Measures of mobility and physical ability evaluated in clinical trials

Common measures of motor function include:

// Hammersmith Infant Neurological Examination (HINE) Section 2[1-4]

// Children's Hospital of Philadelphia Infant Test of Neurological Disorders (CHOP-INTEND)[3,5-7]

// Hammersmith Functional Motor Scale–Expanded (HFMSE)[8-14]

// Revised Upper Limb Module (RULM)[7,11,12,15,16]

// 6-Minute Walk Test (6MWT)[12,17-21]

This document outlines the components of each assessment and is meant for educational purposes only. These assessments should be performed by a trained healthcare professional.

HINE-2

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

// Validated in patients up to 39 months of age

// A minimally clinically important difference (MCID) for HINE-2 has not been reported. However, a change of 1 point or more in untreated infants with Type 1 SMA is unlikely[4]

Motor function	Milestone progression score				
	0	1	2	3	4
Voluntary grasp	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick (in supine position)	No kicking	Kicks horizontal; legs do not lift	Upward (vertical)	Touches leg	Touches toes
Head control	Unable to maintain upright	Wobbles	All the time upright		
Rolling	No rolling	Rolling to side	Prone to supine	Supine to prone	
Sitting	Cannot sit	Sits with support at hip	Props	Stable sit	Pivots (rotates)
Crawling	Does not lift head	On elbow	On outstretched hand	Crawling flat on abdomen	On hands and knees
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking	No walking	Bouncing	Cruising (holding on)	Walking independently	

IMPROVEMENT

CHOP INTEND

A 16-item scale developed specifically for evaluating motor function in infants with SMA.

// 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
// Intended for both infants and older people with an infant's repertoire of motor skills
// Validated in patients 3 months to 21 years of age
// An MCID for the CHOP-INTEND has not been reported

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

HFMSE

HFMSE is a scale used to investigate a child's ability to perform various activities and is used in later-onset (Type 2 or Type 3) SMA.

// The scale has 33 items, with each item scored from 0 to 2
// For each function, increased levels of ability are depicted from left to right
// The maximum score is 66
// Validated in patients 2 to 45 years of age and developed specifically for SMA
// A change of 2 to 4 points is considered clinically meaningful
// An MCID for the HFMSE in Type 2 SMA has been estimated to be 3.[13] In later-onset patients (Type 2/3), the clinically meaningful change has been estimated to range from 4.3 to 10.6 points[12]

Item	Lowest item grade (0)	Highest item grade (2)
1 Plinth/chair sitting	Needs 2-hand support to maintain balance or unable to sit	Able to sit using no hand support for a count of 3 or more
2 Long sitting	Able to long sit using 2 hands for a count of 3 or unable to sit with straight legs	Able to sit on floor/plinth with legs straight without hand support for a count of 3
3 1 hand to head in sitting	Unable to bring hand to head even using head and trunk movement	Able to bring 1 hand to head; head and trunk remain stable
4 2 hands to head in sitting	Unable to place both hands on head	Able to place both hands on head with arms free from side; head and trunk remain stable
5 Supine to side-lying	Unable to half roll either way	Able to half roll from supine both ways
6 Rolls prone to supine over right	Unable to turn to supine	Turns to supine with free arms to the right
7 Rolls prone to supine over left	Unable to turn to supine	Turns to supine with free arms to the left
8 Rolls supine to prone over right	Unable to turn to prone	Turns to prone with free arms to the right
9 Rolls supine to prone over left	Unable to turn to prone	Turns to prone with free arms to the left
10 Sitting to lying	Unable or falls over	Able to lie down in a controlled fashion through side-lying or using clothes
11 Props on forearms	Unable	Able to achieve prop on forearms with head up for count of 3
12 Lifts head from prone	Unable	Able to lift head up prone with arms by side for a count of 3
13 Props on extended arms	Unable	Able to prop on extended arms; head up for a count of 3

Item	Lowest item grade (0)	Highest item grade (2)
14 Lying to sitting	Unable	Able by using side-lying
15 4-point kneeling	Unable	Achieves 4-point kneeling; head up for a count of 3
16 Crawling	Unable	Able to crawl forward; moves all 4 points twice or more
17 Lifts head from supine	Unable	When supine, head must be lifted in midline; chin moves toward chest. Held for a count of 3
18 Stands supported	Can stand with hand support but needs knee/hip support for a count of 3; or unable	Can stand with 1-hand support for a count of 3
19 Stands unsupported	Stands only momentarily (less than a count of 3); or unable	Can stand independently for more than a count of 3
20 Stepping	Unable	Able to take more than 4 steps unaided
21 Right hip flexion when supine	Unable	Full hip flexion achieved
22 Left hip flexion when supine	Unable	Full hip flexion achieved
23 High kneeling to right half-kneel	Unable	Arms used for transition; maintains arms free for half-kneel
24 High kneeling to left half-kneel	Unable	Arms used for transition; maintains arms free for half-kneel
25 High kneeling to standing, leading with left leg (through right half-kneel)	Unable	Able with arms free
26 High kneeling to standing, leading with right leg (through left half-kneel)	Unable	Able with arms free
27 Stands to sitting on the floor	Unable	Able to sit down with arms free and no collapse
28 Squats	Unable to initiate	Squats with arms free (at least 90° of hip and knee flexion)
29 Jumps 12 inches forward	Unable to initiate jump with both feet simultaneously	Jumps at least 12 inches with both feet simultaneously
30 Ascends 4 stairs with railing	Unable to ascend 2 stairs using 1 rail	Ascends 4 stairs with aid of railing, alternating feet
31 Descends 4 stairs with railing	Unable to descend 2 stairs with 1 rail	Descends 4 stairs with aid of railing, alternating feet
32 Ascends 4 stairs without arm support	Unable to ascend 2 stairs arms-free	Ascends 4 stairs, arms-free, alternating feet
33 Descends 4 stairs without arm support	Unable to descend 2 stairs arms-free	Descends 4 stairs, arms-free, alternating feet

RULM

RULM is a scale used to investigate the upper limb function of ambulatory and nonambulatory patients with SMA.

- // The scale has 19 scorable items
- // Each item is scored from 0 to 2
  - 0=Unable
  - 1=Able, with modification
  - 2=Able, no difficulty
- // The maximum score is 37; one item is scored on a can/cannot score
- // Patients are scored on both upper limbs
- // RULM is applicable to both children and adults with SMA
- // Validated in patients 2 to 52 years of age
- // An MCID for the RULM in patients with later-onset SMA ranges from 2 to 6.4[12,15]

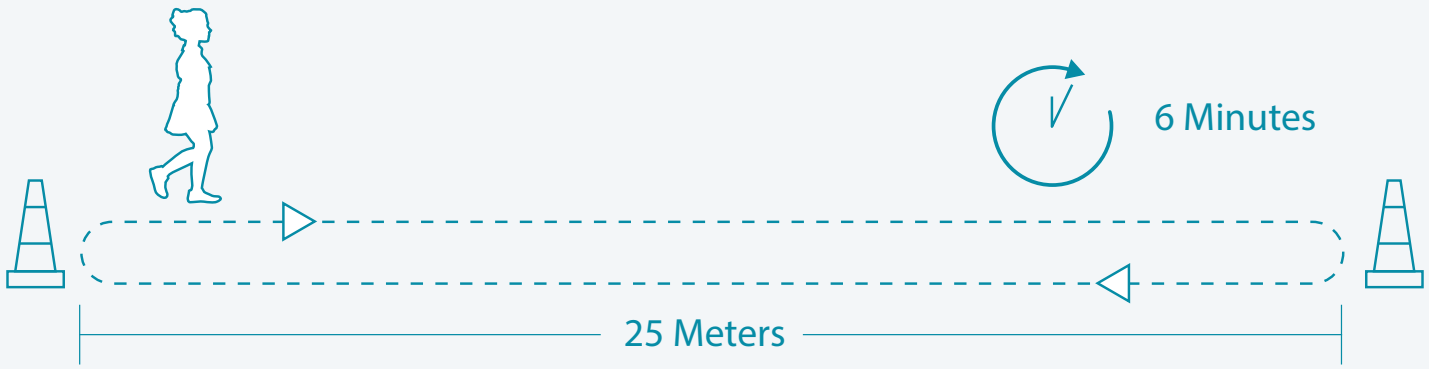
Description	0 (lowest score)	2 (highest score)
Bring hands from lap to table	Unable to bring 1 hand to table	Brings 2 hands completely to table, either together or 1 at a time
Complete the path bringing the car to the finish line without stopping or taking pencil off of paper	With pencil in hand, unable to hold it or make a mark	Able to complete the path without stops or raising pencil from paper
Pick up coins/tokens	Cannot pick up 1 coin/token	Can pick up and hold 2 coins/tokens
Place coin/token into cup On table: horizontal At shoulder height: vertical	Unable to bring coin/token	Able to bring coin/token into cup placed at shoulder level
Reach to the side and touch the coin/token Bring hand at shoulder height and above	Cannot bring hand to shoulder height	Brings hand above shoulder height, elbow at least at eye level
Push button light with 1 hand	Unable to turn the light on with 1 hand	Able to turn the light on permanently with fingers and/or thumb of 1 hand
Tearing paper	Cannot tear piece of paper folded in 2	Tears the sheet of paper folded in 4, beginning from the folded edge
Open Ziploc® container	Unable to open	Able to completely open container on table or against body; 1-point maximum
Raise cup with 200 g to mouth	Unable to get cup to mouth	Cup with 200 g to mouth with 1 hand
Lift weight and bring it from 1 circle to the other without sliding between horizontal circles; MIDLINE CIRCLE to OUTER on tested side	Unable	Lift 200-g weight
Lift weight and bring it from 1 circle to the other without sliding between horizontal circles; MIDLINE to OUTER CIRCLE on tested side	Unable	Lift 500-g weight
Lift weight and bring it from 1 circle to the other without sliding between diagonal circles; ACROSS MIDLINE, INNER TO OUTER CIRCLE on opposite side	Unable	Lift 200-g weight

Description	0 (lowest score)	2 (highest score)
Bring 500-g sand weight from lap to table or eye level	Unable to bring weight to table using 2 hands	Brings weight to eye level using 2 hands
Bring both arms above head–shoulder abduction	Unable	Can abduct both arms simultaneously, elbows in extension in a full circle until they touch above the head
4-point kneeling	Unable	Achieves 4-point kneeling; head up for a count of 3
Bring 500-g weight above shoulder height–shoulder abduction	Unable to lift 500-g weight even with compensation	Able to lift 500-g weight without compensation
Bring 1-kg weight above shoulder height–shoulder abduction	Unable to lift 1-kg weight even with compensation	Able to lift 1-kg weight without compensation
Bring hand above shoulder height–shoulder flexion	Unable	Able without compensation
Bring 500-g weight above shoulder height–shoulder flexion	Unable to lift 500-g weight even with compensation	Able to lift 500-g weight without compensation
Bring 1-kg weight above shoulder height–shoulder flexion	Unable to lift 1-kg weight even with compensation	Able to lift 1-kg weight without compensation

6MWT

An objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type 2 or Type 3) SMA.

// Test is based on distance; individual walks as far as possible in 6 minutes
// Test is performed on a linear 25-meter marked course
// Validated in patients 3 to 49 years of age
// An MCID for 6MWT has been estimated to be 30 meters in neuromuscular disorders[17] and ranges from 48 to 72 meters in later-onset SMA[12]



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.

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.

REFERENCES: 1. Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. *J Pediatr.* 1999;135(2 Pt 1):153-161. **2.** Bishop KM, Montes J, Finkel RS, et al. Motor milestone assessment of infants with spinal muscular atrophy using the Hammersmith Infant Neurological Exam-Part 2: Experience from a nusinersen clinical study. *Muscle Nerve.* 2018;57(1):142-146. **3.** Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile onset spinal muscular atrophy. *N Engl J Med.* 2017;377(18):1723-1732. **4.** De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord.* 2016;26(11):754-759. **5.** Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord.* 2010;20(3):155-161. **6.** Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatr Phys Ther.* 2011;23(4):322-326. **7.** Glanzman AM, Mazzone ES, Young SD, et al. Evaluator training and reliability for SMA global nusinersen trials. *J Neuromuscul Dis.* 2018;5(2):159-166. **8.** O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. *Neuromuscul Disord.* 2007;17(9-10):693-697. **9.** Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. *J Child Neurol.* 2011;26(12):1499-1507. **10.** Pera MC, Coratti G, Forcina N, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. *BMC Neurol.* 2017;17(1):39. **11.** Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med.* 2018;378(7):625-635. **12.** Stolte B, Bois JM, Bolz S, et al. Minimal clinically important differences in functional motor scores in adults with spinal muscular atrophy. *Eur J Neurol.* 2020 Aug 11. doi: 10.1111/ene.14472 **13.** Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One.* 2010;5(8):e12140. **14.** Swoboda KJ, Scott CB, Reyna SP, et al. Phase II open label study of valproic acid in spinal muscular atrophy. *PLoS One.* 2009;4(5):e5268. **15.** Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. *Muscle Nerve.* 2019;59(4):426-430. **16.** Mazzone ES, Mayhew A, Montes J, et al. Revised upper limb module for spinal muscular atrophy: Development of a new module. *Muscle Nerve.* 2017;55(6):869-874. **17.** Dunaway Young S, Montes J, Kramer SS, et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle Nerve.* 2016;54(5):836-842. **18.** Montes J, McDermott MP, Martens WB, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;74(10):833-838. **19.** Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. *Neurology.* 2019;92(21):e2492-e2506. **20.** 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. **21.** 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

225 Binney Street, Cambridge, MA 02142

Biogen

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 and as clinically needed (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 and constipation in patients with infantile-onset SMA (6.1)
- pyrexia, headache, vomiting, and back pain in patients with later-onset SMA (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-844-477-4672 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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. The use of external filters is not required.
- 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 *[see Adverse Reactions (6.3)]*.

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 the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

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

In clinical studies, 346 patients (47% male, 76% Caucasian) were treated with SPINRAZA, including 314 exposed for at least 6 months, 258 exposed for at least 1 year, and 138 exposed for at least 2 years. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days to 16 years of age at first dose) with symptomatic SMA; in a sham-controlled trial in infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=84 for SPINRAZA, n=42 for control); in an open-label study in presymptomatic infants (Study 3, n=25) and other studies in symptomatic infants (n=54) and later-onset patients (n=103). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)

In Study 1, 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%).

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 and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in Study 1 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 with Infantile-Onset SMA (Study 1)

Adverse Reactions	**SPINRAZA 12 mg[1] N = 80 %**	**Sham-Procedure Control N = 41 %**
Lower respiratory infection[2]	55	37
Constipation	35	22
Teething	18	7
Urinary tract infection	9	0
Upper respiratory tract congestion	8	2
Ear infection	6	2
Flatulence	5	2
Decreased weight	5	2

[1] Loading doses followed by 12 mg (5 mL) once every 4 months
[2] Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, Influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenzal, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis.

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.

Clinical Trial in Later-Onset SMA (Study 2)

In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

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 pyrexia, headache, vomiting, and back pain.

Table 2. 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 with Later-Onset SMA (Study 2)

Adverse Reactions	SPINRAZA 12 mg[1] N=84 %	Sham-Procedure Control N=42 %
Pyrexia	43	36
Headache	29	7
Vomiting	29	12
Back pain	25	0
Epistaxis	7	0
Fall	5	0
Respiratory tract congestion	5	2
Seasonal allergy	5	2

[1] Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

6.2 Immunogenicity

As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, 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 nusinersen in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenic response to nusinersen was evaluated in 294 patients with post-baseline plasma samples for anti-drug antibodies (ADAs). Seventeen patients (6%) developed treatment-emergent ADAs, of which 5 were transient, 12 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, "persistent" is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.

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. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested *(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.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.

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.Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. 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

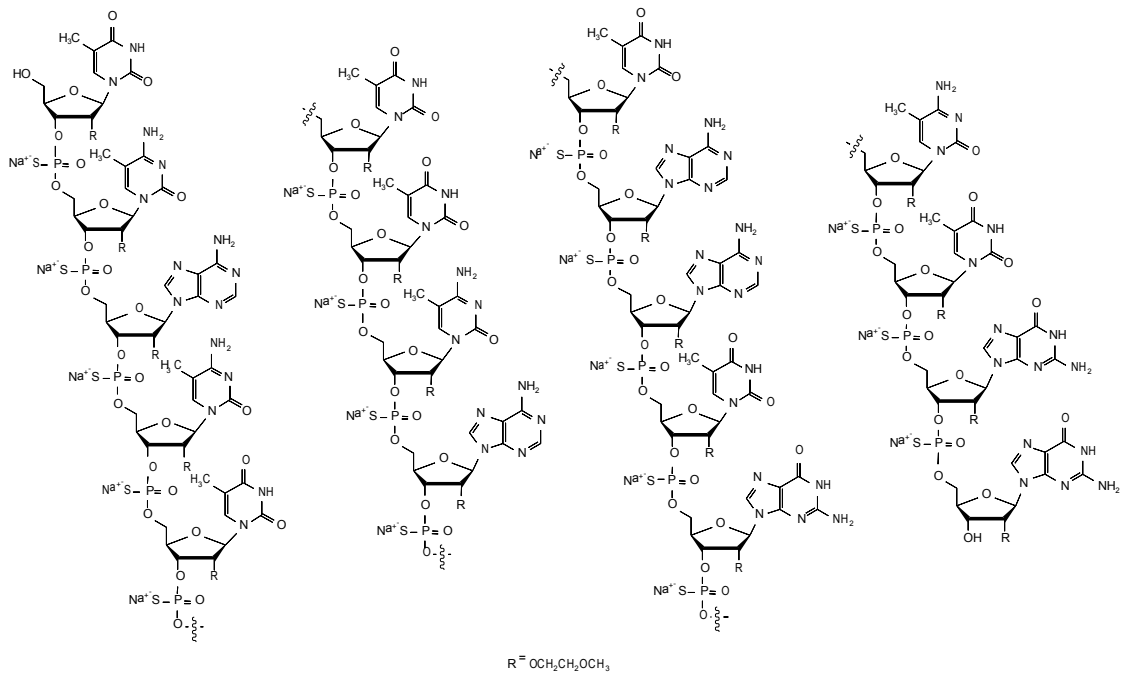
In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, 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

Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Nusinersen 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 $C_{234}H_{323}N_{61}O_{128}P_{17}S_{17}Na_{17}$ 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

Across the sham-controlled studies in 247 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 4 (2.4%) 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 two double-blind, sham-procedure controlled clinical trials in symptomatic infantile-onset and later-onset SMA patients (Study 1 and Study 2) and was supported by open-label clinical trials conducted in presymptomatic and symptomatic SMA patients. The overall findings from these trials support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

14.1 Infantile-Onset SMA

Study 1 (NCT02193074) 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 12 mg SPINRAZA or sham injection as a series of loading doses administered intrathecally followed by maintenance doses administered every 4 months. Patients in this study were deemed most likely to develop Type 1 SMA.

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 (52 patients in the SPINRAZA-treated group and 30 in the sham-control group), 44% were male, 87% were Caucasian, 2% were Black, and 4% were Asian. Age at first treatment ranged from 30 to 262 days (median 181). 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. 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 the

definition of a motor milestone responder in the SPINRAZA group (40%) compared to the sham-control group (0%). Results from the final analysis were consistent with those from the interim analysis (Table 3). Fifty-one percent of patients in the SPINRAZA group achieved the definition of a motor milestone responder compared to 0% of patients in the sham-control group. 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 for patients in the final efficacy set who did not die or withdraw from the study.

The primary endpoint assessed at the final analysis was time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy). Statistically significant effects on event-free survival and overall survival were observed in patients in the SPINRAZA group compared to those in the sham-control group (Table 4). A 47% reduction in the risk of death or permanent ventilation was observed in the SPINRAZA group (p=0.005) (Figure 2). Median time to death or permanent ventilation was not reached in SPINRAZA group and was 22.6 weeks in the sham-control group. A statistically significant 63% reduction in the risk of death was also observed (p=0.004).

At the final 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 3.

Table 3. Motor Milestone Response and CHOP-INTEND Results of the Final Analysis of Patients with Infantile-Onset SMA (Study 1)

Endpoint	SPINRAZA-treated Patients (n=73)	Sham-control Patients (n=37)
Motor function		
Motor milestones[1] Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)[2,3]	37 (51%) P<0.0001	0 (0%)
CHOP-INTEND[1] Proportion achieving a 4-point improvement	52 (71%) p<0.0001	1 (3%)
Proportion achieving a 4-point worsening[4]	2 (3%)	17 (46%)

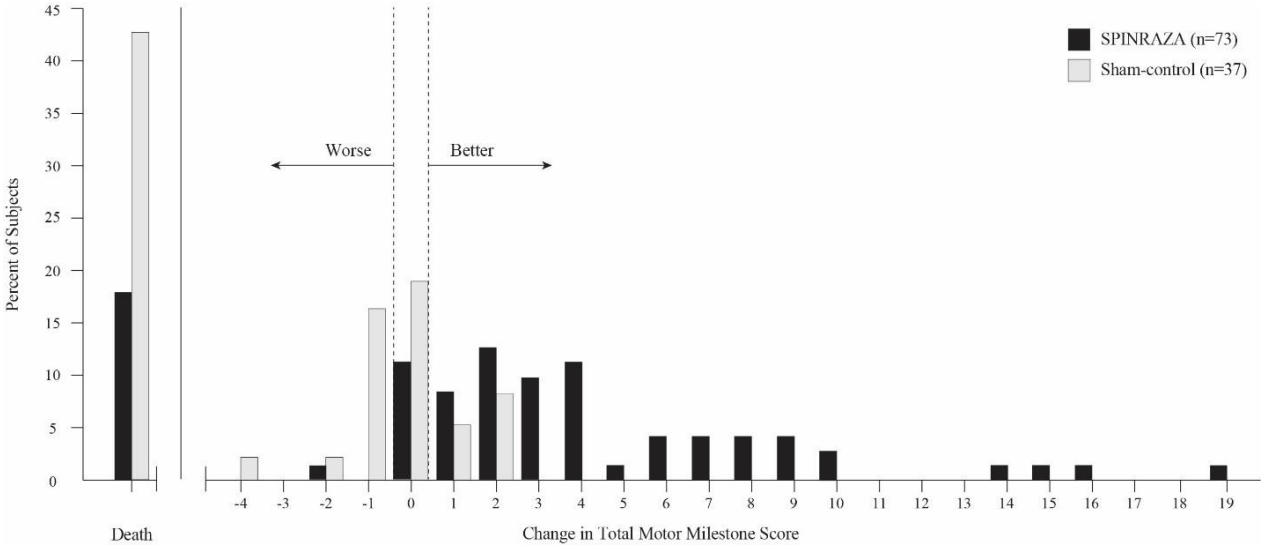
[1]At the final analysis, CHOP-INTEND and motor milestone analyses were conducted using the Efficacy Set (SPINRAZA n=73; Sham-control n=37).
[2]Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
[3]According to HINE section 2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening), defined as a responder for this primary analysis.
[4]Not statistically controlled for multiple comparisons

Table 4. Survival Results of Patients with Infantile-Onset SMA (Study 1)

Endpoint	SPINRAZA-treated Patients (n=80)	Sham-control Patients (n=41)
Survival		
Event-free survival[1] Number of patients who died or received permanent ventilation	31 (39%)	28 (68%)
Hazard ratio (95% CI)	0.53 (0.32 -0.89)	
p-value[2]	p=0.005	
Overall survival[1] Number of patients who died	13 (16%)	16 (39%)
Hazard Ratio (95% CI)	0.37 (0.18 – 0.77)	
p-value[2]	p=0.004	

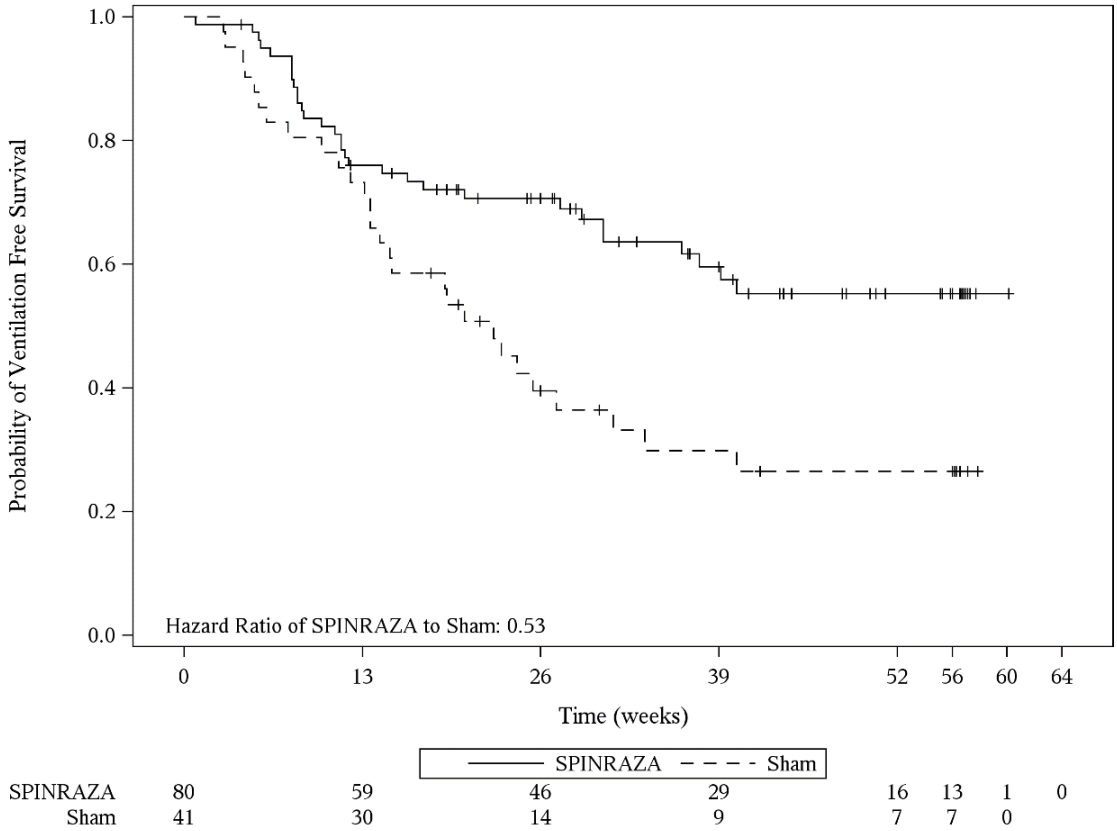
[1]At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT SPINRAZA n=80; Sham-control n=41).
[2]Based on log-rank test stratified by disease duration

Figure 1. Percent of Patients Who Died and Net Change from Baseline in Total Motor Milestone Score (HINE) Among Patients Alive in the Final Efficacy Set of Study 1 *



*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.

Figure 2. Event-Free Survival in the Intent to Treat Set



14.2 Later-Onset SMA

Study 2 (NCT02292537) was a multicenter, randomized, double-blind, sham-procedure controlled study in 126 symptomatic children with later-onset SMA (symptom onset after 6 months of age). Patients were randomized 2:1 to either SPINRAZA 12 mg or sham injection as a series of loading doses administered intrathecally followed by maintenance doses administered every 6 months.

The median age at screening was 3 years (range 2-9 years), and the median age of onset of clinical signs and symptoms of SMA was 11 months (range 6-20 months). Of the 126 patients included in the study, 47% were male, 75% were Caucasian, 2% were Black, and 18% were Asian. Length of treatment ranged from 324 to 482 days (median 450 days). At baseline, patients had a mean Hammersmith Functional Motor Scale – Expanded (HFMSE) score of 21.6, all had achieved independent sitting, and no patients had achieved independent walking. Patients in this study were deemed most likely to develop Type 2 or 3 SMA.

The primary endpoint assessed was the change from baseline score at Month 15 on the HFMSE. The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising of 33 scored activities that give objective information on motor ability and clinical

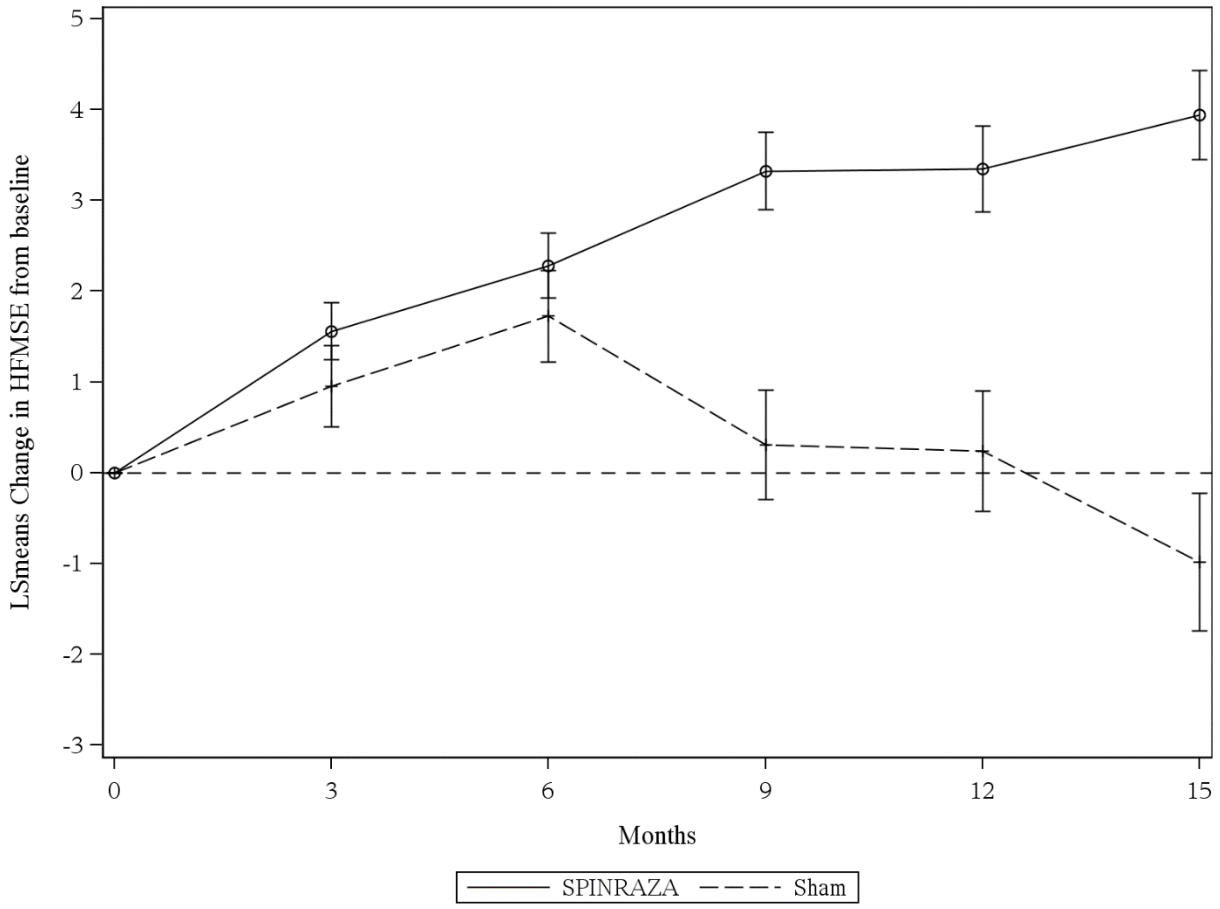
progression, such as the ability to sit unassisted, stand, or walk. Each item is scored from 0-2, with a maximum total score of 66. Higher scores indicate better motor function. The primary analysis was conducted in the Intent to Treat (ITT) population, which included all subjects who were randomized and received at least 1 dose of SPINRAZA or at least one sham procedure. At the final analysis, a statistically significant improvement in HFMSE scores from baseline to Month 15 was observed in the SPINRAZA-treated group compared to the sham-control group (Table 5).

Table 5: HFMSE Results in Patients with Later-Onset SMA (Study 2)

Endpoint	**SPINRAZA-treated Patients (n=84)**	**Sham-control Patients (n=42)**
HFMSE score		
Change from baseline in total HFMSE score at 15 months[1,2,3]	3.9 (95% CI: 3.0, 4.9) p=0.0000001	-1.0 (95% CI: -2.5, 0.5)
Proportion of patients who achieved at least a 3-point improvement from baseline to Month 15[1]	56.8% (95% CI: 45.6, 68.1) p=0.0006[4]	26.3% (95% CI: 12.4, 40.2)

[1]Assessed using the Intent to Treat population who received at least one dose of SPINRAZA or at least one sham procedure (SPINRAZA n=84; Sham-control n=42); data for patients without a Month 15 visit were imputed using the multiple imputation method
[2]Least squares mean
[3]Negative value indicates worsening, positive value indicates improvement.
[4]Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline

Figure 3. Mean Change from Baseline in HFMSE Score Over Time in the Intent to Treat Set[1, 2](Study 2)



[1]Data for patients without a Month 15 visit were imputed using the multiple imputation method
[2]Error bars denote +/- standard error

14.3 Presymptomatic SMA

The results of the sham-controlled trial in infantile-onset (Study 1) (NCT02193074) and later-onset (Study 2) (NCT02292537) SMA patients were supported by an open-label uncontrolled trial conducted in 25 presymptomatic SMA patients who had a genetic diagnosis of 5q SMA and 2 or 3 copies of SMN2 (Study 3) (NCT02386553). In Study 3, 15 patients (60%) who had 2 SMN2 copies, and 10 patients (40%) who had 3 SMN2 copies; 48% were male, 56% were Caucasian, 12 % were Asian, 4% were American Indian or Alaska Native, and 28% were of another race, or had no race reported. Patients ranged in age from 3 days to 42 days (median 22 days) at the time of first dose. Patients received 12 mg SPINRAZA as a series of loading doses administered intrathecally, followed by maintenance doses administered every 4 months. Patients were assessed with the World Health Organization (WHO) motor milestones, a set of 6 milestones in motor development that would be expected to be attained by 24 months of age in healthy children. An interim analysis was performed after all patients had received SPINRAZA

for at least 14 months (median 25 months, range 14 to 34 months). Patients ranged in age from 14 to 34 months (median age of 26 months) at the time of the analysis. At the time of interim analysis (data cutoff May 2018), all patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation, and beyond what would be expected based on their SMN2 copy number. All 25 patients (100%) had achieved the WHO motor milestone of sitting without support, and 22 patients (88%) had achieved the milestone of walking with assistance. Of the 22 patients who were older than the age expected to have achieved the ability to walk independently (as defined by the 95th percentile of the WHO expected age of achievement), 17 (77%) achieved the milestone of walking alone (i.e., walking independently).

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)]*.

49655-08

Manufactured for:
Biogen
Cambridge, MA 02142
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