SPINRAZA™ FACT SHEET

- For Canadian Media-

SPINRAZA
nusinersen injection

About SMA[1-5]

Spinal muscular atrophy (SMA) is rare condition, occurring in approximately 1 out of every 6,000 live births. About 1 out of 40 people are genetic carriers of the disease, meaning that they carry the mutated gene but do not have SMA.

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. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing.

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 SMA, the form that requires the most intensive and supportive care, 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.

Individuals with later-onset 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 for use in Canada for the treatment of 5q SMA[6], which refers to the most common form of the disease and represents approximately 95% of all SMA cases[1], caused by an autosomal recessive condition that results from mutations or homozygous deletions in the *SMN1* gene, located on chromosome 5q13.[10]

SPINRAZA was approved in the United States for the treatment of SMA in pediatric and adult patients and in the EU for the treatment of 5q SMA.

SPINRAZA is under regulatory review in Japan, Australia, Switzerland, and Brazil and Biogen plans to initiate additional filings in other countries in 2017.

SPINRAZA is an antisense oligonucleotide (ASO) that is designed to treat SMA caused by mutations or deletions in the *SMN1* gene located in 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.[7] 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 full-length SMN protein in individuals with SMA.

SPINRAZA is administered via intrathecal injection, which delivers therapies directly to the cerebrospinal fluid (CSF) around the spinal cord,[8] where motor neurons degenerate in patients with SMA due to insufficient levels of SMN protein.[9]

There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. headache, backpain, vomiting). Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Renal toxicity has been observed after administration of some antisense oligonucleotides.

SPINRAZA Clinical Trial Program

SPINRAZA has been studied in both pre-symptomatic and symptomatic individuals with SMA including those with infantile-onset and later-onset SMA. The SPINRAZA Phase 3 program is comprised of two sham-controlled studies, ENDEAR and CHERISH. The Health Canada approval of SPINRAZA was based on positive results from multiple clinical studies in more than 170 patients. The data package included the interim analysis of ENDEAR, a Phase 3 controlled study evaluating SPINRAZA in infantile-onset, as well as open-label data in pre-symptomatic and symptomatic patients with, or likely to develop, infantile and later-onset SMA[6].

ENDEAR was a thirteen-month, double blind, placebo controlled study investigating SPINRAZA in 121 infants with infantile-onset SMA (most likely to develop Type 1), including infants with the onset of signs and symptoms of SMA at up to six months of age. In this study, infants 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.

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.

CHERISH was a fifteen-month, randomized, double-blind, sham-controlled study investigating SPINRAZA in 126 non-ambulatory children with later-onset SMA (most likely to develop Type 2 or Type 3), including individuals with the onset of signs and symptoms at greater than 6 months and an age of 2 to 12 years at screening.

Following the positive interim analyses of ENDEAR and CHERISH, the studies were stopped and participants were transitioned 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 individuals 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 infants up to six weeks of age at the time of first dose, who were genetically diagnosed with SMA but have not yet experienced any symptoms. 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 showed treated infants generally achieved motor milestones in timelines consistent with normal development than what is observed in the natural history of individuals 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.

Biogen intends to continue the EMBRACE, NURTURE and the SHINE studies to follow individuals in a clinical study setting and continue to collect important data to better understand the long-term safety and efficacy of SPINRAZA.

---

[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] Biogen Canada Inc. Product Monograph June 2017.
[7] 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):16344-44.
[8] Evers MM, Toonen LJ, van Roon-Mom WM. Antisense oligonucleotides in therapy for neurodegenerative disorders. Adv Drug Deliv Rev. 2015;87:90-103.
[9] Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008;371(9630):2120-2133.
[10] Farrar. Genetics of spinal muscular atrophy: progress and challenges. Neurotherapeutics. 2015 Apr;12(2):290-302