text{-}12month}$)[27] and the changes from baseline in CHOP INTEND total score[28] on Days 169 and 337 in subjects enrolled in a foreign phase II study involving patients with infantile SMA (initial application documents, CTD 5.3.5.2-1, Study CS3A), exposure-response relationships are shown in Figure 1. Higher nusinersen CSF exposure tended to result in a greater improvement in CHOP INTEND total score.

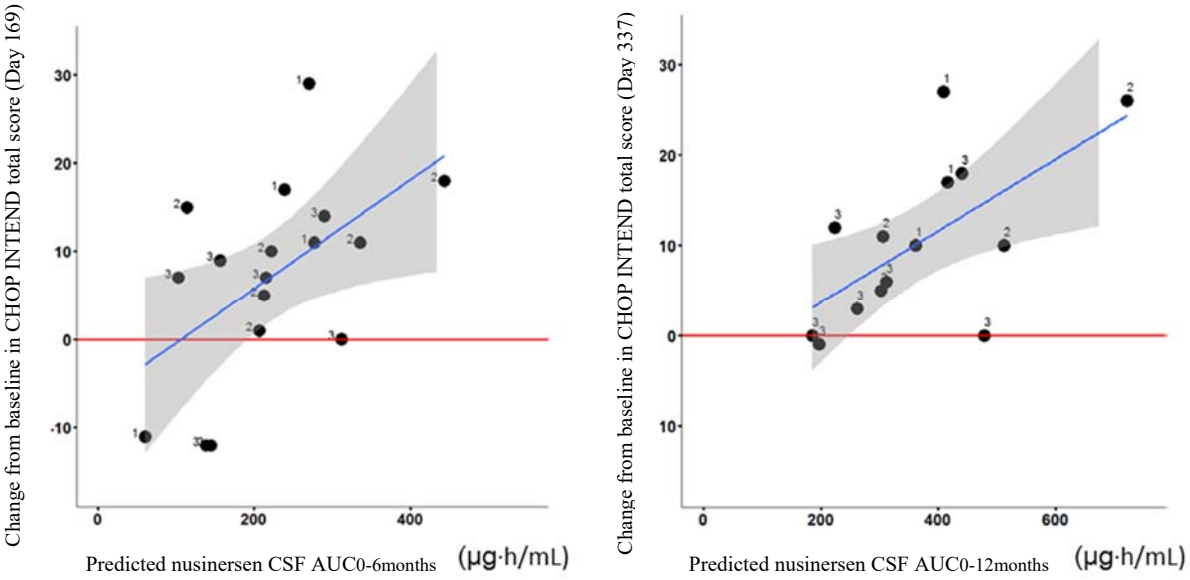


Figure 1. Exposure-response relationship between nusinersen CSF exposure ($AUC_{0\text{-}6month}$ or $AUC_{0\text{-}12month}$) and change from baseline in CHOP INTEND total score on Day 169 or 337 in Study CS3A
(Group 1, 1-85 days of age; Group 2, 86-169 days of age; Group 3, 170-337 days of age)

- If maintenance doses of nusinersen are administered every 4 months in patients with non-infantile SMA as in patients with infantile SMA, loading doses should also be administered on the same schedule as in patients with infantile SMA so as to achieve the required nusinersen trough concentration in CSF earlier.
- Given that the dose of nusinersen was established, taking account of CSF volumetric changes with age (see Section 7.R.7 in the Review Report (1) for the initial application) and that systemic exposure following administration of nusinersen is expected to decrease with age in non-infantile SMA patients as they grow, the safety of nusinersen administered using the dosing regimen selected for infantile SMA in patients with non-infantile SMA can be explained by the results from the multi-regional phase III study in patients with infantile SMA (initial application documents, CTD 5.3.5.1-1, Study CS3B).
- Based on the above points, the applicant claimed that the dosing regimen for infantile SMA patients used in Study CS3B should be selected also for patients with non-infantile SMA, which was accepted in Europe and the US, and the same dosing regimen has been selected for all types of SMA.

27) Assuming that among 20 patients enrolled in Study CS3A, patients in Cohort 1 receive 6-mg scaled equivalent IT doses of nusinersen (half the dose indicated in the table presented in the proposed dosage and administration) and patients in Cohort 2 receive 12-mg scaled equivalent IT doses of nusinersen (the same dose as indicated in the table presented in the proposed dosage and administration) on Days 1, 15, and 85 and then all patients receive nine 12-mg scaled equivalent IT doses of nusinersen every 126 days during maintenance phase, based on parameters obtained from PPK analysis (initial application documents, CTD 5.3.3.5-1, IS11 analysis), nusinersen CSF $AUC_{0\text{-}6month}$ and $AUC_{0\text{-}12month}$ were simulated.

28) A motor function scale developed for patients with Type I SMA, which evaluates the movements of the head, trunk, upper limbs, lower limbs, etc. It consists of 16 items, and 64 is the maximum possible score (*Neuromuscul Disord*. 2010; 20: 155‑61).

In Figure 1, Study CS3A showed a trend towards incidentally higher nusinersen CSF exposure in younger patients ("Group 1" and "Group 2" in Figure 1), but the applicant has not particularly investigated whether age and nusinersen CSF exposure are confounded.

With regard to plots of nusinersen CSF exposure and the change from baseline in CHOP INTEND total score in Study CS3A (Figure 1), (1) the small number of patients were analyzed and (2) the results of Study CS3A were biased: higher nusinersen CSF exposure in younger patients, but higher efficacy of nusinersen was observed in patients with onset at lower age or patients with lower age at baseline (Table 7). Taking account of these points, PMDA asked the applicant to explain the relationship between age/nusinersen CSF exposure and efficacy in other clinical studies as well.

The applicant's explanation on Study CS4:

- As PMDA pointed out, Study CS4 showed higher efficacy in patients with onset at lower age/lower age at baseline and patients with a shorter disease duration (Table 7). When the proportion of HFMSE responders[26)] by age at the start of treatment was analyzed (Table 15), likewise, higher efficacy was observed in patients with lower age at the start of treatment.

Table 15. Proportion of HFMSE responders in Study CS4 (ITT Set, multiple imputation method [a)])

| Age at start of treatment | Proportion of responders | | Treatment difference [95% CI] |
|---|---|---|---|
| | Sham-procedure control | Nusinersen | |
| ≤2 years | 25.68 (16) | 96.19 (20) | 70.51 [42.06, 98.96] |
| 3-4 years | 21.67 (18) | 58.28 (43) | 36.61 [9.39, 63.84] |
| ≥5 years | 11.68 (8) | 17.74 (21) | 6.06 [-27.61, 39.72] |

Proportion (%) (No. of evaluable subjects)

a) Missing values were imputed using data from all subjects in the sham-procedure control or nusinersen group, regardless of age group.

- Nusinersen CSF exposures in HFMSE responders[26)] and nonresponders[26)] in Study CS4 are shown in Figure 2, and there was no trend towards higher exposure in responders.

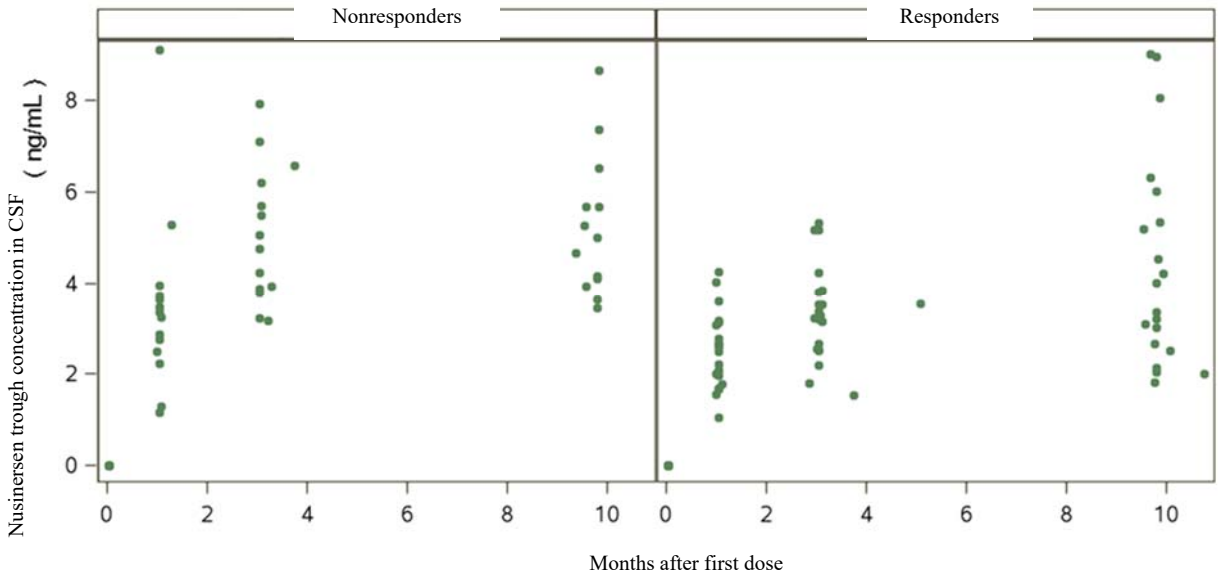


Figure 2. Nusinersen trough concentrations in CSF in HFMSE responders (right figure) and nonresponders (left figure) in Study CS4

The applicant's explanation on Study CS3B:

- The proportion of patients who achieved improvement in motor milestones as evaluated by Section 2[29] (7 items[30]) of the HINE[31] stratified by the median age at baseline, the median age of onset, and the median disease duration is shown in Table 16. Except for age of onset, the proportion of motor milestone responders in the nusinersen group tended to be higher in the subgroup of patients with lower age at baseline and the subgroup of patients with a shorter disease duration.

Table 16. Proportion of patients who achieved improvement in motor milestones as evaluated by Section 2 (7 items) of the HINE by patient characteristics in Study CS3B (Interim Efficacy Set)[32]

| | | Proportion of responders | | Treatment difference [95% CI][a] |
|---|---|---|---|---|
| | | Sham-procedure control | Nusinersen | |
| Age at baseline | ≤166 days | 0 (0/10) | 48.3 (14/29) | 48.3 [12.0, 76.6] |
| | >166 days | 0 (0/17) | 31.8 (7/22) | 31.8 [0.4, 59.2] |
| Age of onset | ≤8 weeks | 0 (0/16) | 36.4 (12/33) | 36.4 [7.4, 61.9] |
| | >8 weeks | 0 (0/11) | 50.0 (9/18) | 50.0 [12.6, 77.9] |
| Disease duration | ≤13.1 weeks | 0 (0/14) | 53.8 (14/26) | 53.9 [22.5, 78.2] |
| | >13.1 weeks | 0 (0/13) | 28.0 (7/25) | 28.0 [-6.2, 57.5] |

Proportion (%) (n/N)
a) Exact confidence interval for the difference in proportions

- CSF nusinersen concentrations in responders and nonresponders[31] in Study CS3B are shown in Table 17. On Day 302, as there were responders with a high outlier value, the mean value tended to be higher in responders. However, CSF exposure was generally similar between responders and nonresponders.

29) Neurological examination to assess infants from 2 to 24 months of age. The assessment consists of 37 items, divided into 3 sections: Section 1, neurologic examination (cranial nerve functions, posture, movements, tone, reflexes, reactions), Section 2, motor developmental milestones, and Section 3, behavioral assessment. Section 2 includes 8 items (voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, walking) scored on a 3- to 5-point scale according to the level of development.
30) 7 items of the HINE Section 2: ability to kick, head control, rolling, sitting, crawling, standing, and walking, with the exclusion of voluntary grasp
31) Attainment of motor milestones was scored at each time point, and then the scores at baseline were compared with the scores at the last visit through the data cutoff date. Improvement was defined as a ≥1-point increase (a ≥2-point increase in ability to kick or achievement of maximal score) and worsening was defined as a ≥1-point decrease (a ≥2-point decrease in ability to kick or decrease to the lowest possible score). A responder was defined as more categories with improvement than worsening.
32) Assessment at the later of the Day 183, 302, or 394 study visits in subjects who had the opportunity to be assessed at the Day 183 visit at the interim analysis.

Table 17. CSF nusinersen concentrations in responders and nonresponders in Study CS3B (ng/mL)

| | Nonresponders | Responders |
|---|---|---|
| Day 15 | 4.03 ± 2.57 (24)<br>(0.45, 10.05) | 3.89 ± 2.32 (21)<br>(1.58, 10.72) |
| Day 29 | 4.64 ± 1.93 (28)<br>(0.61, 8.12) | 6.66 ± 4.34 (21)<br>(2.80, 18.90) |
| Day 64 | 6.80 ± 4.62 (23)<br>(2.51, 18.93) | 6.30 ± 2.76 (19)<br>(2.16, 13.67) |
| Day 183 | 5.95 ± 2.66 (17)<br>(2.69, 11.48) | 7.41 ± 2.64 (19)<br>(2.86, 12.48) |
| Day 302 | 7.94 ± 3.15 (6)<br>(4.18, 11.97) | 12.74 ± 7.74 (13)<br>(2.52, 32.76) |

Upper row: Mean ± SD (No. of evaluable subjects)
Lower row: (Min., Max.)

PMDA's view:

The dosing regimen for Study CS4 was based on the assumptions that the PD of nusinersen are similar between rats and humans and that the pharmacokinetics of nusinersen are similar between monkeys and humans, etc. Its appropriateness is unclear at present, but taking account of the seriousness of SMA and a highly invasive administration route (intrathecal injection), it was unavoidable to examine based on the limited data available at the time of initiating Study CS4. Given that Study CS4 demonstrated the efficacy and safety of nusinersen and showed no marked differences in the pharmacokinetics of nusinersen according to age group [see Section 6.R.1], there are no major problems with the dose and dosage regimen used in Study CS4.

Although the applicant explained that more frequent dosing is necessary for patients with non-infantile SMA to achieve higher nusinersen CSF exposure than in Study CS4, in view of the following points, more frequent dosing than in Study CS4 is not appropriate, and the same dosing regimen as that used in a confirmatory study, Study CS4, should be selected. A final conclusion on the appropriateness of dosage and administration will be made, taking also account of comments from the Expert Discussion.

- Though the applicant's explanation is not necessarily adequate in some aspects, based on non-clinical and clinical data, the dosing regimen for Study CS4 was selected so as to achieve the required spinal cord tissue concentration of nusinersen [see Section 7.R.7.1].
- Taking account of the following points, even if nusinersen is administered more frequently than in Study CS4 and higher nusinersen CSF exposure than in Study CS4 is achieved in patients with non-infantile SMA, higher efficacy is not necessarily expected.
  - (a) Figure 1 shows the relationship between nusinersen CSF exposure and efficacy (the change in CHOP INTEND total score). Given that there was a trend towards higher nusinersen CSF exposure in younger patients, it cannot be concluded based on these data that higher exposure will result in higher efficacy.
  - (b) In Studies CS4 and CS3B, there was a trend towards higher efficacy in patients with lower age at the start of treatment, whereas there was no trend towards higher nusinersen CSF exposure in responders. Taking account of these findings, nusinersen CSF exposure in the range of those observed in the clinical studies of nusinersen has no major impact on the efficacy of nusinersen, and instead, age at the start of treatment is more likely to have a major impact.
  - (c) Based on the above, taking account of the number of evaluable subjects in each study and the consistency of the trend between the studies, nusinersen CSF exposure is considered to have no major impact on the efficacy of nusinersen.

- Regarding safety, more frequent dosing than in Study CS4 is not recommended, taking account of the following points.
  (a) Since cumulative dose-dependent adverse events such as renal and hepatic impairment and effect on platelet count are known with therapeutic oligonucleotides (*Nucleic Acid Ther*. 2016; 26: 199-209; see Section 7.R.7 in the Review Report (1) for the initial application), increased nusinersen exposure resulting from more frequent dosing may raise safety concerns.
  (b) Nusinersen is administered by lumbar puncture. Given that the incidence of serious lumbar puncture-related adverse events (post lumbar puncture syndrome, vomiting) in each clinical study already conducted was approximately 1% to 4% and that serious lumbar puncture-related adverse events (meningitis) have been reported in marketing experience overseas, more frequent dosing increases the risk.
  (c) In light of the survival prognosis of patients with Type II or III SMA, nusinersen is expected to be used over a long period of time, i.e. at least 20 to 30 years. Nusinersen will be used over a longer period of time in these patients compared to patients with infantile SMA (48.7% of patients with infantile SMA die or require permanent ventilation by 13 months of treatment with nusinersen). However, if nusinersen is administered more frequently, cumulative dose-dependent adverse events may occur earlier, and consequently, there will be a possibility that patients can receive nusinersen over a shorter period of time.

**7.R.7.3 Dose for age groups of patients who were not included in Study CS4**

Taking into account that patients enrolled in Study CS4 were aged 2 to 9 years at the start of treatment, PMDA asked the applicant to explain the appropriateness of the dose for age groups of patients who were not enrolled in Study CS4.

The applicant's explanation:

The pharmacokinetics of nusinersen are unlikely to be substantially different between patients with infantile SMA and patients with non-infantile SMA.

The applicant's explanation on the appropriateness of the dose for patients <2 years of age and patients ≥10 years of age:

- Taking account of age-related volumetric changes of CSF in humans (*Cereb Cortex*. 2001; 11:335-42) and the dose (12 mg/dose) and CSF volume (150 mL) in patients ≥2 years (731 days) of age, the dose for patients <2 years of age is adjusted (age-based dosing) so that the CSF nusinersen concentration is equivalent across all age groups (the table presented in the proposed dosage and administration). A clinical study in patients ≥52 days of age showed that nusinersen CSF exposure after age-based dosing was similar across all age groups. Furthermore, the mean plasma nusinersen concentration at 2 hours after the first 12-mg scaled equivalent dose of nusinersen tended to be lower in Study CS4 compared to Study CS3B (288 ± 202 ng/mL and 838 ± 589 ng/mL, respectively), which is considered due to differences in the body size of patients and is not considered to reflect essential differences in the pharmacokinetics of nusinersen. Thus, the dose for patients <2 years of age should be the same as that for patients with infantile SMA.

- Given that no major volumetric changes of CSF occur in humans ≥2 years of age (*Cereb Cortex*. 2001; 11:335-42), the pharmacokinetics of nusinersen in CSF are unlikely to differ substantially in patients ≥10 years of age.
- Based on the above, the dose for patients with non-infantile SMA, including patients <2 years of age and patients ≥10 years of age who were not enrolled in Study CS4, should be the same as that for patients with infantile SMA.

PMDA accepted the above.

**7.R.8 Post-marketing investigations**

PMDA's view:

Based on the presented clinical data etc., the applicant should collect the following information via post-marketing surveillance: the safety and efficacy of nusinersen in Japanese patients, the long-term efficacy of nusinersen, the impact of patient characteristics (especially *SMN2* copy number) on the efficacy of nusinersen, the occurrence of lumbar puncture-related adverse events, CNS adverse events, renal impairment, and hepatic impairment, effect on the blood coagulation system, the occurrence of adverse events related to QT/QTc interval prolongation and proarrhythmia, and effect on growth.

The applicant's explanation:

Since there is limited clinical experience with nusinersen in Japanese patients with SMA, a use-results survey, covering all patients treated with nusinersen, is planned as post-marketing surveillance of nusinersen (observation lasts until the registered patient dies, treatment with nusinersen ends, or the survey period (8 years) completes, whichever comes first).

A final decision on the appropriateness of these measures will be made, taking account of comments from the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that nusinersen has efficacy in the treatment of non-infantile SMA and that nusinersen has acceptable safety in view of its benefits. Nusinersen is clinically meaningful because it offers a new treatment option for patients with SMA. The appropriateness of dosage and administration, etc. needs to be further discussed at the Expert Discussion.

PMDA has concluded that the application may be approved if Spinraza (nusinersen) is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

August 22, 2017

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Spinraza Intrathecal injection 12 mg |
| **Non-proprietary Name** | Nusinersen Sodium |
| **Applicant** | Biogen Japan Ltd. |
| **Date of Application** | July 5, 2017 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in the Review Report (1).

PMDA also discussed the following points and took action as necessary.

### 1.1 Efficacy of nusinersen

The expert advisors raised the following comments at the Expert Discussion:

When the changes from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) score over time in individual Japanese patients in a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4) (Table 5) were examined, there was a trend towards improvement at 6 months in the sham-procedure control group compared to the nusinersen group. While the difference in the change from baseline in HFMSE score between the sham-procedure control and nusinersen groups in the overall population tended to become greater at ≥9 months, the data beyond 9 months were very limited in Japanese patients. Taking account of these points, the currently available data from Study CS4 cannot provide adequate evidence to support that the efficacy of nusinersen in Japanese patients is similar to that in the overall population.

The applicant's explanation:

Although presenting clear evidence is difficult due to the limited number of Japanese subjects, the above finding can be explained by the following: comparison of age at screening between the sham-procedure control and nusinersen groups among Japanese patients showed that age at screening was lower in the sham-procedure control group (sham-procedure control group, 2 years, 4 years, and 7 years [1 patient each]; nusinersen group,

3 years, 4 years, 6 years, 7 years, and 9 years [1 patient each]). Thus, patients in the sham-procedure control group showed a trend towards improvement in HFMSE score as they grew.

PMDA's view:
Given that there are no major differences in the intrinsic or extrinsic ethnic factors potentially affecting the efficacy and safety of nusinersen and that there was no trend towards major differences in the change in HFMSE score over time in the nusinersen group between the Japanese subgroup and the overall population and taking account of the applicant's explanation, a certain level of efficacy is expected in Japanese patients. However, the results from Study CS4 has limitations to explaining efficacy including long-term efficacy in Japanese patients. The applicant should provide sufficient information regarding the efficacy of nusinersen to healthcare professionals in clinical practice, and should continue an investigation of efficacy in Japanese patients via post-marketing surveillance.

The expert advisors supported the above conclusion by PMDA.

**1.2 Indication**
The expert advisors supported PMDA's view (the appropriate indication is "spinal muscular atrophy") [see Section 7.R.6 in the Review Report (1)].

The expert advisors raised the following comments at the Expert Discussion:
Given the late onset and slow progression of Type IV SMA, the benefits/risks of nusinersen are unclear in this patient population. Thus, the use of nusinersen should be determined carefully in patients with spinal muscular atrophy (SMA) consistent with Type IV who were not enrolled in a multi-regional phase III study (CTD 5.3.5.1-1, Study CS4). Information regarding patients with advanced disease in whom the efficacy of nusinersen is not expected should also be provided appropriately.

PMDA's view:
The precautions for the "Indication" section of the package insert should state that the benefits/risks of nusinersen should be considered prior to the use of nusinersen in patients with ≥4 copies of the *SMN2* gene, for the following reasons: (i) very few patients with ≥4 copies of the *Survival Motor Neuron 2* (*SMN2*) gene were enrolled in Study CS4 (the number of patients with 4 copies of the *SMN2* gene in the ITT Set, 1 patient in the sham-procedure control group and 2 patients in the nusinersen group), and (ii) patients with SMA consistent with Type IV have ≥4 copies of the *SMN2* gene (Table 14). The results of subgroup analyses according to patient characteristics (Table 7) should be included in informative materials for healthcare professionals, and the following information should be provided: efficacy may be reduced in patients with advanced disease, e.g., patients with scoliosis.

PMDA instructed the applicant to address the above points, and the applicant responded appropriately.

**1.3 Dosage and administration**

The expert advisors supported PMDA's view (it is unclear if more frequent dosing than in a multi-regional phase III study [CTD 5.3.5.1-1, Study CS4] results in higher efficacy, and more frequent dosing of nusinersen may raise safety concerns. Thus, the same dosing regimen as that used in Study CS4 should be selected [see Section 7.R.7 in the Review Report (1)]). The expert advisors commented that the scientific basis for changing the dosing regimen from the one selected for Study CS4 to the proposed dosing regimen is unclear at present and that there is no reason for approving the dosing regimen different from the one selected for Study CS4. The applicant explained that the dosing regimen was changed from 12-mg doses of nusinersen administered every 6 months to every 4 months for patients who completed Study CS4 and participated in an extension study [initial application documents, reference data, CTD 5.3.5.4-3, Study CS11; see Section 7.1 in the Review Report (1)]. PMDA has concluded that the above conclusion remains unchanged.

Based on the above, PMDA instructed the applicant to change the proposed dosage and administration as shown below, and the applicant responded appropriately.

**Dosage and Administration**

Infantile spinal muscular atrophy

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 4 doses at Weeks 0, 2, 4 and 9 followed by dosing every 4 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

Non-infantile spinal muscular atrophy

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 3 doses at Weeks 0, 4 and 12 followed by dosing every 6 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

| Age on the day of dosing | Dose | Injection volume |
|---|---|---|
| 0-90 days | 9.6 mg | 4 mL |
| 91-180 days | 10.3 mg | 4.3 mL |
| 181-365 days | 10.8 mg | 4.5 mL |
| 366-730 days | 11.3 mg | 4.7 mL |
| ≥731 days | 12 mg | 5 mL |

(Underline denotes additions.)

**1.4 Risk management plan (draft)**

In view of the discussions presented in Section 7.R.8 in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for nusinersen should include the safety and efficacy specifications presented in Table 18, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 19.

Table 18. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| · None | · Coagulation abnormalities<br>· Renal impairment<br>· Hepatic impairment<br>· CNS effects, and effects on memory/learning<br>· Hypersensitivity<br>· Use in patients ≤2 months of age<br>· QT prolongation<br>· Use in patients with ≥4 copies of the *SMN2* gene<br>· Use in patients with renal impairment | · Safety profile of long-term treatment<br>· Effect of drug substance batch-to-batch differences in impurity profile on safety<br>· Adverse events associated with interactions with the genes other than the *SMN2* gene (infections, CNS disease, etc.)<br>· Safety in tissues/organs where nusinersen accumulates<br>· Carcinogenicity |
| Efficacy specification | | |
| · Long-term efficacy of nusinerusen and its impact on survival prognosis<br>· Efficacy of nusinerusen in patients with 1 copy or ≥4 copies of the *SMN2* gene<br>· Efficacy of nusinerusen in patients with onset at >20 months of age<br>· Efficacy of nusinerusen in patients with advanced disease<br>· Efficacy of nusinerusen in patients on permanent ventilation | | |

Table 19. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

| Additional pharmacovigilance activities [a)] | Additional risk minimization activities [a)] |
|---|---|
| · Early post-marketing phase vigilance<br>· Use-results survey (all-case surveillance) | · Early post-marketing phase vigilance<br>· Development and distribution of informative materials for healthcare professionals. |

a) Additional pharmacovigilance activities and risk minimization activities associated with the present application only are listed.

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to address the above issues.

The applicant explained that they will conduct a use-results survey of patients with non-infantile spinal muscular atrophy shown in Table 20.

Table 20. Outline of use-results survey (draft)[a)]

| | |
|---|---|
| Objective | To ascertain the safety and efficacy of nusinersen in routine clinical settings. |
| Survey method | All-case surveillance |
| Population | All patients with non-infantile SMA treated with nusinersen after the market launch |
| Observation period | Until death or the end of nusinersen treatment, whichever comes first (up to 8 years). |
| Planned sample size | Not specified. |
| Main survey items | · Patient characteristics (gender, age, body weight, height, age of onset, *SMN2* copy number, motor function at baseline, use of respiratory care, etc.)<br>· Administration of nusinersen (dose per administration, number of doses, the reason for changing dose, drug product lot number, etc.)<br>· Previous medications, concomitant medications, concomitant therapies<br>· HFMSE score<br>· Occurrence of adverse events, clinical laboratory values, ECG<br>· Verbal communication |

a) A single use-results survey of patients with non-infantile SMA and patients with infantile SMA is planned to be conducted.

PMDA accepts the above. The applicant should promptly provide the survey results to healthcare professionals in clinical practice.

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1. PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 2.2. PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection verified that the clinical study as a whole was conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. Although the outcome of the overall assessment of the study was not affected significantly, the inspection revealed the following findings at some of the study sites used by the applicant and the heads of the relevant medical institutions (study sites) were notified of these findings requiring improvement.

[Findings requiring corrective action]

Study sites

- Some of the source documents for the clinical study were not maintained.
- Protocol deviations (some missing data pertaining to vital signs, body weight, and ulna length; and adverse events/changes in concomitant medications at telephone contacts)

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following conditions. The re-examination period for the present application should be the remainder of the re-examination period (10 years) for the initial approval of the product for the indication of "infantile spinal muscular atrophy" (until July 2, 2027).

**Indication**

~~Infantile~~ Spinal muscular atrophy

(Strike-through denotes deletion.)

**Dosage and Administration**

Infantile spinal muscular atrophy

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 4 doses

at Weeks 0, 2, 4 and 9 followed by dosing every 4 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

Non-infantile spinal muscular atrophy

The usual dose of nusinersen is shown in the table below. Spinraza treatment should be initiated with 3 doses at Weeks 0, 4 and 12 followed by dosing every 6 months. Spinraza should be administered as an intrathecal bolus injection over 1 to 3 minutes.

| Age on the day of dosing | Dose | Injection volume |
|---|---|---|
| 0-90 days | 9.6 mg | 4 mL |
| 91-180 days | 10.3 mg | 4.3 mL |
| 181-365 days | 10.8 mg | 4.5 mL |
| 366-730 days | 11.3 mg | 4.7 mL |
| ≥731 days | 12 mg | 5 mL |

(Underline denotes additions.)

**Conditions of Approval**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Due to the very limited number of patients studied in Japan, the applicant is required to conduct a use-results survey, covering all patients treated with the product, during the re-examination period, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.