SPINRAZA® (nusinersen) injection 12 mg/5 mL

CLINICAL OVERVIEW

INDICATION

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

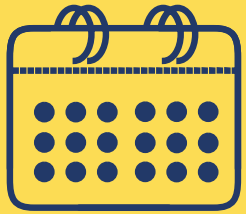
SELECTED IMPORTANT SAFETY INFORMATION

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.

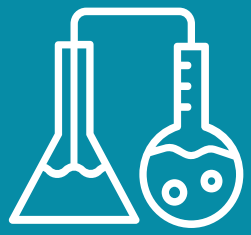
Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

SPINRAZA IS SUPPORTED BY THE LONGEST CLINICAL TRIAL PROGRAM IN SMA TO DATE[1]



11+
years[1]

350+
clinical trial patients[2]



10
clinical trials[3]

SPINRAZA has been studied in multiple controlled and uncontrolled open-label trials that included presymptomatic and symptomatic patients who had or were likely to develop SMA Type 1, 2, or 3.[1]

SMA=spinal muscular atrophy.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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%).

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

References: 1. Data on File. Biogen, Cambridge, MA. **2.** Data on file. Biogen, Cambridge, MA. **3.** Data on file. Biogen, Cambridge, MA.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA CONTROLLED STUDIES

ENDEAR

STUDY

Patients with infantile-onset SMA, most likely SMA Type 1 (n=121)[1,2]

- Phase 3, multicenter, randomized, double-blind, sham-procedure–controlled study
- Infants had symptom onset at age <6 months*

ENDPOINTS

- **Primary endpoints:** proportion of patients meeting the criteria for a trial endpoint named "motor milestone response" using HINE-2, event-free survival[1-3]
- **Secondary endpoints:** overall survival, CHOP INTEND, CMAP, percentage of infants not requiring mechanical ventilation, event-free survival in patients with disease duration of ≤12 weeks and >12 weeks[1-3]
- **Additional assessment:** safety[1,2,3]

RESULTS

- **47% reduction in risk of death or permanent ventilation with SPINRAZA** compared with untreated patients (HR=0.53; *P*=0.005)[2]
  - **63% reduction in risk of death alone** (HR=0.37; *P*=0.004)
- **More patients treated with SPINRAZA achieved a HINE-2 response** compared with untreated patients[1,2,4]
  - Interim analysis: 40% SPINRAZA (n=52) vs 0% untreated (n=30) (*P*<0.0001)†
  - Final analysis: 51% SPINRAZA (n=73) vs 0% untreated (n=37) (*P*<0.0001)
- More patients treated with SPINRAZA had a **≥4-point improvement from baseline in CHOP INTEND score** compared with untreated patients: 71% (52/73) vs 3% (1/37), respectively (*P*<0.001)[2]
  - Fewer patients treated with SPINRAZA had a **≥4-point worsening:** 3% (2/73) vs 46% (17/37), respectively[4]
- **The most common ARs** that occurred in at least 20% of patients treated with SPINRAZA and occurred at least 5% more frequently than in control patients were lower respiratory infection and constipation[1]

AR=adverse reaction; CHOP INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP=compound muscle action potential; HINE-2=Hammersmith Infant Neurological Examination Section 2; HR=hazard ratio.

*Inclusion criteria.

†The interim analysis in the Finkel et al publication indicates a motor milestone responder rate of 41%. This reflects 78 patients, excluding 4 patients who died and were not enrolled early enough to reach the day 183 cutoff.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

References: 1. SPINRAZA. [Prescribing Information]. Cambridge, MA: Biogen. **2.** Finkel RS, Mercuri E, Darras BT, et al; for the ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1723-1732. **3.** Data on File. Biogen, Cambridge, MA. **4.** Finkel RS, Mercuri E, Darras BT, et al; for the ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy [supplemental appendix]. *N Engl J Med*. 2017;377(18):1723-1732.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA CONTROLLED STUDIES (cont'd)

CHERISH

STUDY

Patients with later-onset SMA Type 2 or Type 3 (n=126)[1]

- Phase 3, multicenter, randomized, double-blind, sham-procedure–controlled study
- Patients (aged 2 years to 12 years) had symptom onset at age >6 months*

ENDPOINTS

- **Primary endpoint:** change from baseline in HFMSE score at month 15[1,2]
- **Secondary endpoints:** HFMSE (≥3-point change), WHO motor milestones, RULM, standing alone, walking with assistance[1,2]
- **Additional assessment:** safety[1,2]

RESULTS

- Patients treated with SPINRAZA demonstrated a **clinically meaningful change (≥3-point increase) in HFMSE total score** from baseline, improving in ≥2 motor skills compared with untreated patients[1]
  - Change from baseline at month 15 (least squares mean†): SPINRAZA 3.9 +/- 0.49 (n=84); untreated patients -1.0 +/- 0.76 (n=42) (*P*=0.0000001)
- Patients treated with SPINRAZA demonstrated a **clinically meaningful improvement in upper limb function** (change in RULM total score from baseline) compared with untreated patients[1]
  - Change from baseline at month 15 (least squares mean): SPINRAZA 4.2 +/- 0.40 (n=84); untreated patients 0.5 +/- 0.56 (n=42)
- **The most common ARs** that occurred in at least 20% of patients treated with SPINRAZA and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain[3]

*Inclusion criteria.

†Least squares mean: a mathematical analysis that accounts for the estimation of missing data values of children who had not completed the study at the time of the efficacy analysis.

HFMSE=Hammersmith Functional Motor Scale–Expanded; RULM=Revised Upper Limb Module; WHO=World Health Organization.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

References: 1. Mercuri E, Darras BT, Chiriboga CA, et al; for the CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378(7):625-635. **2.** Mercuri E, Darras BT, Chiriboga CA, et al; for the ENDEAR Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy [supplemental appendix]. *N Engl J Med*. 2018;378(7):625-635. **3.** SPINRAZA [Prescribing Information]. Cambridge, MA: Biogen.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA OPEN-LABEL STUDIES

NURTURE

STUDY

Presymptomatic, genetically diagnosed infants (N=25)[1]

- Phase 2, ongoing, open-label, single-arm, multinational, long-term, supportive study

ENDPOINTS

- **Primary endpoint:** median time to death or respiratory ventilation[1]
- **Other endpoints:** WHO motor milestones, HINE-2, CHOP INTEND[1]

RESULTS

- The NURTURE clinical trial is ongoing
- At the initial interim analysis performed after all infants had received SPINRAZA for at least 14 months (median, 25 months; range, 14 to 34 months), 100% (25/25) of infants were alive without the need for permanent ventilation*, 100% (25/25) were sitting without support, 88% (22/25) were walking with assistance, and 77% (17/22) were walking independently[2]
- As of 15 February 2021, after nearly 5 years of being treated with SPINRAZA, **all children (25/25) were still alive and did not require permanent ventilation**; 16% (4/25) required respiratory intervention[3]
- **All 25 infants achieved the WHO motor milestone of sitting without support**, 96% (24/25) were able to walk with assistance, and 92% (23/25) were walking alone. Most children achieved these motor milestones (84% [21/25] sitting without support, 60% [15/25] walking with assistance, and 64% [16/25] independent walking) within the 99th-percentile age window established by the WHO for healthy children[3]
- **88% (22/25) of those treated** achieved a maximum score on the CHOP INTEND[3]
- Mean (SE) change improvement from baseline (first evaluable assessment after Day 700) in **HFMSE scores continued to show improvement over time** (3 SMN2 copies: slope [95% CI]=6.99 [4.98,9.00]; n=10; 2 SMN2 copies: slope [95% CI]=6.30 [4.70, 7.90]; n=14)[3]
- **All infants experienced an adverse event** (mild [24%], moderate [52%], severe [24%]), and no new safety concerns were identified[3]

*Permanent ventilation is defined as ventilation for ≥16 hours/day for >21 days in absence of an acute reversible event, or tracheostomy.

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

References: 1. De Vivo DC, Bertini E, Swoboda KJ, et al; on behalf of the 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. **2.** SPINRAZA [Prescribing Information]. Cambridge, MA: Biogen. **3.** Crawford TO, Swoboda KJ, De Vivo DC, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. *Muscle Nerve*. 2023;68(2):157-170. doi:10.1002/mus.27853.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA OPEN-LABEL STUDIES (cont'd)

CS2/CS12

STUDY

Patients with later-onset SMA Type 2 or Type 3 (N=28)

- Phase 1b/2a, multiple-dose study (CS2=253 days) with an open-label extension (CS12=715 days)
- Patients were aged 2 years to ≤15 years at time of first dose*

Study Limitations:

- Differences in dosing compared with the approved SPINRAZA schedule and no control group

ENDPOINTS

- **Primary endpoints:** efficacy and safety of SPINRAZA administered intrathecally
  - Efficacy was assessed using HFMSE, ULM, 6MWT, CMAP, and motor unit number estimation

RESULTS

- *Results at day 1150 in patients receiving SPINRAZA:*
  - **10.8-point increase in HFMSE score** from baseline of 21.3 (patients with SMA Type 2; n=11)
  - **1.8-point increase in HFMSE score** from baseline of 48.9 (patients with SMA Type 3; n=17)
  - **92.0-meter increase in 6MWT walking distance** from baseline of 253.3 meters (patients with SMA Type 3; n=13)
- Some nonambulant patients with later-onset SMA were able to walk independently:
  - At least **1 of 11 patients** with SMA Type 2 **gained the ability to walk for the first time**
  - At least **2 of 4 patients** with SMA Type 3 **regained the ability to walk that they had lost previously**

- **The most common ARs** that occurred in at least 20% of patients treated with SPINRAZA were post-lumbar puncture syndrome, headache, nasopharyngitis, upper respiratory tract infection, puncture site pain, back pain, scoliosis, pyrexia, joint contracture, rhinorrhea, and vomiting

6MWT=6-Minute Walk Test; ULM=Upper Limb Module.

*Inclusion criteria.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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%).

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: Darras BT, Chiriboga CA, Iannaccone ST, et al; ISIS-396443-CS2/ISIS-396443-CS12 Study Groups. Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies. *Neurology*. 2019;92(21):e2492-e2506.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA OPEN-LABEL STUDIES (cont'd)

SHINE

STUDY

Patients with infantile- and late-onset SMA (n=292)

- Phase 3, ongoing, open-label, multinational, nonrandomized, sham-procedure–controlled study

ENDPOINTS

- **Primary endpoints:** safety and tolerability as assessed by the incidence of adverse events
- **Secondary endpoints:** percentage of participants who attained motor milestones as assessed by WHO criteria
  - Motor tests include HINE-2, CHOP INTEND, HFMSE, RULM, 6MWT, CMAP

RESULTS

This SHINE clinical trial final results are pending.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: Biogen. A study for participants with spinal muscular atrophy (SMA) who previously participated in nusinersen (ISIS396443) investigational studies (SHINE). Cambridge, MA. https://clinicaltrials.gov/ct2/show/study/NCT02594124. 2021. Accessed July 28, 2023.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA REAL-WORLD INDEPENDENT OBSERVATION STUDY

INDEPENDENT OBSERVATIONAL STUDY (HAGENACKER T, ET AL)

STUDY

Adult patients with later-onset SMA Type 2 or Type 3 (n=139, enrolled)

- Prospective, multicenter, 14-month, observational study by an independent, third-party group
- Adult patients aged 16 to 65 years
- **Study limitations:** no control group; observational design. Study powered on primary endpoint only. Statistics for other endpoints are descriptive only

ENDPOINTS

- **Primary endpoint:** change from baseline in HFMSE score at 6, 10, and 14 months. Patients with missing baseline HFMSE scores were excluded from these analyses
- **Secondary endpoints:** change from baseline in RULM and 6MWT scores at 6, 10, and 14 months

RESULTS

- **The majority of ARs** were consistent with those in the SPINRAZA pivotal trials
- **Other reported ARs were**
  - Nausea
  - Diffuse pain
  - Constipation
  - Vertigo
  - Bladder disorder not otherwise specified
  - Infection
  - Meningitis, aseptic
  - Tinnitus, aggravated

- **Mean HFMSE scores with SPINRAZA were increased from baseline (1.73 at 6 months [n=124], 2.58 at 10 months [n=92], and 3.12 at 14 months [n=57]).** A clinically meaningful (≥3-point) increase in HFMSE score for motor function was seen in 28% of patients at 6 months, 35% of patients at 10 months, and 40% of patients at 14 months*
  - 14 of 124 patients (11%) showed worsening motor function under treatment as measured by HFMSE
  - 139 patients completed an assessment at 6 months,105 at 10 months, and 61 at 14 months

- **Mean walking distances on the 6MWT improved from baseline** to 22.1 meters at 6 months (n=47, 6.9% increase), 31.1 meters at 10 months (n=37, 8.8% increase), and 46.0 meters at 14 months (n=25, 12.4% increase)
- **Arm motor function improved from baseline** (RULM scores were 0.66 at 6 months [n=120], 0.59 at 10 months [n=90], and 1.09 at 14 months [n=58])
  - At 6 months, 28 (23%) of 120 patients showed ≥2-point improvement in RULM from baseline (ie, a clinically meaningful improvement), whereas 74 (61%) showed no meaningful change,18 (15%) showed a decline of ≥1 point, and 10 (8%) showed a decline of ≥2 points
  - Of the 28 patients who showed a clinically meaningful improvement in RULM score at 6 months, 75% (n=21) maintained these milestones at 14 months

*Exploratory endpoint.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a noninterventional, multicentre, observational cohort study. *Lancet Neurol*. 2020;19(4):317-325.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA REAL-WORLD INDEPENDENT OBSERVATION STUDY (cont'd)

INDEPENDENT OBSERVATIONAL STUDY (MAGGI L, ET AL)

STUDY

Adult patients with later-onset SMA Type 2 or Type 3 (N=116)

- Retrospective, 14-month, observational cohort study by an independent, third-party group
- Adult patients aged 18 to 72 years (SMA Type 2, n=13; SMA Type 3, n=103)
- **Study limitations:** retrospective design, small SMA Type 2 sample size, missing data for some variables, and some results supported only by "nominal statistical significance"

ENDPOINTS

- **Primary endpoints:** changes in overall motor function measured by HFMSE, changes in upper limb function measured by RULM, changes in walking ability measured by 6MWT

RESULTS

- **The majority of ARs** were consistent with those in the SPINRAZA clinical trials
  - The most frequently reported ARs were postprocedural headache (37.1%) and lumbar pain (8.6%)
  - 5 patients were hospitalized for headache
  - Other reported ARs were transient worsening of existing hand tremor (2 patients) and renal colic (1 patient)

- **Median HFMSE scores for patients with SMA Type 3 increased by 1 point at 6 months (range -5 to 8), 2 points at 10 months (range -3 to 9), and 3 points at 14 months (range -3 to 11),** with improvements in the sitter (median 3-point increase) and walker (median 2-point increase) subgroups
  - SMA Type 2 subgroup showed positive trends in HFMSE, but results were not statistically significant, potentially due to the small number of patients

- **Improvements in median 6MWT distance** were seen at 6 months (11 meters) and 10 months (25 meters); additionally, there was a nominally significant 20-meter increase at 14 months
- **Median RULM score for patients with SMA Type 3 increased** by 0.5 points from baseline to 14 months
  - Nominally significant changes were observed at 10 months (1 point) and 14 months (2 points) in nonambulant patients
  - In ambulant patients with SMA Type 3 who showed a "ceiling" effect, RULM score did not change
  - Median RULM score for patients with SMA Type 2 did not change, but a positive trend was observed by 14 months
- **Responders in at least 1 of 3 outcomes were defined as "overall responders":** +3 points on HFMSE, +2 points on RULM, or +30 meters on 6MWT. Within the entire cohort study, clinically meaningful improvements were seen in 53% of patients at 6 months, 63% of patients at 10 months, and 69% at 14 months

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: 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.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

OBSERVATIONAL STUDY (DUONG T ET AL)

STUDY

Adult patients with SMA Type 2 and 3 (n=42)

- Prospective, multicenter, longitudinal study by a third-party group
- Adult patients 17 years and older (SMA Type 2, n=18; SMA Type 3, n=24)
- **Study limitations:** Lack of a concurrent control group, lack of blinding, some selection bias, a small number of patients and broad range of functional abilities in subgroup analyses, and variable timing of and circumstances surrounding evaluations

ENDPOINTS

- **Primary endpoints:** mean annual rate of change (slope) for each motor and respiratory outcome

RESULTS

- **The majority of ARs** were rare, mild, transient, and generally consistent with those in the SPINRAZA pivotal trials
  - No new safety concerns were identified
  - The most common AR was post-lumbar puncture headache, of which all cases resolved spontaneously. Two cases of mild thrombocytopenia (platelet counts between 100,000-150,000) were reported and resolved spontaneously

- **Motor function scores improved from the progressive decline expected in untreated adults**
  - CHOP-ATEND mean slope (n=24): 3.59 points/year (95% CI: 0.67-6.51)

- **Trend improvements for other motor function scales were found, including the HFMSE, RULM, and 6MWT, but results were not statistically significant**
  - HFMSE (n=31): 0.86-point mean slope annual increase (95% CI: -0.52, 2.24)
  - RULM (n=39): 0.11-point mean slope annual increase (95% CI: -0.45, 0.67)
  - 6MWT (n=10): 3.29-meter mean slope annual increase (95% CI: -28.04, 34.62)

CI=confidence interval.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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%).

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: Duong T, Wolford C, McDermott MP, et al. Nusinersen treatment in adults with spinal muscular atrophy. *Neurol Clin Pract*. 2021;11(3):e317-e327.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA REAL-WORLD INDEPENDENT META-ANALYSIS

INDEPENDENT META-ANALYSIS (CORRATI G, ET AL)

META-ANALYSIS

An independent critical review and meta-analysis of 19 peer-reviewed publications that include real-world data of motor function in patients treated with nusinersen

- SMA Type 2 and 3 patients
- Adult and pediatric patients
- 10- to 14-month observational period
- Using PRISMA guidelines—a 4-phase approach to guide the identification, screening, eligibility, and inclusion of studies into a meta-analysis—13 articles (out of 14,627 identified hits) were included in the meta-analysis of **the HFMSE results** listed below
- **Study limitations:** Details on respiratory function or safety concerns were not systematically addressed in all the studies analyzed. Small number of participants overall or in the subgroups analyzed. Broad confidence intervals indicating high variability in the various cohorts. Due to variability across the studies, a direct comparison with studies reporting data from untreated patients could not be made. Other variables, such as age, SMN2 copies, or functional ability at baseline could not be analyzed due to missing data. This review only focused on functional motor abilities, as these were the measures most commonly used

ENDPOINTS

- **Primary endpoints:** motor function scores (and change in overall baseline) as assessed by the following motor function tests: HFMSE, RULM, 6MWT, MFM, MRC, HINE-2, CHOP INTEND, and CHOP ATEND

RESULTS

- All 13 publications in the HFMSE analysis reported improved mean HFMSE scores for treated groups. Overall, treated patient cohorts had an improvement in functional motor scores as shown by the 2.27-point increase in the HFMSE pooled mean score from baseline (95% CI, 1.41-3.13)
- **Adult and pediatric patients reported an increase in the HFMSE score:**

1.87 (95% CI, 1.05-2.68) Adult pooled mean change	2.98 (95% CI, 0.97-4.99) Pediatric pooled mean change

No statistical difference in pooled mean changes between the 2 populations.

- **SMA Type 2 and SMA Type 3 population reported a significant increase in the HFMSE score:**

2.54 (95% CI, 1.00-4.09) SMA Type 2 pooled mean change	2.26 (95% CI, 1.06-3.47) SMA Type 3 pooled mean change

No statistical difference in pooled mean changes between the 2 populations.

- **Ambulant and nonambulant populations reported a significant increase in the HFMSE score:**

1.99 (95% CI, 0.24-3.74) Ambulant pooled mean change	2.39 (95% CI, 0.99-3.79) Nonambulant pooled mean change

No statistical difference in pooled mean changes between the 2 populations.

MFM=motor function measurement; MRC=medical research council scale for muscle strength; SMN2=Survival of motor neuron 2.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

Reference: 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.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA IS BACKED BY ROBUST CLINICAL DATA AND EXTENSIVE REAL-WORLD EXPERIENCE[1-4]

SPINRAZA has more than 6 years of real-world experience in the treatment of SMA.[1]

Patients treated with SPINRAZA range in age from **3 days to 80 years.**[1,5,*,†]

More than 4600 adult patients have been treated with SPINRAZA worldwide.[6,†]

More than **13,000 patients** with SMA have been treated with SPINRAZA worldwide.[6,†]

*Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Clinical studies included patients from 3 days to 16 years of age at first dose.
†Based on commercial patients, early access patients, and clinical trial participants through May 2022.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

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.

Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.

References: 1. SPINRAZA [Prescribing Information]. Cambridge, MA: Biogen. **2.** Data on file. Biogen, Cambridge, MA. **3.** Elsheikh B, Severyn S, Zhao S, et al. Safety, tolerability, and effect of nusinersen in non-ambulatory adults with spinal muscular atrophy. *Front Neurol.* 2021;12:650532. **4.** Konersman CG, Ewing E, Yaszay B, Naheedy J, Murphy S, Skalsky A. Nusinersen treatment of older children and adults with spinal muscular atrophy. *Neuromuscul Disord.* 2021;31(3):183-193. **5.** Data on file. Biogen, Cambridge, MA. **6.** Data on file. Biogen, Cambridge, MA.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

IMPORTANT SAFETY INFORMATION

INDICATION

SPINRAZA® (nusinersen) 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.

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.

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%).

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.

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.

Please see accompanying full Prescribing Information.