SPINRAZA®
(nusinersen) injection 12 mg/5 mL

DESIGNED TO TREAT SPINAL MUSCULAR ATROPHY (SMA)

As an antisense oligonucleotide (ASO), SPINRAZA directly targets an underlying cause of motor neuron loss[1,2]

SPINRAZA was shown to increase exon 7 inclusion in *SMN2* mRNA transcripts and production of full-length SMN protein[1]

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

mRNA, messenger ribonucleic acid; SMN, survival motor neuron; *SMN2*, survival motor neuron 2 gene.

INDICATION

SPINRAZA® (nusinersen) 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.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

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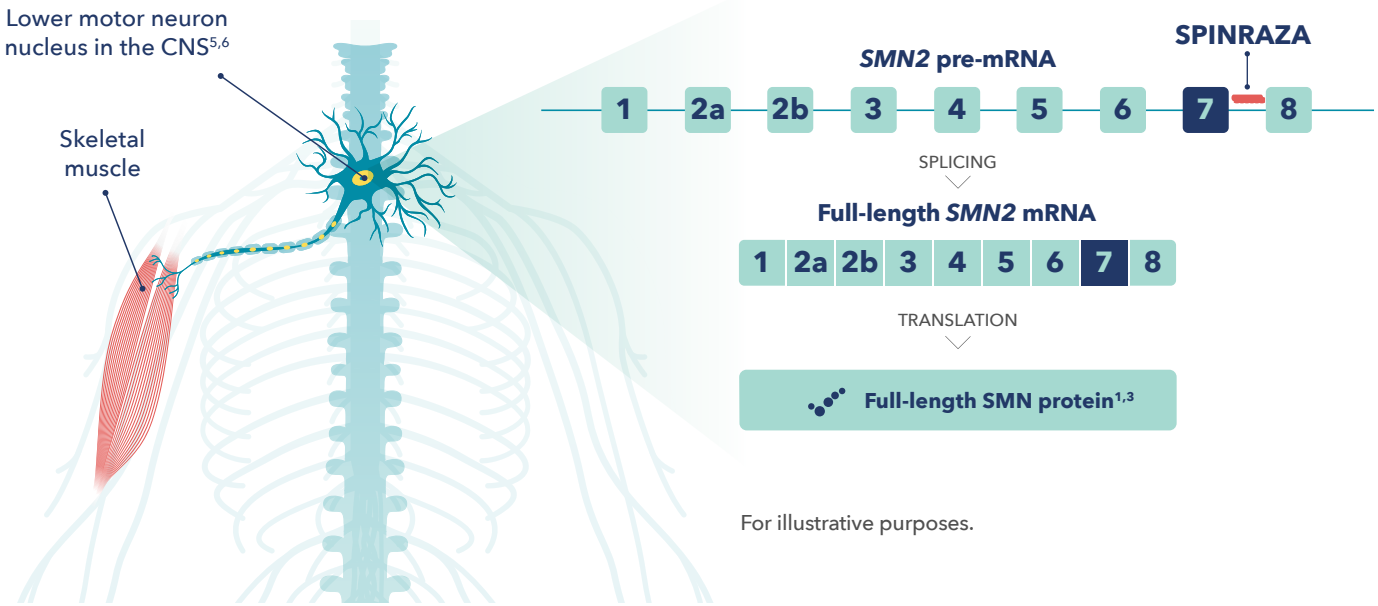
The targeted nature of an ASO treatment

SPINRAZA is designed to target a specific sequence in the *survival motor neuron 2* (*SMN2*) pre-mRNA to modify splicing and increase functional SMN protein production[1,3]

SPINRAZA is delivered intrathecally in the cerebrospinal fluid (CSF), bypassing the blood-brain barrier and directly accessing the central nervous system (CNS).[1,3] It targets an underlying cause of motor neuron loss in SMA by binding to specific *SMN2* pre-mRNA within the nuclei of cells (eg, motor neurons) to increase SMN protein.[1-4] Motor neuron cell bodies are only located in the brain and spinal cord.[5]

- As an ASO, SPINRAZA binds to a specific site on *SMN2* pre-mRNA that is typically occupied by an intronic splicing silencer (ISS-N1)[1,3,4]
- Displacement of ISS-N1 by SPINRAZA facilitates accurate splicing and results in the synthesis of *SMN2* mRNA transcripts containing exon 7[1,3]
- Increasing exon 7 inclusion in *SMN2* mRNA transcripts results in increased production of full-length functional SMN protein[1]



For illustrative purposes.

Why target *SMN2*?

Individuals with SMA have a mutated *SMN1* gene and rely on the *SMN2* gene to produce functional SMN protein. But the *SMN2* gene by itself can only produce about 10% of the full-length functional protein that is normally produced by *SMN1*.[2,6]

ASO, antisense oligonucleotide; CNS, central nervous system; CSF, cerebrospinal fluid; mRNA, messenger ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene.

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 the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

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About ASOs

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Years of research have made ASO technology available for therapeutic use. In the US, as of November 2023, there are at least 13 FDA-approved ASO therapies for a variety of disorders. Many of these treatments are pivotal for the care of neurodegenerative diseases, including SMA.[1,4]

- Are sequences of genetic material[4]
- Designed to target specific sequences in mRNA or pre-mRNA[4]
- Designed to interfere with RNA processing to enhance the production of a protein that is lacking or not functioning[4]

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

SPINRAZA is the first and only intrathecal ASO treatment for SMA[1,7-9]

SPINRAZA represents the culmination of decades of development, discovery, and refinement in ASO technology for the treatment of SMA[10]

ASO, antisense oligonucleotide; FDA, Food and Drug Administration; mRNA, messenger ribonucleic acid; SMA, spinal muscular atrophy.

SELECTED IMPORTANT SAFETY INFORMATION

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.

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.

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ASOs such as SPINRAZA are delivered locally by injection[1,3,4]

Intrathecal delivery concentrates nusinersen in the cerebrospinal fluid (CSF) and bypasses the blood-brain barrier[1,3]

Targets CNS tissues[1]

- Distribution from the CSF to where lower motor neurons live[1,5]
- Infuses motor neurons with nusinersen to increase full-length functional SMN protein that motor neurons need[1,2]

Persists in target tissues[1]

- Maintains high concentration and long half-life in the CSF between prescribed doses
  - Half-life of up to 5.9 months (estimated to be 135-177 days)

Consistent drug exposure[11]

- Drug exposure consistent regardless of age or weight
  - Biogen pharmacokinetics Data on File from 2-15 years of age

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

ASO, antisense oligonucleotide; CNS, central nervous system; CSF, cerebrospinal fluid; SMN, survival motor neuron.

SELECTED IMPORTANT SAFETY INFORMATION

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

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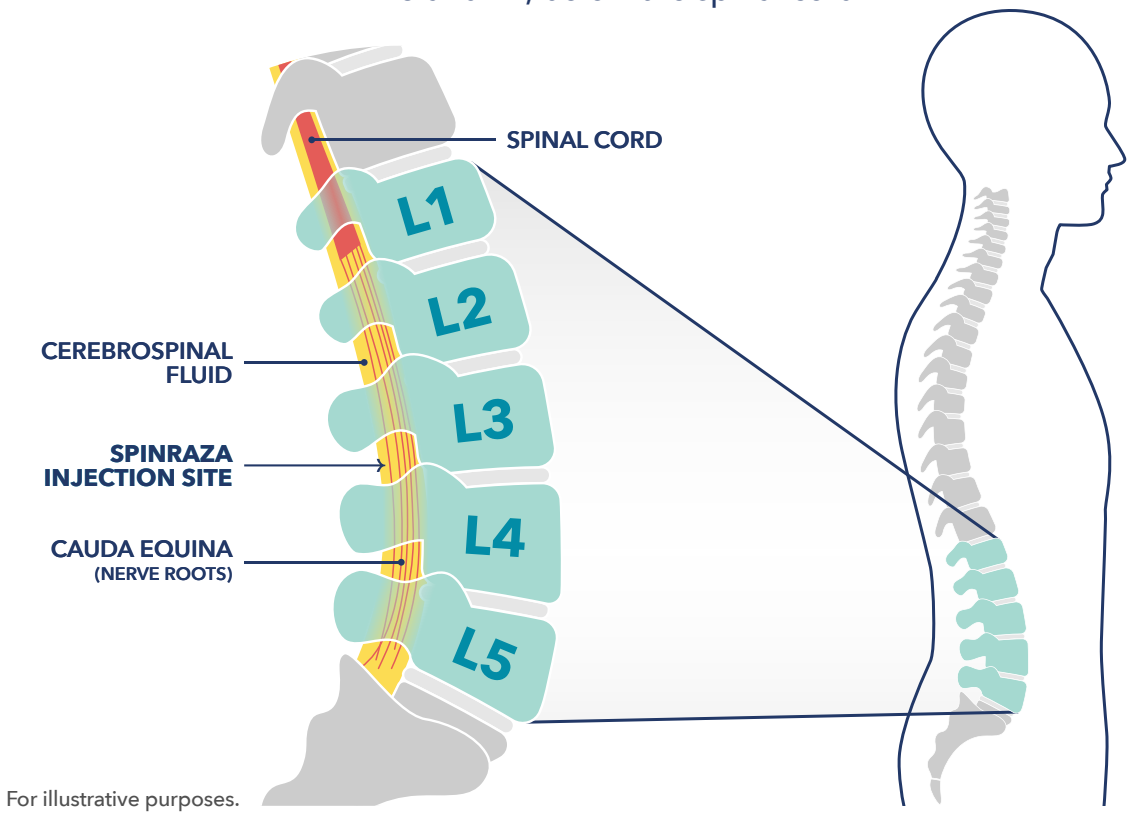
Intrathecal injection may be possible for many patients, including infants, children, teens, and adults[12-17]

SPINRAZA is injected in the lumbar area of the spine—typically between L3 and L4, below the spinal cord[16,18]



For illustrative purposes.

Consider sedation and ultrasound or other imaging techniques at the discretion of the healthcare provider[1]

Post-lumbar puncture syndrome has been reported with SPINRAZA.[1]

Monitoring Information: Due to the risk of coagulation abnormalities, thrombocytopenia, and renal toxicity, the following laboratory tests are recommended at baseline and prior to each dose of SPINRAZA and as clinically needed: platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine protein testing.[1]

SELECTED IMPORTANT SAFETY INFORMATION

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In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

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An HCP's Perspective

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"The motor neurons that are involved in spinal muscular atrophy sit in the anterior portion of the spinal cord. It's important to be able to deliver a treatment exactly where those motor neuron cell bodies are sitting.

By administering SPINRAZA into the intrathecal space, it's getting where it needs to be."

– Crystal Proud, MD

Pediatric Neuromuscular Neurologist
Children's Specialty Group and
Children's Hospital of The King's Daughters

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

HCP, healthcare professional.

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 the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

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One dosing regimen for all patients, regardless of age or weight[1]

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SPINRAZA is given only 3 times a year, every 4 months, after an initial loading-dose period

The recommended dosage of SPINRAZA is 12 mg (5 mL) per administration

SPINRAZA is an intrathecal injection administered by, or under the direction of, healthcare professionals (HCPs) experienced in performing lumbar punctures.[1] Because SPINRAZA is administered intrathecally[1]:

- No daily administration required
- It is an option for patients with any bulbar status
- Medication is shipped directly to HCP. Patient is not responsible for storage
- Biogen Support Services can help patients coordinate logistics of treatment

For people with SMA of all ages and severities, from infants to adults, SPINRAZA is the first-ever FDA-approved treatment for SMA, delivered intrathecally[1,7]

What if a patient misses a dose or doses of SPINRAZA?

Reinitiation of SPINRAZA is based on the time since last dose.[1] See the guidance for restarting treatment at **spinrazahcp.com**

FDA, Food and Drug Administration; HCP, healthcare professional; SMA, spinal muscular atrophy.

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Talking with your patients about SPINRAZA

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It's natural for patients to feel concerned and have questions about SPINRAZA and intrathecal delivery. Here are common concerns and key points that can help you and your patient make the best decision for them

Do other drugs use intrathecal delivery, or just SPINRAZA?

- SPINRAZA is not the only medication delivered this way. This method is used to administer other types of drugs, such as anesthetic agents and pain medications[1,19]

How long will the injection take?

- SPINRAZA is delivered over 1-3 minutes[1]
- However, there is also preparation and recovery time
- Each patient is unique, so the amount of time before and after SPINRAZA is given can vary

What will dosing day at your facility look like?

- It's possible that the patient may feel pain during and after the injection[1,15-17,20]
- Sedation can be used, depending on the patient's clinical condition[1]
- Ultrasound or other imaging techniques may be considered to guide injection[1]
- Each patient is unique; together with their doctor, they can determine a plan for the procedure[1]

Is SPINRAZA delivered directly into the spinal cord?

- No, SPINRAZA is delivered into the CSF. From the CSF it is then distributed to the target CNS tissues[1]
- The spinal cord ends at L1-L2 in adults and above L3 in children[18]
- Each patient has unique physiology, which comes with specific considerations that should be reviewed with your patients

CSF, cerebrospinal fluid; CNS, central nervous system.

SELECTED IMPORTANT SAFETY INFORMATION

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Other common questions include:

- What happens during intrathecal injection?
- Who will be performing the intrathecal procedure and how experienced are they? Will I meet them prior to my dosing day?
- How will I be transferred to and placed on the procedure table?
- Are there sedation medication options?

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The depth and breadth of data for SPINRAZA in SMA

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Backed by a growing body of real-world evidence and the longest clinical trial program to date[17,20-24]

Pivotal and supportive studies have evaluated the efficacy and safety of SPINRAZA in presymptomatic, early-onset, and later-onset SMA.[1]

- These studies have assessed several endpoints, including survival, overall motor function, and walking ability

The most published real-world studies to date in SMA.[25] These studies of SPINRAZA include older children, teens, and adults up to 72 years old. Two of the longest studies to date evaluated up to 30 and 38 months of SPINRAZA treatment.[17,20-23]

- These studies are relevant to the safety and efficacy of long-term treatment with SPINRAZA, and include multiple motor function measures, such as HFMSE, RULM, CHOP INTEND, and 6MWT

Learn more about clinical and real-world trial data at **spinrazahcp.com**

6MWT, 6-minute walk test; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale–Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

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SMA360°™ is a circle of support for your patients*

The Biogen SMA360° support program provides services, including logistics, education, insurance benefits investigation, and financial assistance options for patients and their families that address nonmedical barriers to access to SPINRAZA

SMA360™ Support services from Biogen

From infants to adults across the disease spectrum, **more than 14,000** people living with SMA have been treated with SPINRAZA worldwide.[26†] With decades of supporting patients on Biogen therapies, Biogen is committed to helping you and your patients.

*SMA360° patient services from Biogen are available only to those who have been prescribed SPINRAZA. SMA360° is intended for US residents only.
†Based on commercial patients and early access patients receiving treatment with SPINRAZA as of June 2024.

SMA, spinal muscular atrophy.

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INDICATION

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Please see full Prescribing Information.

As a courtesy, our full Prescribing Information is also available *en Español*. For prescribing decisions, please refer to official approved labeling.

References: 1. SPINRAZA. Prescribing Information. Biogen; 2024. **2.** Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet*. 2008;371(9630):2120-2133. **3.** Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. *Neurology*. 2016;86:1-8. **4.** Collotta D, Bertocchi I, Chiapello E, Collino M. Antisense oligonucleotides: a novel frontier in pharmacological strategy. *Front Pharmacol*. 2023;14:1304342. doi:10.3389/fphar.2023.1304342 **5.** Zayia LC, Tadi P. Neuroanatomy, motor neuron. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available at: https://ncbi.nlm.nih.gov/books/NBK554616/ **6.** Darras BT, Royden Jones H Jr, Ryan MM, De Vivo DC, eds. *Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach.* 2nd ed. London, UK: Elsevier; 2015. **7.** FDA approves first drug for spinal muscular atrophy. News release. US Food and Drug Administration. December 23, 2016. Accessed September 5, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-spinal-muscular-atrophy **8.** Evrysdi. Prescribing Information. Genentech; 2024. **9.** Zolgensma. Prescribing Information. Novartis; 2024. **10.** Qiu J, Wu L, Qu R, et al. History of development of the life-saving drug "Nusinersen" in spinal muscular atrophy. *Front Cell Neurosci*. 2022;16:942976. doi:10.3389/fncel.2022.942976 **11.** Biogen, Data on File as of 09/21. **12.** Finkel RS, Mercuri E, Darras BT, et al; ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Eng J Med*. 2017;377(18):1723-1732. **13.** De Vivo DC, Bertini E, Swoboda KJ, et al; NURTURE Study Group. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29(11):842-856. **14.** Mercuri E, Darras BT, Chiriboga CA, et al; CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378(7):625-635. **15.** Stolte B, Totzeck A, Kizina K, et al. Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy. *Ther Adv Neurol Disord*. 2018;11:1-9. doi:10.1177/1756286418803246 **16.** Haché M, Swoboda KJ, Sethna N, et al. Intrathecal injections in children with spinal muscular atrophy: nusinersen clinical trial experience. *J Child Neurol*. 2016;31(7):899-906. **17.** Łusakowska A, Wójcik A, Frączek A, et al. Long-term nusinersen treatment across a wide spectrum of spinal muscular atrophy severity: a real-world experience. *Orphanet Rare Dis*. 2023;18(1):230. doi:10.1186/513023-023-02769:4 **18.** Ganapathy MK, Reddy V, Tadi P. Neuroanatomy, Spinal Cord Morphology. [Updated 2022 Oct 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK545206/ **19.** Hussien RM, Rabie AH. Sequential intrathecal injection of fentanyl and hyperbaric bupivacaine at different rates: does it make a difference? A randomized controlled trial. *Korean J Anesthesiol*. 2019;72(2):150-155. **20.** Günther R, Wurster CD, Brakemeier S, et al. Long-term efficacy and safety of nusinersen in adults with 5q spinal muscular atrophy: a prospective European multinational observational study. *Lancet Reg Health Eur*. 2024;39:100862. doi:10.1016/j.lanepe.2024.100862 **21.** Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. *Lancet Neurol*. 2020;19(4):317-325. **22.** Maggi L, Bello L, Bonanno S, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1166-1174. **23.** Coratti G, Cutrona C, Pera MC, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. *Orphanet J Rare Dis.* 2021;16(1):430. **24.** Biogen, Data on File as of 09/21. **25.** Biogen, Data on File as of 01/24. **26.** Biogen, Data on File as of 07/24.

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