SPINRAZA™ (nusinersen) injection 12 mg/5 mL

About SMA[1-5]

Spinal muscular atrophy (SMA) is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Due to a loss of, or defect in, the SMN1 gene, people with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the maintenance of motor neurons.

The severity of SMA correlates with the amount of SMN protein. People with infantile-onset (consistent with Type 1) SMA, a severe life-threatening form, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. These infants can become paralyzed and have difficulty performing basic life functions, like breathing and swallowing.

Children with later-onset (most likely to develop Type 2 or Type 3) SMA produce greater amounts of SMN protein and have less severe, but still life-altering forms of SMA. They can experience significant muscle weakness and disability, such as inability to stand or walk independently.

About SPINRAZA™ (nusinersen)

SPINRAZA has been approved in the U.S. for the treatment of SMA in pediatric and adult patients. Biogen and Ionis Pharmaceuticals, a leader in antisense technology, conducted an innovative clinical development program that moved SPINRAZA from its first dose in humans in 2011 to approval in five years. Biogen exercised its option to worldwide rights to SPINRAZA in August 2016.

SPINRAZA is an antisense oligonucleotide (ASO) that is designed to treat SMA caused by mutations in the chromosome 5q that leads to SMN protein deficiency. SPINRAZA alters the splicing of SMN2 pre-mRNA in order to increase production of full-length SMN protein.[6]

ASOs are short synthetic strings of nucleotides designed to selectively bind to target RNA and regulate gene expression. Through use of this technology, SPINRAZA has the potential to increase the amount of SMN protein in patients with SMA.

In October 2016, the European Medicines Agency (EMA) validated Biogen's Marketing Authorization Application (MAA) for SPINRAZA as a treatment for SMA, and the EMA's Committee for Medicinal Products for Human Use (CHMP) granted Accelerated Assessment status. In addition, Biogen has submitted regulatory filings in Japan, Canada and Australia and will initiate additional filings in other countries in 2017.

SPINRAZA Clinical Development Program

SPINRAZA has been studied in both pre-symptomatic and symptomatic patients with SMA including patients with infantile-onset and later-onset SMA. The SPINRAZA Phase 3 program is comprised of two registrational sham-controlled studies, ENDEAR and CHERISH:

ENDEAR was a thirteen-month, double blind, placebo controlled study investigating SPINRAZA in 122 patients with infantile-onset SMA (consistent with Type 1), including patients with the onset of signs and symptoms of SMA at up to six months of age.

- In ENDEAR, a pivotal controlled clinical study, infantile-onset SMA patients treated with SPINRAZA achieved and sustained clinically meaningful improvement in motor function compared to untreated study participants.
- In addition, a greater percentage of patients on SPINRAZA survived compared to untreated patients.

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- In open-label studies, some patients achieved milestones such as ability to sit unassisted, stand or walk when they would otherwise be unexpected to do so and maintained milestones at ages when they would be expected to be lost.
- The overall findings of these studies support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment.
- The most common adverse reactions reported for SPINRAZA were upper respiratory infection, lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients. Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

CHERISH was a fifteen-month, randomized, double-blind, sham-controlled study investigating SPINRAZA in 126 non-ambulatory patients with later-onset SMA (consistent with Type 2), including patients with the onset of signs and symptoms at greater than 6 months of age, and an age of 2 to 12 years at screening.

- An interim analysis of CHERISH found that children receiving SPINRAZA experienced a highly statistically significant and clinically meaningful improvement in motor function compared to those who did not receive treatment (p=0.0000002) as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). Data from the other efficacy endpoints analyzed were consistently in favor of children who received treatment.
- SPINRAZA demonstrated a favorable safety profile in the study. The majority of adverse events were considered to be either related to SMA disease, common events in the general population, or events related to the lumbar puncture procedure. No patients discontinued the study.
- While the findings of CHERISH were not included in the regulatory submission, the FDA was made aware of the results.

Following the positive interim analyses of both ENDEAR and CHERISH, the studies will be stopped and participants will be able to transition into the **SHINE open-label extension study** to receive SPINRAZA.

Two additional Phase 2 studies, EMBRACE and NURTURE, were designed to collect additional data on SPINRAZA:

EMBRACE is an ongoing open-label study in a small subset of patients with infantile or later-onset SMA who do not meet the age and other criteria of ENDEAR or CHERISH.

NURTURE is an ongoing open-label study in babies up to six weeks of age at time of first dose, who were genetically diagnosed with SMA and had not experienced any symptoms by the time of first dose. The goal of the study is to determine if treatment before symptoms begin would prevent or delay the onset of SMA symptoms.

- An interim analysis of NURTURE (June 2016) showed infants treated for up to one year with SPINRAZA achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with infantile-onset SMA.
- Three infants experienced adverse events considered possibly related to SPINRAZA, all of which resolved. In addition, no infants have discontinued or withdrawn from the study and no new safety concerns have been identified. NURTURE is currently active and enrolling.

Biogen intends to continue the EMBRACE, NURTURE and SHINE open-label extension studies to follow patients in a clinical study setting and continue to collect important data to better understand the long-term safety and efficacy of SPINRAZA. All studies are being conducted on a global scale.

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References:

1. Darras B, Markowitz J, Monani U, De Vivo D. Chapter 8 - Spinal Muscular Atrophies. In: Vivo BTD, ed. Neuromuscular Disorders of Infancy, Childhood, and Adolescence (Second Edition). San Diego: Academic Press; 2015:117-145.
2. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155-165.
3. Mailman MD, Heinz JW, Papp AC, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. Genet Med. 2002;4(1):20-26.
4. Monani UR, Lorson CL, Parsons DW, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. Hum Mol Genet. 1999;8(7):1177-1183.
5. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain. 2014;137(Pt 11):2879-2896.
6. Hua Y, Sahashi K, Hung G, Rigo F, Passini MA, Bennett CF, Krainer AR. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. Genes Dev. 2010 Aug 1; 24(15):16344-4