The first and only treatment for individuals with spinal muscular atrophy (SMA)¹

INDICATION
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

SELECTED IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.

Confidential and proprietary to Biogen.
Mechanism of action

SPINRAZA is an antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to survival motor neuron (SMN) protein deficiency.

SPINRAZA was shown to increase production of full-length SMN protein by increasing exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA), using in vitro assays and studies in transgenic animal models of SMA.

SPINRAZA, administered intrathecally, delivers concentrations in the cerebrospinal fluid (CSF), and has been shown to be distributed in the central nervous system and peripheral tissues, including skeletal muscle, liver, and kidney.

SPINRAZA was shown to increase exon 7 inclusion in SMN2 mRNA transcripts and production of full-length SMN protein.

SELECTED IMPORTANT SAFETY INFORMATION

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In a clinical study (mean treatment exposure 7 months), 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.

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The SPINRAZA clinical trial program is the largest in SMA to date\(^1\)

**SPINRAZA was evaluated in a controlled study of 121 infants**

**Study details**

- Study was a multicenter, double-blind, randomized, sham-procedure controlled study in 121 symptomatic patients
- Patients were randomized 2:1 to receive either SPINRAZA or sham injection

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Disease duration (median)</th>
<th>Age at first treatment (median, all ≤7 months)</th>
<th>Length of treatment (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPINRAZA</td>
<td>14 weeks</td>
<td>175 days</td>
<td>261 days (range 6 to 442 days)</td>
</tr>
<tr>
<td>Sham-control</td>
<td></td>
<td>206 days</td>
<td></td>
</tr>
</tbody>
</table>

- 98% of patients in both groups had 2 copies of SMN2

**Planned interim efficacy analysis was conducted based on 82 patients who: completed at least 183 days of treatment, died, or withdrew from the study**

- **Primary endpoint:** Proportion of patients with an improvement in motor milestones according to Hammersmith Infant Neurological Examination (HINE) Section 2
- **Additional assessments**
  - Change in Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)—not statistically controlled for multiple comparisons
  - Safety

**Supportive open-label trials**

- Additional open-label uncontrolled trials included patients who had or were likely to develop Type 1, 2, or 3 SMA
  - **Symptomatic** patients who ranged in age from 30 days to 15 years at time of first dose
  - **Presymptomatic** patients who ranged in age from 8 days to 42 days at time of first dose

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**SELECTED IMPORTANT SAFETY INFORMATION**

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Improvements in motor milestones with SPINRAZA™

In a controlled trial, significantly more patients with infantile-onset SMA treated with SPINRAZA achieved motor milestone improvements, including head control, rolling, or sitting, compared with sham-control patients, at the time of the planned interim analysis.

**PRIMARY ENDPOINT**
Patients who met the definition of motor milestone responder at day 183*

| SPINRAZA (n=52) | 40% (21) | VS | P<0.0001 | Sham-control (n=30) | 0% (0) |

SPINRAZA was studied in a multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants ≤7 months of age at the time of first dose, diagnosed with SMA (symptom onset before 6 months of age).

*The planned interim analysis included all subjects who were alive with the opportunity for at least a 6-month (day 183) assessment and all subjects who died or withdrew from the study at the time of the planned interim analysis.

**PRIMARY ENDPOINT AT PLANNED INTERIM ANALYSIS**
Motor milestone responder

Achieving a level of improvement in motor milestones according to HINE Section 2 (which measures motor function). Milestones were ability to kick, head control, rolling, sitting, crawling, standing, and walking. Patient was considered a responder if he/she achieved:

\[
\text{MOTOR MILESTONE RESPONSE = (} \begin{cases} 
\geq 2\text{-point increase (or maximal score of 4) in ability to kick} & \text{OR} \\
\geq 1\text{-point increase in head control, rolling, sitting, crawling, standing, or walking} & \text{AND} \\
\text{Improvement in more categories of motor milestones than worsening} 
\end{cases}
\]

**SELECTED IMPORTANT SAFETY INFORMATION**
The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Results with SPINRAZA in the interim efficacy set

The planned interim efficacy analysis was conducted based on 82 patients who: completed at least 183 days of treatment, died, or withdrew from the study.

In a controlled trial, some patients with infantile-onset SMA treated with SPINRAZA saw improvement in motor milestones achieved and lower mortality.

Net change from baseline in total motor milestone score (HINE) by percent of subjects in the interim efficacy set

For subjects who were alive and ongoing in the study, the change in total motor milestone score was calculated at the later of day 183, day 302, or day 394.

A smaller percentage of patients treated with SPINRAZA died, and a greater percentage saw improvements in motor milestones achieved, as well as a greater magnitude of improvement in motor milestone score compared to sham-control patients.

SELECTED IMPORTANT SAFETY INFORMATION

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Motor function improvement in SMA

Patients with infantile-onset SMA treated with SPINRAZA (nusinersen) saw greater improvements in motor function compared with sham-control patients at the time of the planned interim analysis

Change in CHOP INTEND

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA (n=52)</th>
<th>Sham-control (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP INTEND improvement from baseline*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4 points</td>
<td>33 (63%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>CHOP INTEND worsening from baseline*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4 points</td>
<td>2 (4%)</td>
<td>12 (40%)</td>
</tr>
</tbody>
</table>

*Analyses included all subjects who were alive with the opportunity for at least a 6-month (day 183) assessment and all subjects who died or withdrew from the study at the time of the planned interim analysis
†Not statistically controlled for multiple comparisons at the planned interim analysis

CHOP INTEND
- An evaluation of motor skills in patients with infantile-onset SMA

SELECTED IMPORTANT SAFETY INFORMATION

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney. In a clinical study (mean treatment exposure 7 months), 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Effectiveness in presymptomatic and symptomatic patients¹

The efficacy of SPINRAZA in the controlled trial in patients with infantile-onset SMA was supported by open-label uncontrolled trials in presymptomatic and symptomatic patients.

Some patients treated with SPINRAZA who had or were likely to develop Type 1, 2, or 3 SMA:

**ACHIEVED MOTOR MILESTONES**
such as the ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so

**MAINTAINED MOTOR MILESTONES**
at ages when they would be expected to be lost

**SURVIVED TO AGES UNEXPECTED**
considering their number of SMN2 gene copies

The overall findings support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

**SELECTED IMPORTANT SAFETY INFORMATION**

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.
Cases of rash were reported in patients treated with SPINRAZA.
SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study.
It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Coagulation abnormalities and thrombocytopenia

- Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides (ASOs). Patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

- In a clinical study, 11% of patients treated with SPINRAZA with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Renal toxicity

- Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some ASOs.

- SPINRAZA is present in and excreted by the kidney. In a clinical study (mean treatment exposure 7 months), 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of patients with later-onset SMA patients (mean treatment exposure 34 months), 69% had elevated urine protein.

- No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.
Exposure to SPINRAZA (nusinersen) was studied in 173 patients, including 120 exposed for at least 6 months and 83 exposed for at least 1 year.

Adverse reactions that occurred in at least 5% of SPINRAZA patients and occurred at least 5% more frequently or at least 2 times as frequently than in control patients in the controlled study in infants with symptomatic SMA

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>SPINRAZA* (n=80)</th>
<th>Sham-control (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lower respiratory infection(^1)</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Upper respiratory infection(^2)</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\)Four loading doses followed by 12 mg (5 mL) once every 4 months

\(^2\)Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia bacterial, bronchitis, bronchitis viral, pneumonia moraxella, pneumonia parainfluenzae viral, lower respiratory tract infection viral, lung infection, pneumonia influenza, pneumonia pseudomonal, pneumonia respiratory syncytial viral

SPINRAZA has no contraindications and no known drug-drug interactions.
Baseline characteristics in the controlled study

- Baseline disease characteristics were largely similar in SPINRAZA-treated patients and sham-control patients.
  - There was some imbalance in age at symptom onset with 88% of subjects in the SPINRAZA group and 77% in the control group experiencing symptoms within the first 12 weeks of life.
- However, SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of:
  - Paradoxical breathing (89% vs 66%)
  - Pneumonia or respiratory symptoms (35% vs 22%)
  - Swallowing or feeding difficulties (51% vs 29%)
  - Requirement for respiratory support (26% vs 15%)

Adverse reactions in the controlled study

- In the controlled study, 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 upper respiratory infection, lower respiratory infection, and constipation.
- Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%).
- Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study.

Adverse events in the open-label studies

- The most common adverse events in the open-label studies in later-onset patients were headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%). Most of these events occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with adverse events observed in the controlled study.

Additional events

- Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand 10 months after the start of SPINRAZA treatment, which resolved over 3 months.
  - Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.
- SPINRAZA may cause a reduction in growth as measured by height when administered to infants. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.
- In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Please see Important Safety Information and full Prescribing Information by clicking the buttons on the top right.
Consider starting treatment with SPINRAZA (nusinersen) as early as possible after diagnosis with the recommended dosing

**SPINRAZA is injected into the CSF and targets the central nervous system (CNS) tissues**

SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures. Initiate SPINRAZA treatment with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

**SPINRAZA is delivered as a 12-mg (5-mL) dose at each injection**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading Dosing</td>
<td>14 days</td>
<td>14 days</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td>Maintenance Dosing</td>
<td>every 4 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If a loading dose is delayed or missed, administer SPINRAZA as soon as possible with at least 14 days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

**SELECTED IMPORTANT SAFETY INFORMATION**

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Important dosing information to consider when administering SPINRAZA

**Administration**

- Prior to administration, remove 5 mL of CSF
- Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation
- Administer SPINRAZA within 4 hours of removal from vial

**Considerations**

- Consider sedation as indicated by the clinical condition of the patient
- Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients

**Laboratory testing**

Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed:

- Platelet count
- Prothrombin time; activated partial thromboplastin time
- Quantitative spot urine protein testing

**SELECTED IMPORTANT SAFETY INFORMATION**

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SPINRAZA is supplied as a single-dose vial

SPINRAZA is a sterile, clear, and colorless solution for intrathecal injection.
- Supplied as a 12-mg/5-mL (2.4-mg/mL) solution in a single-dose glass vial
- Free of preservatives
- NDC is 64406-058-01

Storage and handling

Store in a refrigerator between 2°C and 8°C (36°F-46°F) in the original carton to protect from light. Do not freeze.

SPINRAZA should be protected from light and kept in the original carton until time of use. If no refrigeration is available, SPINRAZA may be stored in its original carton, protected from light, at or below 30°C (86°F) for up to 14 days.

SELECTED IMPORTANT SAFETY INFORMATION

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Welcome to SMA360°

A support service from Biogen created to help families navigate the SPINRAZA (nusinersen) treatment journey*

We understand that for a caregiver or an individual living with SMA, life can be challenging. SMA360° is a support service from Biogen created to help families navigate the following areas of the treatment process with SPINRAZA:

Treatment logistics

Once a completed Start Form has been submitted to Biogen, a dedicated Family Access Manager (FAM) will reach out to begin helping with the logistics surrounding your patient’s treatment. The FAM will be the go-to person whenever there is a question or concern related to the logistics of the treatment journey while on SPINRAZA. The FAM can provide information on SMA360° support services and how a caregiver or individual living with SMA may be eligible for programs tailored to their needs.

The FAM can:

- Coordinate the logistics of getting started with treatment
- Prepare the individual with SMA for the treatment journey by educating him/her on what to expect
- Connect with the caregiver or individual with SMA at the treatment center, if he/she chooses, to help with logistics as necessary

Insurance and financial assistance

Today’s ever-changing insurance landscape can be overwhelming. SMA360° Insurance and Financial Assistance Programs are designed to help individuals with SMA and their families understand their insurance benefits for SPINRAZA, and find an affordable way to start treatment and continue as prescribed by their healthcare provider.

To help inform decisions regarding care, SMA Support Coordinators can:

- Investigate insurance benefits to help individuals with SMA and their families understand their current coverage
- Collaborate with healthcare providers so that they can obtain prior authorizations for treatment
- Provide support in the event of denied insurance claims
- Educate individuals with SMA and their families on the eligibility details of the $0 Copay Program† from Biogen, which can potentially cover both the SPINRAZA prescription and the treatment procedure
- Supply background and resources for referral to third-party charity organizations
- Counsel individuals with SMA and their families on the possibility of adding or changing insurance coverage

*SMA360° services from Biogen are available only to those who have been prescribed SPINRAZA. SMA360° is available only in the US.

† Depending on the individual’s income or, in some cases, if their medication is obtained from an out-of-network provider, there may be an annual cap that limits the amount of assistance they can receive over 1 year. Federal and state laws and other factors may prevent or otherwise restrict eligibility. Individuals receiving coverage from Medicare, Medicaid, the VA/DoD, TRICARE®, or any other governmental or pharmaceutical assistance may not be eligible. The $0 Copay Program is only available once a claim has been submitted to and paid for by the insurance company. Individuals may remain enrolled in the $0 Copay Program for as long as eligibility criteria are met. Contact an SMA Coordinator for full eligibility requirements.

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SELECTED IMPORTANT SAFETY INFORMATION

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Cases of rash were reported in patients treated with SPINRAZA.

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HINE SECTION 2

A motor function assessment tool designed to be a simple method for evaluating motor skills in infants

Section 2, the motor milestones portion of the HINE, includes 8 items: voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking

- For each function, increased levels of ability are depicted from left to right
- Each transition to a successive level of ability from a previous assessment is scored 1 point
- Total HINE score is the sum of points from each item and can range from 0 to 26

An improvement in motor function is a 1-point increase in this scale

<table>
<thead>
<tr>
<th>Voluntary grasp</th>
<th>No grasp</th>
<th>Uses whole hand</th>
<th>Index finger and thumb but immature grasp</th>
<th>Pincer grasp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to kick (in supine position)</td>
<td>No kicking</td>
<td>Kicks horizontal; legs do not lift</td>
<td>Upward (vertical)</td>
<td>Touches leg</td>
</tr>
<tr>
<td>Head control</td>
<td>Unable to maintain upright</td>
<td>Wobbles</td>
<td>All the time upright</td>
<td></td>
</tr>
<tr>
<td>Rolling</td>
<td>No rolling</td>
<td>Rolling to side</td>
<td>Prone to supine</td>
<td>Supine to prone</td>
</tr>
<tr>
<td>Sitting</td>
<td>Cannot sit</td>
<td>Sits with support at hips</td>
<td>Props</td>
<td>Stable sit</td>
</tr>
<tr>
<td>Crawling</td>
<td>Does not lift head</td>
<td>On elbow</td>
<td>On outstretched hand</td>
<td>Crawling flat on abdomen</td>
</tr>
<tr>
<td>Standing</td>
<td>Does not support weight</td>
<td>Supports weight</td>
<td>Stands with support</td>
<td>Stands unaided</td>
</tr>
<tr>
<td>Walking</td>
<td>No walking</td>
<td>Bouncing</td>
<td>Cruising (holding on)</td>
<td>Walking independently</td>
</tr>
</tbody>
</table>
CHOP INTEND<sup>3</sup>

A 16-item scale that measures motor function in infants
- Each of the 16 items is graded on a scale of 0 to 4
  - 0 = No response
  - 4 = Complete response
- Total score ranges from 0 to 64

<table>
<thead>
<tr>
<th>Item</th>
<th>Lowest item grade (0)</th>
<th>Highest item grade (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Spontaneous upper extremity movement</td>
<td>No movement of limbs</td>
<td>Moving elbow off surface in supine position</td>
</tr>
<tr>
<td>2 Spontaneous lower extremity movement</td>
<td>No movement of limbs</td>
<td>Moving feet/knees off surface in supine position</td>
</tr>
<tr>
<td>3 Hand grip</td>
<td>No attempt to maintain grasp</td>
<td>Maintains hand grip with shoulder off bed</td>
</tr>
<tr>
<td>4 Head movement</td>
<td>Head falls to side, no attempts to regain midline</td>
<td>Rotates from maximum rotation to midline</td>
</tr>
<tr>
<td>5 Hip abductors</td>
<td>No attempt to maintain knees off surface</td>
<td>Keeps knee off surface of bed &gt;5 seconds or lifts foot off surface</td>
</tr>
<tr>
<td>6 Rolling from legs</td>
<td>Pelvis lifted passively off support surface</td>
<td>When traction is applied at the end of maneuver, rolls to prone with lateral head righting</td>
</tr>
<tr>
<td>7 Rolling from arms</td>
<td>Head turns to side; body remains limp or shoulder lifts passively</td>
<td>Rolls to prone with lateral head righting</td>
</tr>
<tr>
<td>8 Shoulder and elbow flexion and horizontal abduction</td>
<td>No attempt</td>
<td>Clears hand from surface with antigravity arm movement</td>
</tr>
<tr>
<td>9 Shoulder and elbow flexion</td>
<td>No attempt to lift arm</td>
<td>Abducts or flexes shoulder to 60°</td>
</tr>
<tr>
<td>10 Knee extension</td>
<td>No visible knee extension</td>
<td>Extends knee to &gt;45°</td>
</tr>
<tr>
<td>11 Hip flexion and foot dorsiflexion</td>
<td>No active hip, knee, or ankle motion</td>
<td>Hip flexion or knee flexion &gt;30°</td>
</tr>
<tr>
<td>12 Head control</td>
<td>No response; head hangs</td>
<td>Attains head upright from flexion and turns head side to side</td>
</tr>
<tr>
<td>13 Elbow flexion score with item 14</td>
<td>No visible contraction</td>
<td>Flexes elbow</td>
</tr>
<tr>
<td>14 Neck flexion score with item 13</td>
<td>No muscle contraction</td>
<td>Lifts head off bed</td>
</tr>
<tr>
<td>15 Head/neck extension (Landau)</td>
<td>No head extension</td>
<td>Extends head to horizontal plane or above</td>
</tr>
<tr>
<td>16 Spinal incurvation (Galant)</td>
<td>No response</td>
<td>Twists pelvis toward stimulus off axis</td>
</tr>
</tbody>
</table>

HINE was developed at Hammersmith Hospital in London.<sup>4</sup> CHOP INTEND was developed at the Children’s Hospital of Philadelphia.<sup>3</sup>
INDICATION

SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mL and no patient developed a sustained low platelet count despite continued drug exposure.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney. In a clinical study (mean treatment exposure 7 months), 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).


For additional Important Safety Information, please see full Prescribing Information by clicking on the button on the top right.
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 4th loading dose should be administered 30 days after the 3rd 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.

See 17 for PATIENT COUNSELING INFORMATION.

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  2.1 Dosing Information
  2.2 Important Administration Instructions
  2.3 Laboratory Testing and Monitoring to Assess Safety
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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FULL PRESCRIBING INFORMATION

1  INDICATIONS AND USAGE
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2  DOSAGE AND ADMINISTRATION

2.1 Dosing Information
SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage
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 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose
If a loading dose is delayed or missed, administer SPINRAZA as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

2.2 Important Preparation and Administration Instructions
SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation
- Store SPINRAZA in the carton in a refrigerator until time of use.
- Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use external heat sources.
- Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored.
- Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
- Administer SPINRAZA within 4 hours of removal from vial.

Administration
- Consider sedation as indicated by the clinical condition of the patient.
• Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
• Prior to administration, remove 5 mL of cerebrospinal fluid.
• Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation.

2.3 Laboratory Testing and Monitoring to Assess Safety

Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:
• Platelet count
• Prothrombin time; activated partial thromboplastin time
• Quantitative spot urine protein testing

3 DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia and Coagulation Abnormalities

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In a clinical study, 6 of 56 (11%) SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal, compared to 0 of 28 sham-procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in this study and no patient developed a sustained low platelet count despite continued drug exposure.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.
5.2 Renal Toxicity

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In a clinical study (mean treatment exposure 7 months), 17 of 51 (33%) SPINRAZA-treated patients had elevated urine protein, compared to 5 of 25 (20%) sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 36 of 52 (69%) had elevated urine protein. No elevations in serum creatinine or cystatin C were observed in these studies. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in detail in other sections of the labeling:

- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of SPINRAZA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to SPINRAZA in 173 patients (50% male, 82% Caucasian), including 120 exposed for at least 6 months and 83 exposed for at least 1 year. The safety of SPINRAZA was studied in infants with symptomatic SMA, approximately 1 month to 8 months of age at study entry; in a sham-controlled trial (n=80 for SPINRAZA, n=41 for control); in open-label studies in presymptomatic and symptomatic infants (n=37), and in open-label studies in later onset patients (n=56, 2 to 15 years of age at study entry). In the controlled study in symptomatic infants, 41 patients were exposed for at least 6 months and 19 patients were exposed for at least 12 months.

In the controlled study, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

In the controlled study, 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. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study.
Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients in the Controlled Study in Infants with Symptomatic SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg</th>
<th>Sham-Procedure Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=80</td>
<td>N=41</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lower respiratory infection²</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Upper respiratory infection³</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Four loading doses followed by 12 mg (5 mL) once every 4 months
² Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia bacterial, bronchitis, bronchitis viral, pneumonia moraxella, pneumonia parainfluenzae viral, lower respiratory tract infection viral, lung infection, pneumonia influenza, pneumonia pseudomonal, pneumonia respiratory syncytial viral
³ Includes upper respiratory tract infection, nasopharyngitis, rhinitis, pharyngitis, or tracheitis

In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse events in the open-label studies in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%). Most of these events
occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with adverse reactions observed in the controlled study.

6.2 Immunogenicity

The immunogenic response to nusinersen was determined in 126 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Five (4%) patients developed treatment-emergent ADAs, of which 3 were transient and 2 were considered to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to SPINRAZA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. No adverse effects on embryofetal development were observed in animal studies in which nusinersen was administered by subcutaneous injection to mice and rabbits during pregnancy (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

8.2 Lactation

Risk Summary
There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established [see Clinical Studies (14.1)].

Juvenile Animal Toxicity Data

In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use

SMA is largely a disease of children and young adults; therefore, there is no geriatric experience with SPINRAZA.

11 DESCRIPTION

SPINRAZA contains nusinersen, which is a modified antisense oligonucleotide, where the 2’-hydroxy groups of the ribofuranosyl rings are replaced with 2’-O-2-methoxyethyl groups and the phosphate linkages are replaced with phosphorothioate linkages. Nusinersen binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript. The structural formula is:
SPINRAZA is supplied as a sterile, preservative-free, colorless solution for intrathecal use in a single-dose glass vial. Each 1 mL solution contains 2.4 mg of nusinersen (equivalent to 2.53 mg of nusinersen sodium salt). Each 1 mL also contains calcium chloride dihydrate (0.21 mg) USP, magnesium chloride hexahydrate (0.16 mg) USP, potassium chloride (0.22 mg) USP, sodium chloride (8.77 mg) USP, sodium phosphate dibasic anhydrous (0.10 mg) USP, sodium phosphate monobasic dihydrate (0.05 mg) USP, and Water for Injection USP. The product may contain hydrochloric acid or sodium hydroxide to adjust pH. The pH is ~7.2.

The molecular formula of SPINRAZA is C₂₃₄H₃₂₃N₆₁O₁₂₈P₁₇S₁₇Na₁₇ and the molecular weight is 7501.0 daltons.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SPINRAZA is an antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, SPINRAZA was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein.

12.2 Pharmacodynamics

Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.

Cardiac Electrophysiology
In 121 patients with spinal muscular atrophy who received either SPINRAZA or sham-control, QTcF values >500 ms and change from baseline values >60 ms were observed in 5% of patients receiving SPINRAZA. Compared to the sham-control, there was no increase in the incidence of cardiac adverse reactions associated with delayed ventricular repolarization in patients treated with SPINRAZA.

12.3 Pharmacokinetics

Absorption
Intrathecal injection of SPINRAZA into the cerebrospinal fluid (CSF) allows nusinersen to be distributed from the CSF to the target central nervous system (CNS) tissues. Following intrathecal administration, trough plasma concentrations of nusinersen were relatively low, compared to the trough CSF concentration. Median plasma T_{max} values ranged from 1.7 to 6.0 hours. Mean plasma C_{max} and AUC values increased approximately dose-proportionally up to a dose of 12 mg.

Distribution
Autopsy data from patients (n=3) showed that SPINRAZA administered intrathecally was distributed within the CNS and peripheral tissues, such as skeletal muscle, liver, and kidney.

Elimination

Metabolism
Nusinersen is metabolized via exonuclease (3’- and 5’)-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes.

Excretion
The mean terminal elimination half-life is estimated to be 135 to 177 days in CSF, and 63 to 87 days in plasma. The primary route of elimination is likely by urinary excretion for nusinersen and its chain-shortened metabolites. At 24 hours, only 0.5% of the administered dose was recovered in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of nusinersen have not been performed.

Mutagenesis
Nusinersen demonstrated no evidence of genotoxicity in in vitro (Ames and chromosomal aberration in CHO cells) and in vivo (mouse micronucleus) assays.

Impairment of Fertility
When nusinersen (0, 3, 10, or 25 mg/kg) was administered by subcutaneous injection to mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on male or female fertility were observed.

14 CLINICAL STUDIES

The efficacy of SPINRAZA was demonstrated in a double-blind, sham-procedure controlled clinical trial in symptomatic infantile-onset SMA patients and was supported by open-label clinical trials conducted in presymptomatic and symptomatic SMA patients.

14.1 Clinical Trial in Infantile-Onset SMA

This study was a multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants ≤ 7 months of age at the time of first dose, diagnosed with SMA (symptom onset before 6 months of age). Patients were randomized 2:1 to receive either SPINRAZA or sham injection.

A planned interim efficacy analysis was conducted based on patients who died, withdrew, or completed at least 183 days of treatment. Of the 82 patients included in the interim analysis, 44% were male and 56% were female. Age at first treatment ranged from 30 to 262 days (median 181). Eighty-seven (87%) of subjects were Caucasian, 2% were Black, and 4% were Asian. Length of treatment ranged from 6 to 442 days (median 261 days). Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The SPINRAZA and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number (2 copies in 98% of subjects in both groups). Median disease duration was 14 weeks. There was some imbalance in age at symptom onset with 88% of subjects in the SPINRAZA group and 77% in the control group experiencing symptoms within the first 12 weeks of life.

The primary endpoint assessed at the time of interim analysis was the proportion of responders: patients with an improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE). This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each, depending on the milestone, and a total maximum score of 26. A treatment responder was defined as any patient with at least a 2-point increase (or maximal score of 4) in ability to kick (consistent with improvement by at least 2 milestones), or at least a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking (consistent with improvement by at least 1 milestone). To be classified as a responder, patients needed to exhibit improvement in more categories of motor milestones than worsening. Of the 82 patients who were eligible for the interim analysis, a statistically significantly greater percentage of patients achieved a motor milestone response in the SPINRAZA group compared to the sham-control group (see Table 2). Figure 1 is a descriptive display of the distribution of net change from baseline in the total motor milestone score for Section 2 of the HINE.

Although not statistically controlled for multiple comparisons at the interim analysis, the study also assessed treatment effects on the Children’s Hospital of Philadelphia Infant Test of
Neuromuscular Disorders (CHOP-INTEND), which is an evaluation of motor skills in patients with infantile-onset SMA. The CHOP-INTEND results are displayed in Table 2.

Table 2. Motor Milestone Response and CHOP-INTEND Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA-treated patients (n=52)</th>
<th>Sham-control patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Milestone (HINE Section 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achievement of a motor milestone response</td>
<td>21 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHOP-INTEND Improvement from Baseline(^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4-points</td>
<td>33 (63%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>CHOP-INTEND Worsening from Baseline(^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4-points</td>
<td>2 (4%)</td>
<td>12 (40%)</td>
</tr>
</tbody>
</table>

1. Analyses included all subjects who were alive with the opportunity for at least a 6-month (Day 183) assessment and all subjects who died or withdrew from the study at the time of the interim analysis

2. Not statistically controlled for multiple comparisons at interim analysis

Figure 1. Net Change from Baseline in Total Motor Milestone Score (HINE) by Percent of Subjects in the Interim Efficacy Set*  

*For subjects who were alive and ongoing in the study, the change in total motor milestone score was calculated at the later of Day 183, Day 302, or Day 394.

The results of the controlled trial in infantile-onset SMA patients were supported by open-label uncontrolled trials conducted in symptomatic SMA patients who ranged in age from 30 days to 15 years at the time of first dose, and in presymptomatic patients, who ranged in age from 8 days to 42 days at the time of first dose. The patients in these studies had or were likely to develop
Type 1, 2, or 3 SMA. Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.

The overall findings of the controlled trial in infantile-onset SMA and the open-label uncontrolled trials support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SPINRAZA injection is a sterile, clear and colorless solution supplied as a 12 mg/5 mL (2.4 mg/mL) solution in a single-dose glass vial free of preservatives. The NDC is 64406-058-01.

16.2 Storage and Handling

Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

SPINRAZA should be protected from light and kept in the original carton until time of use. If no refrigeration is available, SPINRAZA may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days.

Prior to administration, unopened vials of SPINRAZA can be removed from and returned to the refrigerator, if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours at a temperature that does not exceed 25°C (77°F).

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs [see Warnings and Precautions (5.1)].

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity [see Warnings and Precautions (5.2)].