

## New Drug Evaluation: Nusinersen Injection, Intrathecal

**Date of Review:** July, 2017  
**Generic Name:** Nusinersen  
**PDL Class:** Miscellaneous

**End Date of Literature Search:** 06/01/17  
**Brand Name (Manufacturer):** Spinraza™ (Biogen)  
**AMCP Dossier Received:** Yes

### Research Questions:

1. What is the efficacy and effectiveness of nusinersen in reducing symptoms, improving functional outcomes and improving mortality in patients with spinal muscular atrophy (SMA)?
2. What are the harms of nusinersen in SMA patients?

### Conclusions:

- The efficacy of nusinersen in improving motor function in infants with SMA type 1 was evaluated in one unpublished, low quality phase 3 trial with a high risk of bias.<sup>1</sup> At 6 months into the 13 month trial design the study was halted and became a nonrandomized observational study without intent to treat analysis. Primary and secondary outcomes were revised; the definition of the new primary outcome was changed, and the 78 (65%) of 122 original subjects who had not died, become ventilator dependent or withdrawn from the study became the new analysis group. Response was defined as a participant who was alive and participating in the study and demonstrated at least a two-point (level) increase in the ability to kick or a one-point increase using the HINE-2 assessment in head control, rolling, sitting, crawling, standing, or walking. A greater percentage of subjects achieved a one point change in Hammersmith Infant Neurological Exam (HINE) motor milestone response from baseline to the 6 month assessment in the nusinersen group (40%) compared to the control group (0%)( $p < 0.0001$ ).<sup>2</sup> There is insufficient evidence to evaluate long-term effects on survival, clinical course and ventilator dependency at this time.
- There is insufficient data to evaluate nusinersen safety at this time due to small sample sizes and short term trials.
- Nusinersen may increase the risk of bleeding complications due to thrombocytopenia; thrombocytopenia developed in 6 of 56 (11%) patients after administration of nusinersen in the Phase 3 clinical trial. None of the patients in the control cohort developed thrombocytopenia. Platelet testing is required at baseline and before each dose.<sup>2</sup>
- Nusinersen also has a risk for renal toxicity. Proteinuria occurred in 17 of 51 (33%) nusinersen patients compared to 5/25 (20%) sham control subjects during the Phase 3 clinical trial. Quantitative spot urine testing for proteinuria is required at baseline and prior to each dose.<sup>2</sup>
- Additional trials in patients with SMA types 2 and 3 are currently ongoing and not published. At this time, there is insufficient evidence of the safety and efficacy in these SMA populations.

### Recommendations:

- Revise PA criteria to insure nusinersen utilization in SMA populations in which the drug is been studied.

- Consider referring nusinersen to the Health Evidence Review Commission (HERC) for funding placement as a medication with high cost and marginal clinical benefit.

**Background:**

SMA is characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles, and hypotonia. SMA is caused by homozygous deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13.<sup>3</sup> The SMN gene region consists of two almost identical genes: SMN1 and SMN2.<sup>4</sup> The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced truncated and nonfunctional SMN protein.<sup>4</sup> Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), a small part (10–15%) of the mRNA transcripts contains exon 7, resulting in a normal SMN protein.<sup>4</sup> The number of copies of SMN2 correlate with the functional status of SMA.<sup>4</sup> The majority of the severely affected patients with SMA type 1 have two SMN2 copies with a level of functional SMN protein of approximately 20 to 30%.<sup>5</sup> The presence of 3 or more copies of SMN2 is associated with milder SMA symptoms.

SMA is a rare disease, and the incidence ranges from 1 to 10 per 100,000 live births.<sup>4</sup> However, SMA is the most common genetic cause of death in infants.<sup>4</sup> The phenotype is extremely variable, and patients are classified as SMA type 0-IV based on age at onset and clinical course. SMA type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.<sup>3</sup> These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. These infants rarely achieve improvements in motor function or acquire motor developmental milestones.<sup>4</sup> Children with SMA type 2 exhibit muscle weakness that is more prominent in the lower extremities. They are able to sit unassisted, but are never able to independently walk. Respiratory failure is less severe and develops later in life compared to children with SMA type 1.<sup>4</sup> Children with SMA type 3 develop variable muscle weakness after 18 months of age and are able to walk. However, as the disease progresses, they may become wheelchair bound. Respiratory muscles are rarely affected and life expectancy is normal in this group of SMA patients.<sup>4</sup> SMA type 4 generally occurs in the second or third decade of life and is the mildest form of the disease characterized by mild muscle weakness and normal life expectancy. The characteristics of each SMA type are described in **Table 1**.

**Table 1.** SMA classification and characteristics<sup>4</sup>

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1%
I	2	1 - 6 months	Never able to sit unassisted	<2 years	3.2 – 7.1 (45% of cases)
II	2-4	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
III	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5 – 4.6 (30 % of cases)
IV	4-8	10 - 30 years	Ambulatory	Normal	5% of cases

\*Natural history may vary depending on supportive interventions

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60.<sup>6</sup> It is not possible to predict the severity of the SMA phenotype from carrier screening. Several methods for newborn

screening have been developed to diagnose SMA from DNA extracted from newborn blood spots. Methods include a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis to identify SMN1 and SMN2 deletions and quantify copy numbers of both genes, and real-time polymerase chain reaction.<sup>5</sup>

Due to the difficulties in quantifying motor abilities in these patients, several functional motor scales were developed to assess functional status in children with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients.<sup>7</sup> The assessment incorporates the limited abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16 item assessment of functional muscle strength and is scored on a 0–4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a maximum score of 64 points. It was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months). The relationship between CHOP INTEND scores correlated with subject age (r = -0.51, p = 0.007) and BiPAP utilization (r = -0.74, P < .0001).<sup>8</sup> The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.<sup>9</sup> It includes 26 items assessing cranial nerve function, posture, quality and quantity of movements, muscle tone, and reflexes and reactions. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0 to 78). At 9 or 12 months, a score greater than or equal to 73 is considered optimal.<sup>9</sup> Sequential use of the HINE allows for the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.<sup>10</sup> For example, in preterm infants assessed between 6 and 15 months corrected age, scores greater than 64 predict independent walking with a sensitivity of 98% and specificity of 85%.<sup>10</sup> Conversely, scores less than 52 are highly predictive of cerebral palsy and other severe motor impairments.<sup>10</sup> The HINE-2 screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.<sup>5</sup> Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 78.<sup>11</sup> The Hammersmith Functional Motor Scale (HFMS) was developed by physical therapists to assess SMA type 2 and 3 patients.<sup>12</sup> The assessment provides information on motor ability and clinical progression in children with limited ambulation.<sup>12</sup> The HFMS motor assessment includes upper and lower limb activities as well as head and trunk control. Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4 point kneeling, crawling and standing. Each item is scored on a 3 point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter-observer agreement greater than 99%.<sup>12</sup> For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running, and jumping which resulted in the HFME (HFMS Extended) score.<sup>13</sup> It is scored on a 3 point scale similar to the HFME, but scores range from 0 to 66. The Upper Limb Module (ULM) is used in non-ambulatory patients greater than 2 years of age.<sup>14</sup> This assessment was designed to assist in evaluating the ability of young children to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. The Six-Minute Walk Test is used only in ambulatory SMA patients more than 4 years of age.<sup>15</sup> The different motor function tests used in nusinersen trials are summarized in **Table 1**.

**Table 1. Motor Function Assessments used in SMA trials**

Test	Description	Score	SMA Patient Population
CHOP INTEND	Measure motor function in 16 items to assess neck, trunk, and limb strength	0 (least function to 4 (most function)) Maximum score = 64 points	Presymptomatic and Infantile Onset
HINE-2	Measure functional ability and motor milestones in 26 items	0 (least function) to 4 (most function) Maximum score = 78 points	Presymptomatic and Infantile Onset
HFSM	Head, trunk, upper, and lower limb control on 20 items	0 = inability 1 = needs assistance 2 = unaided Maximum score = 40 points	Presymptomatic and Infantile Onset
HFSME	Added 13 additional items to HFSM to assess walking, running and jumping for a total of 33 items	0 = inability 1 = needs assistance 2 = unaided Maximum score = 66 points	Later Onset (types 2 and 3) – Ambulatory Patients

Abbreviations: CHOPINTEND = Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSM = Hammersmith Functional Motor Scale; HFSME = Hammersmith Functional Motor Scale Expanded; HINE =Hammersmith Infant Neurological Exam

There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Difficulties in feeding and swallowing can lead to lower respiratory infection, gastrointestinal complications and malnutrition. Full time noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Nusinersen is the first Food and Drug Administration (FDA) approved therapy for treatment of SMA. It is an antisense oligonucleotide which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein. As a result, the amount of functional SMN protein increases which can partially compensate for mutations/deletions of the SMN1 gene. Nusinersen must be administered intrathecally. Treatment is initiated with 4 loading doses; the first three doses are administered every 2 weeks, and the fourth dose is given 30 days after the third dose. Maintenance doses are given every 4 months.

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

#### **Clinical Efficacy:**

The U.S. Food and Drug Administration (FDA) approved nusinersen based on an interim analysis of a phase 3, multicenter, randomized, double blind, sham controlled study of nusinersen in 121 patients with infantile-onset SMA (ENDEAR). The trial has not been published as of June 2017. Details of this study were accessed from the summary report of nusinersen posted on the FDA website and the clinical trials.gov website.<sup>1,16</sup> Due to the orphan drug status of nusinersen, the FDA approval was fast tracked. Participants included in the trial were diagnosed with SMA symptoms before 7 months of age, were born between 37 and 42 weeks, and had 2 copies of the SMN gene. The nusinersen dose was 12 mg (or a scaled equivalent dose based on body weight) intrathecally on days 1, 15, 29, and 64 (loading dose) followed by 12 mg maintenance dosing every 4 months for 2 additional doses (days 183 and 302). The duration of the trial was 10 months. Interim analysis was based on the 78 (65%) of the original 121 subjects who had not died, become ventilator dependent, or withdrawn from the study at 6 months into the 13 month study design. The FDA approved a request to exchange the primary and secondary outcomes, redefine the new primary outcome, to

not perform statistical analysis on any outcomes except the new primary outcome, and to not perform intent-to-treat analysis. This had the effect of losing the benefits of randomization. Differences between the sample of 78 subjects and the original 121 subjects were not analyzed, so selection bias could not be assessed. Interim analysis was performed by an unblinded contract research organization and reviewed by the unblinded senior management team from Ionis and Biogen. The management team was prohibited by the FDA to have further involvement in the study. The original primary outcome was time to death or permanent ventilation during the 13 month follow-up period. Prior to the interim analysis, the investigators added an additional efficacy endpoint to include assessment of the proportion of responders achieving motor milestones using the HINE-2 exam. The change was approved by the FDA so that the new drug application would not rely solely on Phase 2 open label trial data. The interim analysis only included data from 78 (65%) infants who completed a 6 month assessment. The 42 subjects dropped from the analysis had died, become ventilator dependent, or withdrawn from the study before reaching their 6 month assessment date but were not identified so their characteristics could not be compared. Median age for symptom onset in the nusinersen cohort was 6.4 weeks and 8 weeks for the sham control group. The nusinersen arm had more severe baseline characteristics (earlier symptom onset, history of pneumonia, more swallowing/feeding difficulties) compared to the sham group. The interim motor function analysis included 55 patients total (39 nusinersen and 16 control) due to withdrawal of 2 patients and demise of 21 additional patients. Motor milestones were assessed using the HINE-2 assessment on days 64, 183, 302, and 394. A responder was defined as a participant who was alive and participating in the study, demonstrated at least a two-point increase in the ability to kick or a one-point increase in head control, rolling, sitting, crawling, standing, or walking. In addition, the participant had to improve in more categories than those in which he or she worsened.<sup>16</sup> A greater proportion of participants in the nusinersen group (n=21, 40%) than in the control group (n=0, 0%) met motor responder criteria ( $p<0.0001$ ) at approximately six months.<sup>16</sup> Improvements were most common in the categories of head control, rolling, sitting, and ability to kick. Nine (18%) patients achieved full head control, 5 (10%) patients were able to independently sit, and 1 (2%) patient was able to stand.<sup>16</sup> At the time of the interim analysis for the intention to treat (ITT) dataset, 11/51 (21.6%) participants in the nusinersen group and 10/27 (37%) in the control group had died or required permanent ventilation (hazard ratio for event-free survival = 0.71; confidence intervals and p-values were not reported).<sup>16</sup> The FDA approved nusinersen based on the interim analysis which only included data from 65% of the subjects with a six month follow-up period instead of the originally planned 13 month follow-up. Based on the results of the interim analysis, the study was suspended. Because the interim analysis was of short duration (6 months), in a small number of patients (n=78), and used a different primary outcome from the original study design, the quality of the study was adversely affected. The lack of intent to treat analysis or comparison between the 78 subjects and the 43 subjects excluded from the analysis weakened the strength of randomization and introduced significant risk of selection bias. In terms of quality at this point the trial became a nonrandomized observational study. Due to attrition of 21 subjects, data was only analyzed for a total of 55 patients (n = 39 nusinersen and n= 16 control). Furthermore, the involvement of the funders in the study may have contributed an additional risk of bias. Due to high risk of selection, performance, detection, attrition and reporting bias, the study is rated as poor quality based on the Cochrane Collaboration standards for evaluating risk of bias in clinical trials.<sup>17</sup>

A phase 2, open-label, dose escalating study assessed safety and efficacy in patients with infantile-onset SMA type 1 (EMBRACE).<sup>11</sup> Subjects enrolled in the trial were between 3 weeks and 7 months old with a SNM1 homozygous gene deletion or mutation and SMA symptoms. Clinical efficacy was assessed by change in baseline of the HINE-2 and CHOP-INTEND motor function tests. The investigators powered the study to assess safety and tolerability of nusinersen, but not efficacy. Twenty patients were included in the trial and followed from 2 to 32 months. The first 4 participants received a loading dose of 6 mg on days 1, 15 and 85 followed by 12 mg on day 253 and every 4 months thereafter. The next 16 subjects received 12 mg doses on the same schedule. Follow-up visits occurred on days 16, 29, 86, 92, 169, 254, 337 and 442 and then every 4 months up to 32 months total. The data published by the investigators is an interim data analysis as the trial is currently ongoing. Improvements from baseline of 2 or more levels in at least one motor milestone were found in 13 participants including grasping (n=13), ability kick (n=9) and sitting (n=8). Change in HINE-2 score from baseline to day 92 were reported by the investigators as significant for both 6 and 12 mg dosing cohorts combined ( $p=0.0002$ ) and for participants in the 12 mg dose group ( $p<0.0001$ ).<sup>11</sup> The specific data were not reported, only the summary of the change in scores. The data for HINE-2 score changes in the 6 mg cohort were not reported. Motor function using the CHOP-INTEND score showed a mean

increase of 11.5 points ( $p=0.008$ ) from baseline to 92 days with 14 out of 18 patients showing improvement on this assessment.<sup>11</sup> In the 12 mg cohort, 12 of 14 subjects had an increase from baseline to 92 days with a mean increase of 15.2 points. When compared to a natural history case series of infants with SMA type 1 who had a mean decline of 1.27 points per year this 15.2 point improvement in CHOP-INTEND scores was considered significant ( $p = 0.0013$ ) by the investigators.<sup>11</sup> There were 77 serious adverse events reported in 16 participants, all considered by study investigators not related or unlikely related to the study drug, with the most common being respiratory distress or failure or respiratory infections, which are commonplace in infants with spinal muscular atrophy.<sup>11</sup> This study has several limitations including small sample size ( $n=20$ ), open label, and short duration of follow-up (2-32 months). No information was provided on the patients that were screened but not included in the trial. No a priori definition of a clinically important change in outcome measures was established. Only 14 subjects (70%) were included in the motor outcome analysis. Finally, this study was funded by Ionis and Biogen so the investigators may have had a potential conflict of interest. For these reasons, this study is rated as poor quality using the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) assessment tool.<sup>18</sup> A second open label, multicenter, phase 2 trial (NURTURE) focused on the efficacy of nusinersen in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA is currently ongoing with anticipated results in 2019.

A phase 1 trial of nusinersen included 28 medically stable participants with symptomatic SMA types 2 and 3 aged 2 to 14 years.<sup>19</sup> Most of the participants (89%) had 3 or more copies of the SMN2 gene and a life expectancy greater than 2 years per investigator assessment. The trial was an open label, dose finding, multicenter study focused on evaluating nusinersen safety and tolerability after a single dose of medication. Exploratory efficacy outcomes included the HFMSE and Pediatric Quality of Life Inventory (PQLI). However, the study was not powered to detect statistical differences in efficacy as an a priori definition of a clinically important outcome was not stated before the start of the trial. The nusinersen doses ranged from 1 mg ( $n=6$ ), 3 mg ( $n=6$ ), 6 mg ( $n=6$ ) or 9 mg ( $n=10$ ). The pharmacokinetic assessment revealed an extended half-life of 4 to 6 months. In an increase in HFSME score by a mean of 3.1 points was observed 3 months after one 9 mg dose, although this phase 1 trial was not designed to evaluate statistical significance. No information was provided on the subjects that were screened but not included. Only 8 of the 10 patients (80%) who received a 9 mg dose were evaluated at 9-14 months. Finally, this study was funded by Ionis and Biogen. For these reasons, the study is rated as poor quality with a high risk of bias using the ROBINS-I tool.<sup>18</sup> Twenty four (86%) of the participants enrolled in an extension study in which they received additional medication 9 to 14 months after the initial injection. Data from the extension trial was not reported.

### **Clinical Safety:**

The safety profile for nusinersen is based on observations in 173 patients from the Phase 3 RCT, Phase 2 open label study in patients with symptomatic infantile onset SMA, and Phase 1 open label dose finding trial in patients with later onset SMA. Patients with SMA type 4 were not included in the preliminary trials. Due to the small number of patients included in the clinical trials and limited duration of exposure, the safety of nusinersen is not known. The most common adverse reactions that were observed in patients were lower respiratory infection (43% with nusinersen vs. 29% with placebo), upper respiratory infection (39% vs. 34%) and constipation (30% vs. 22%).<sup>2</sup> Thrombocytopenia developed in 6 of 56 (11%) patients after administration of nusinersen.<sup>16</sup> None of the 28 sham procedure patients experienced thrombocytopenia. Five of 173 (3%) nusinersen patients (3%) had a hemorrhagic complication of lumbar puncture. Proteinuria occurred in 17 of 51 (33%) nusinersen patients compared to 5/25 (20%) sham control subjects.<sup>16</sup> Per the manufacturer, lab testing of platelets, prothrombin time and quantitative spot urine protein testing is recommended at baseline and prior to each dose of nusinersen.<sup>2</sup> Repeat testing and further evaluation is recommended for urinary protein concentrations greater than 0.2 g/L.<sup>2</sup> The FDA review noted the following as the main safety concerns for nusinersen: thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, effects on growth, rash and possible vasculitis, and hepatic effects.<sup>2</sup>

In summary, nusinersen may improve motor function in infants with SMA type I as assessed by the HINE-2 or CHOP-INTEND scores within the first six months of therapy. It is not known if improvement in motor function will impact long-term survival or reliance on a ventilator. Furthermore, nusinersen is associated with serious adverse effects including thrombocytopenia and renal toxicity. Long term safety data is currently insufficient. The long term impact on survival or

ventilator dependence is not well documented due to the ongoing data collection in phase III RCTs. Evidence regarding efficacy in SMA type 2, 3 or 4 is not published. As nusinersen is the first drug FDA approved to treat SMA, there are no comparator medications. The pharmacology and pharmacokinetic properties are presented in **Table 2**. Details of the 3 trials submitted to the FDA for approval are outlined in **Table 3**. In general, the Drug Use Research Management team only evaluates randomized controlled trials in the evidence summary. However, due to the limited amount of data currently available to evaluate the safety and efficacy of nusinersen the open label Phase 1 and Phase 2 trials are also included in the evidence tables.

**Look-alike/Sound-alike Error Risk Potential:** No similarities noted.

**Table 2. Pharmacology and Pharmacokinetic Properties.<sup>2</sup>**

Parameter	
Mechanism of Action	Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide
Oral Bioavailability	N/A – Administered via intrathecal injection
Elimination	Urinary excretion
Half-Life	135 to 177 days in CSF and 63 to 87 days in plasma
Metabolism	Hydrolysis

Abbreviations: CSF = cerebral spinal fluid; N/A = not applicable

**Table 3. Evidence Table Summarizing Nusinersen Trials Submitted to the FDA for Approval<sup>1,11,19</sup>**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NN H	Risk of Bias/Applicability (RCTs) Study Limitations (Observational Trials)
Chiriboga et.al. <sup>19</sup>  OL, dose escalating, MC, Phase 1 trial	1. Nusinersen 1 mg IT x1 2. Nusinersen 3 mg IT x1 3. Nusinersen 6 mg IT x1 3. Nusinersen 9mg IT x1	<u>Demographics</u> Average age = 6.1 years, 39% male, 82% Caucasian, 36% were ambulatory  <u>Key Inclusion Criteria:</u> - Patients aged 2-14 years with symptomatic SMA Type 2 and 3 and homozygous SMN1 gene deletion -Medically stable -Life expectancy ≥ 2 years  <u>Key Exclusion Criteria:</u> -Respiratory insufficiency -Active infection -Recent hospitalization for surgery or pulmonary event within past 2 months -History of brain or spinal cord disease or bacterial meningitis -Presence of implanted CSF shunt -Significant laboratory abnormalities	<u>ITT</u> 1. 6 2. 6 3. 6 4. 10  (total n=28 enrolled)  <u>Attrition:</u> Not reported	<u>Primary Endpoint:</u> Number of Adverse Events  Pharmacokinetic Assessment: CSF half-life estimated as 132-166 days  <u>Secondary Endpoint:</u> HFSME evaluated by physical therapist at baseline, day 29, and 85 Mean change at day 85 compared to baseline: 1. +1.0 2. +1.0 3. +0.7 4. +3.1  Mean change at increase at 9-14 months compared to baseline 1.-1.7 2. +0.5 3. +2.5 4.+5.8  PedsQL at baseline, day 29, and day 85 No significant changes reported in any group	N/A     N/A     N/A	<u>Adverse Events:</u> Total of 89% patients reported an adverse event  Adverse events (n) reported as number of events that occurred in > 2 subjects  Prevalence reported as percentage of patients  Most common: - Headache (n = 12 events; 39%)  - Post-LP Headache (n = 7 events; 21%)  - Back Pain (n = 7 events; 18%)	N/A for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> HIGH. No information on patients screened but not included <u>Intervention Bias:</u> HIGH. Open label study design, clinical meaningful changes in HFSME not determined a priori. <u>Missing Data Bias:</u> UNCLEAR. Attrition not reported. <u>Reporting Bias:</u> UNCLEAR. Funded by Ionis and Biogen.  <b>Applicability:</b> <u>Patient:</u> Dosing finding trial in SMA Type 2 and 3 patients. <u>Intervention:</u> One time dosing with 4 different doses – primarily to determine safety and pharmacokinetic parameters. Only 8 patients who received the 9mg dose were evaluated at 9 to 14 months <u>Comparator:</u> For motor function assessment changes in function were compared to natural history cases series of SMA type 1 patients. <u>Outcomes:</u> Changes in motor function reported as mean changes, not individual <u>Setting:</u> 4 study centers in the United States: Columbia University, University of Utah, Boston Children’s Hospital, and University of Texas Southwestern Medical School

<p>Finkel, et al.<sup>11</sup></p> <p>Phase 2, OL, dose escalating</p>	<p>1. Nusinersen IT at 6 mg on days 1,15, 85 and then 12 mg on day 253 and 12 mg every 4 months</p> <p>2. Nusinersen 12mg IT loading doses on days 1,15, 84 and 253, then 12 mg every 4 months</p> <p>Duration: 32 months</p>	<p><b>Demographics:</b> Average age at enrollment: 141 days, 60% male, 80% Caucasian -17/20 (85%) had 2 copies of SNM2 gene - 2/19 (10%) had 3 copies of SNM2 gene</p> <p><b>Key Inclusion Criteria:</b> -Age between 3 weeks and 7 months old -SMA 1 with SMN1 gene deletion -Gestational age between 35-42 weeks -Gestational weight ≥ 2 kg -Body weight &gt; 5<sup>th</sup> percentile</p> <p><b>Key Exclusion Criteria:</b> -Hypoxemia -Active infection -History of brain or spinal cord disease -Presence of implanted CSF shunt -Significant laboratory abnormalities</p>	<p><b>Interim Analysis (ITT):</b> 1. 4 2. 16 (total n=20 enrolled)</p> <p><b>Attrition:</b> 1 infant died prior to 85 day assessment  2 patients withdrew due to infection or respiratory failure  2 patients enrolled but failed screening due to hypoxia, cardiac abnormality</p>	<p><b>Primary Endpoint:</b> Change from baseline of HINE-Part 2 at last visit 1. (6 mg cohort): n = 1 /4 (25%) p=0.0002 2. (12 mg cohort): 15/15 (100%) p&lt;0.0001</p> <p><b>Secondary Endpoint:</b> Change from baseline to last visit (92 days) in CHOP-INTEND 1. (6 mg cohort): not reported 2. (12 mg cohort): 12/14 (85%) Mean increase = 15.2 points (p=0.0013)</p>	<p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p>	<p><b>Safety:</b> Overall, 570 adverse events reports in 100% of patients.</p> <p>Majority of adverse events were mild (63%) or moderate (27%) in severity.</p> <p>Adverse events (n) reported as number of events that occurred in &gt; 4 subjects</p> <p>Prevalence reported as percentage of patients</p> <p>Most common adverse events included:</p> <ul style="list-style-type: none"> <li>- Fever (n =14; 70%)</li> <li>- Respiratory Infection (n = 14; 70%)</li> <li>- Constipation (n=9; 45%)</li> <li>- Vomiting (n = 8; 40%)</li> <li>- Joint Contracture (n = 8; 40%)</li> <li>- Rash (n=5; 25%)</li> </ul>	<p>N/A for all</p>	<p><b>Risk of Bias (low/high/unclear):</b> <b>Selection Bias:</b> HIGH. No information on patients screened but not included <b>Intervention Bias:</b> HIGH. Open label study design. Patients and providers were not blinded. Clinical meaningful changes in HINE-2 and CHOP-INTEND not determined a priori. <b>Missing Data Bias:</b> HIGH. Large attrition rate; 5 patients (25%) withdrew. <b>Reporting Bias:</b> HIGH. Funded by Ionis and Biogen. CHOP-INTEND scores only reported for 14 patients (70%) at 92 days.</p> <p><b>Applicability:</b> <b>Patient:</b> Patients with SMA type 1. <b>Intervention:</b> Multiple doses on nusinersen (6mg and 12 mg loading doses) <b>Outcomes:</b> CHOP-INTEND scores only reported for 14 patients (70%) at 92 days. Short follow-up duration (2-32 months) Data regarding long-term functional improvement, quality of life or other clinical outcomes is not available. <b>Setting:</b> Conducted in United States and Canada.</p>
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<p>ENDEAR<sup>1</sup></p> <p>Phase 3, MC, RCT, Sham Control</p>	<p>1. Nusinersen three 12 mg loading doses (day 1, 15, 29, 64), then 12 mg every 4 months IT administration (dosing scaled based on weight) n=80</p> <p>2. Sham control (small needle prick on the lower back) n=41</p> <p>Randomized 2:1 to nusinersen vs. sham control</p>	<p><b>Demographics:</b></p> <ul style="list-style-type: none"> <li>-55% female</li> <li>-86% Caucasian</li> <li>-Median age at enrollment: 175 days (range = 30 -262 days)</li> <li>-12/17 (71%) had 2 SMN2 gene copies</li> <li>-5/17 (29%) had 3 SMN2 gene copies</li> <li>-Median age of symptom onset</li> </ul> <p>1. 6.5 weeks (range = 2-18 weeks)</p> <p>2.8weeks (range = 1-20 weeks)</p> <p>Number of patients requiring respiratory support at baseline</p> <p>1.21(26%)</p> <p>2.6(15%)</p> <p><b>Key Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>- Infants 7 months or younger with SMA 1</li> <li>-At least 2 copies of SMN2</li> <li>-Adequate nutrition and hydration with gastrostomy</li> <li>-Body weight <math>\geq</math> 3<sup>rd</sup> percentile for age</li> <li>-Gestational age 37 to 42 weeks</li> </ul> <p><b>Key Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>-Hypoxemia</li> <li>-Active infection</li> <li>-History of brain or spinal cord disease</li> <li>-Presence of CSF shunt</li> <li>-Significant laboratory abnormalities</li> </ul>	<p><b>Interim Evaluation:</b></p> <p>ITT:</p> <p>1.80</p> <p>2.41</p> <p>PP (excluded patients who died or withdrew from the study):</p> <p>1. 51</p> <p>2. 27</p> <p><b>Attrition:</b></p> <p>1. 1</p> <p>2. 1</p>	<p><b>Primary Endpoint:</b></p> <p>HINE-2 response*(PP population)</p> <p>1.Nusinersen: 41%</p> <ul style="list-style-type: none"> <li>- Full Head Control: n= 9 (18%)</li> <li>- Independent Sitting: n= 5 (10%)</li> <li>- Standing: n=1 (2%)</li> </ul> <p>2. Control: 0%</p> <p>Event free survival defined as time to death or permanent ventilation(original outcome)</p> <p>ITT Population</p> <p>1. n=27 (34%)</p> <p>2. n=20 (49%)</p> <p>HR for event free survival = 0.71 (confidence intervals not reported)</p> <p><b>Secondary Endpoint:</b></p> <p>Proportion of patients with <math>\geq</math>4 point increase from baseline in CHOP-INTEND (based on assessment at day 183, 302, or 394)</p> <p>CHOP-INTEND</p> <p>&gt;4 point increase (improvement)</p> <p>1. 63%</p> <p>2. 3%</p> <p><math>\geq</math> 4 point decrease (worsening)</p> <p>1. 4%</p> <p>2. 40%</p>	<p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p>	<p><b>Outcome:</b></p> <p>Fatal adverse event</p> <p>1. 12 (15%)</p> <p>2. 12 (29%)</p> <p>Only percentages of SAEs reported, not specific numbers of events</p> <p>Respiratory</p> <p>1. 58%</p> <p>2. 63%</p> <p>Infections</p> <p>1. 50%</p> <p>2. 37%</p> <p>Thrombocytopenia</p> <p>1. 11%</p> <p>2. 0%</p> <p>Proteinuria</p> <p>1. 33%</p> <p>2. 20%</p> <p>Statistical significance not reported</p>	<p>N/A for all</p>	<p><b>Risk of Bias (low/high/unclear):</b></p> <p><b>Selection Bias:</b> HIGH. Randomization was stratified based on disease duration (<math>\leq</math>12 weeks vs. &gt;12 weeks). Since trial is not published, methods of randomization and concealment of allocation are not known. Nusinersen patients had earlier disease onset (6.5 weeks vs 8 weeks); more infections, respiratory/swallowing/feeding issues compared to control.</p> <p><b>Performance Bias:</b> Sponsor, parents and key study personnel were blinded.</p> <p><b>Detection Bias:</b> Sponsor, parents and key study personnel were blinded.</p> <p><b>Attrition Bias:</b> HIGH. Two patients withdrew (one from each study group) and 21 patients died (nusinersen = 11 and control = 10).</p> <p><b>Reporting Bias:</b> HIGH. Interim results are from an unblinded analysis completed by a contract research organization and reviewed by senior management team from Ionis and Biogen. Only unpublished data available. Full study results have not been evaluated or published. Primary outcome modified before interim analysis to include motor skill assessment (HINE-2 scores). Funded by Ionis and Biogen.</p> <p><b>Applicability:</b></p> <p><b>Patient:</b> SMA type 1 patients</p> <p><b>Intervention:</b> Doses were scale adjusted based on body weight.</p> <p><b>Comparator:</b> Sham control</p> <p><b>Outcomes:</b> Duration of trial = 6 months, long-term impact on survival and motor development is unknown.</p> <p><b>Setting:</b> Conducted in multiple countries: Australia, Belgium, Canada, France, Germany, Great Britain, Italy, Japan, Korea, Spain, Sweden, Turkey and the United States</p>
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Abbreviations: CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale Expanded; HINE = Hammersmith Infant Neurological Exam; HR = hazard ratio; ITT = intention to treat; IT = Intrathecal; LP = lumbar puncture; MC = Multicenter; n = number; OL = open label; PedsQL = Pediatric Quality of Life Inventory; PP = per protocol

\* Motor function improvement in HINE section 2 defined as 1) a  $\geq 2$  point increase in ability to kick, 2)  $\geq 1$  point increase in head control, rolling, sitting, crawling, standing or walking, and 3) improvement in more categories of motor milestones than worsening

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPINRAZA™ safely and effectively. See full prescribing information for SPINRAZA.

**SPINRAZA (nusinersen) injection, for intrathecal use**  
**Initial U.S. Approval: 2016**

#### INDICATIONS AND USAGE

SPINRAZA is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (1)

#### DOSAGE AND ADMINISTRATION

SPINRAZA is administered intrathecally (2.1)

##### Dosing Information (2.1)

- The recommended dosage is 12 mg (5 mL) per administration
- Initiate SPINRAZA treatment with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4<sup>th</sup> loading dose should be administered 30 days after the 3<sup>rd</sup> dose; a maintenance dose should be administered once every 4 months thereafter

##### Important Preparation and Administration Instructions (2.2)

- Allow to warm to room temperature prior to administration
- Administer within 4 hours of removal from vial
- Prior to administration, remove 5 mL of cerebrospinal fluid
- Administer as intrathecal bolus injection over 1 to 3 minutes

##### Laboratory Testing and Monitoring to Assess Safety (2.3)

- At baseline and prior to each dose, obtain a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing

#### DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/5 mL (2.4 mg/mL) in a single-dose vial (3)

#### CONTRAINDICATIONS

None.

#### WARNINGS AND PRECAUTIONS

- *Thrombocytopenia and Coagulation Abnormalities:* Increased risk for bleeding complications; testing required at baseline and before each dose (5.1, 2.3)
- *Renal Toxicity:* Quantitative spot urine protein testing required at baseline and prior to each dose (5.2, 2.3)

#### ADVERSE REACTIONS

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection, upper respiratory infection, and constipation (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2017

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## FULL PRESCRIBING INFORMATION: CONTENTS\*

Appendix 2: Proposed Prior Authorization Criteria

## Nusinersen

**Goal(s):**

- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

**Length of Authorization:**

- Up to 6 months for initial approval and up to 6 months for renewal.

**Requires PA:**

- Nusinersen

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is this a request for continuation of therapy?	Yes: Go to #9	No: Go to #3
3. Was the patient's gestational age between 37 and 42 weeks?	Yes: Go to #4	No: Pass to RPh. Deny, medical appropriateness.
4. Is the patient $\leq$ 7 months of age at the time of the request?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.

## Approval Criteria

<p>5. Does the patient have type 1 Spinal Muscular Atrophy documented by genetic testing and 2 copies of the SMN2 gene?</p>	<p>Yes: Go to #6</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>6. Is a baseline motor assessment available using the following functional assessment tool:</p> <ul style="list-style-type: none"> <li>Hammersmith Infant Neurological Examination (HINE-2)</li> </ul>	<p>Yes: Go to #7</p>	<p>No: Pass to RPh. Deny medical appropriateness.</p>
<p>7. Is the patient ventilator dependent (using at least 16 hours per day on at least 21 of the last 30 days)?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p>	<p>No: Go to #8.</p>
<p>8. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?</p>	<p>Yes: Approve up to 6 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>9. Has the patient's motor function improved as demonstrated by:</p> <ul style="list-style-type: none"> <li>Improvement in baseline HINE-2 score within one month of renewal request AND</li> <li>More areas of motor function improved than worsened</li> </ul>	<p>Yes: Approve for 6 months</p>	<p>No: Pass to RPh; Deny; medical appropriateness.</p>

P&T Review: 7/17 (dm) 3/17 (DM)  
 Implementation: 5/17