PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PRSPINRAZA™

(nusinersen injection)

Solution for intrathecal injection 2.4 mg/mL nusinersen as nusinersen sodium

Other drugs for disorders of the musculo-skeletal system

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PrSPINRAZA™

(nusinersen injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Nonmedicinal Ingredients
Intrathecal by lumbar puncture	Solution for intrathecal injection 2.4 mg/mL	sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, water for injection

INDICATIONS AND CLINICAL USE

SPINRAZA (nusinersen) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).

The efficacy and safety data supporting the use of SPINRAZA for the treatment of SMA were from:

- a completed randomized, controlled trial and an ongoing open-label clinical trial that included patients with infantile-onset SMA
- a completed randomized, controlled trial and completed open-label clinical trials in children with later-onset SMA and,
- an ongoing open-label clinical trial in presymptomatic infants with genetically diagnosed SMA (see CLINICAL TRIALS).

Knowledge of the disease natural history and the use of management strategies that assist the patient in coping with the manifestations of SMA, which may include decline in motor function, serious respiratory complications and feeding difficulties remain necessary for the overall management of the disease. Treatment with SPINRAZA should only be initiated by healthcare professionals who are experienced in the management of SMA.

Adult: There are limited data from patients over 18 years of age. SPINRAZA has been studied in patients ranging in age from newborn to 19 years (see CLINICAL TRIALS).

Geriatrics (> 65 years of age):
There are no data from patients over the age of 65.

CONTRAINDICATIONS

- SPINRAZA (nusinersen) is contraindicated in patients with known or suspected hypersensitivity to nusinersen or to any of the ingredients in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General

The route of administration for SPINRAZA (nusinersen) is intrathecal injection by lumbar puncture and should be administered by healthcare professionals who are experienced in performing lumbar puncture procedures. Patients should be evaluated for the presence of potential contraindications for lumbar puncture (e.g., skin infection near site of lumbar puncture, suspicion of increased intracranial pressure due to a cerebral mass, uncorrected coagulopathy, acute spinal cord trauma), and all necessary precautions should be taken to avoid serious procedural complications (see DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS, Postmarket Adverse Events).

Hematologic

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after intravenous or subcutaneous administration of some antisense oligonucleotides.

In a combined analysis of the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients 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.

Patients may be at increased risk of bleeding complications due to the risk of thrombocytopenia and coagulation abnormalities with SPINRAZA.

Perform a platelet count and coagulation laboratory testing at baseline and as clinically indicated (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Neurologic

Hydrocephalus

There have been reports of communicating hydrocephalus not related to meningitis or bleeding in patients treated with nusinersen in the post-marketing setting. Some patients were implanted with a ventriculo-peritoneal shunt. In patients with decreased consciousness, an evaluation for hydrocephalus should be considered. The benefits and risks of nusinersen treatment in patients with a ventriculo-peritoneal shunt are unknown at present and the maintenance of treatment needs to be carefully considered.

Renal

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after intravenous or subcutaneous administration of some antisense oligonucleotides. SPINRAZA is found in high concentrations in the kidney, localized mainly in proximal tubule cells, and is excreted by the kidney (see ACTION AND CLINICAL PHARMACOLOGY).

In a combined analysis of 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 as clinically indicated. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

Cardiovascular
(See ADVERSE REACTIONS)

Carcinogenesis and Mutagenesis
(see TOXICOLOGY).

Sexual Function/Reproduction
The effects of SPINRAZA on labor and delivery are not known.

Special Populations:

Pregnant Women:
There are no data from clinical studies on the use of SPINRAZA during pregnancy in humans and the effects of SPINRAZA on labor and delivery are not known. Because the potential developmental risk associated with the use of SPINRAZA in pregnant women is not known, the use of SPINRAZA during pregnancy is not recommended.

In animal studies administration of nusinersen by subcutaneous injection to mice and rabbits during pregnancy did not have toxic effects on embryo-fetal development (see TOXICOLOGY).

Nursing Women:
It is not known if nusinersen is present in human breast milk.

There are no data on the use of SPINRAZA during lactation in humans and the effects of nusinersen on the breastfed infant are not known.

Pediatrics:
In repeated dose toxicity studies in juvenile cynomolgus monkeys, following intrathecal administration of nusinersen (0.3, 1, or 3 mg/ dose for 14 weeks or 0.3, 1, 3 or 4 mg/ dose for 53 weeks) or vehicle control, brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) was observed at the mid- (1 mg/dose) and high doses (3 mg or 4 mg/dose), specifically in the inferior region of the hippocampus. Possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-observed adverse effect level (NOAEL) 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. The clinical significance of these observations in monkeys is not known.

Monitoring and Laboratory Tests
Conduct the following laboratory tests at baseline and as clinically indicated:
- Platelet count (see WARNINGS AND PRECAUTIONS, Hematologic)
- Prothrombin time; activated partial thromboplastin time (see WARNINGS AND PRECAUTIONS, Hematologic)
- Quantitative spot urine testing (see WARNINGS AND PRECAUTIONS, Renal)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of SPINRAZA (nusinersen) was evaluated in infants with SMA in a phase 3 randomized, double-blind, sham-controlled study of symptomatic infants (1 to 7 months of age at study entry, SPINRAZA n=80, control n=41); an ongoing open-label phase 2 study in symptomatic infants (1 to 7 months of age at study entry, n=20); and, an ongoing open- label phase 2 study in pre-symptomatic infants genetically diagnosed with SMA (3 to 42 days old at first dose, n=20). The safety of SPINRAZA in patients with later-onset SMA was evaluated in a phase 3 randomized, double-blind, sham-controlled study (2 to 9 years of age at study entry, SPINRAZA n=84, control n=42); and completed open-label phase 1 and phase 2 studies of patients who were 2 to 16 years of age at first dose (n=56).

A total of 346 patients were exposed to SPINRAZA in the clinical trials for a total duration of 6 to 2028 days (median 627 days); 227 patients were exposed for at least 6 months and 181 were exposed for at least 12 months. In the controlled study in symptomatic infants, 58 patients were exposed to SPINRAZA for at least 6 months and 28 patients were exposed for at least 12 months. In the controlled study in symptomatic, later-onset patients, 83 patients were exposed to SPINRAZA for at least 6 months and 54 patients were exposed for at least 12 months. The nature of the adverse events reported during all clinical trials suggests that the majority may have been related to SMA disease or the lumbar puncture procedure.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of SPINRAZA in infants and children with SMA was assessed in three randomized, double blind, sham controlled studies, two of which were phase 3 (Study 1 and Study 2) and one phase 2 (Study 5), in an open label phase 2 study in symptomatic infants (Study 3), an open label study in pre symptomatic infants genetically diagnosed with SMA (Study 4) and in patients aged 2 to 16 years (at first dose) in an integrated analysis of 4 open label studies (Studies CS2, CS12, CS1, CS10). Study 6 enrolled infantile- and later-onset subjects, including those who completed Studies 1, 2, and CS12. A total of 346 SMA patients were treated with SPINRAZA, with the total time on study ranging from 6 to 2028 days (median 627 days).

In Study 1, 121 patients were dosed, of whom 80 patients received SPINRAZA (median exposure 280 days) and 41 patients received sham control (median exposure 187 days).

In Study 2, 126 patients were dosed, of whom 84 patients received SPINRAZA (median exposure 451 days) and 42 patients received sham control (median exposure 450 days).

Adverse events reported at an incidence at least 5% higher in patients treated with SPINRAZA compared to sham-control in Studies 1 and 2 are summarized in Tables 1 and 2, respectively. Events reported across the open-label studies and the double-blind Study 5 were consistent with those observed in Studies 1 and 2.

The adverse events are presented as MedDRA preferred terms under the MedDRA system organ class (SOC) (MedDRA Version 18.1).

The adverse events are listed by system organ class and are presented in order of decreasing seriousness.

Table 1: Treatment Emergent Adverse Events Reported with an Incidence of at Least 5% Higher in Patients Treated with SPINRAZA Compared to Sham-control in the controlled clinical trial in patients with infantile-onset SMA

System Organ Class	Preferred term	Control N=41	SPINRAZA N=80
	Any adverse event	40 (98%)	77 (96%)
Infections and infestations	Upper respiratory tract infection	9 (22%)	24 (30%)
	Pneumonia	7 (17%)	23 (29%)
	Nasopharyngitis	4 (10%)	15 (19%)
	Respiratory tract infection	2 (5%)	9 (11%)
	Urinary tract infection	0 (0%)	7 (9%)
	Bronchitis	1 (2%)	6 (8%)
	Upper respiratory tract congestion	1 (2%)	6 (8%)
	Bronchitis viral	0 (0%)	5 (6%)
	Influenza	0 (0%)	5 (6%)
	Ear infection	1 (2%)	4 (5%)
Gastrointestinal disorders	Constipation	9 (22%)	28 (35%)
	Teething	3 (7%)	14 (18%)

Adverse events which are verbally communicated, such as those which commonly occur in the setting of lumbar puncture procedure, could not be assessed due to the infantile patient population.

Table 2: Treatment Emergent Adverse Events Reported with an Incidence of at Least 5% Higher in Patients Treated with SPINRAZA Compared to Sham-control in the controlled clinical trial in patients with later-onset SMA

System Organ Class	Preferred term	Control N=42	SPINRAZA N=84
	Any adverse event	42 (100%)	78 (93%)
General disorders and administration site conditions	Pyrexia	15 (36%)	36 (43%)
Nervous system disorders	Headache*	3 (7%)	24(29%)
Gastrointestinal disorders	Vomiting*	5 (12%)	24 (29%)
Respiratory, thoracic and mediastinal disorders	Epistaxis	0	6 (7%)

System Organ Class	Preferred term	Control N=42	SPINRAZA N=84
Musculoskeletal and connective tissue disorders	Back pain*	0	21 (25%)

*Adverse events considered related to the lumbar puncture procedure. These events can be considered manifestations of post-lumbar puncture syndrome.

QTc interval abnormalities
Across the sham-controlled studies in 247patients with SMA who received either SPINRAZA or sham-control, QTc values >500 ms with a change from baseline values >60 ms were observed in 4 (2.4%) of patients receiving SPINRAZA. There were no patients with an adverse event of QTc prolongation and there was no increase in the incidence of cardiac adverse events associated with delayed ventricular repolarization in patients treated with SPINRAZA compared to the sham control.

Effect on growth
A reduction in growth, as measured by height, was suggested in the controlled clinical trial in patients with infantile-onset SMA treated with SPINRAZA. It is not known if any effect of SPINRAZA on growth would be reversible upon discontinuation of treatment.

Rash
Cases of rash were reported in the controlled clinical trial in patients with infantile-onset SMA. One patient developed painless lesions on the forearm, leg and foot, over an 8-week period 8 months after starting treatment with SPINRAZA. The lesions were initially red macular skin lesions that ulcerated and scabbed over in 4 weeks. The patient continued to have recurring painless ulcerative lesions in acral distribution. A second patient developed red macular lesions on the hands 10 months after starting treatment with SPINRAZA, which resolved over a period of 3 months. In both cases there was spontaneous resolution of the rash while the patients continued to receive SPINRAZA.

Hyponatremia
One patient treated with SPINRAZA in an open-label study including patients with infantile onset SMA had a serious adverse event of hyponatremia requiring daily salt supplementation for 14 months.

Immunogenicity
Treatment-emergent antidrug antibody (ADA) status was assessed in 346 patients treated with nusinersen in ongoing and completed clinical studies. Overall, the incidence of ADAs was 15 (4 %) patients were classified as ADA positive overall, of which 4 had a transient response, 5 patients had a persistent response, and 6 patients had responses that could not be classified as transient or persistent yet at the time of data cutoff. The impact of immunogenicity on safety was not formally analyzed because the number of subjects with ADAs was low. However, individual safety data for the treatment-emergent ADA-positive cases were reviewed, and no Adverse Events of interest were identified.

Post-market Adverse Events

Adverse events associated with the lumbar puncture procedure used for administration of SPINRAZA, including serious infection, have occurred in the post market setting. SPINRAZA should be administered by healthcare professionals who are experienced in performing lumbar puncture procedures (see WARNINGS AND PRECAUTIONS, General; DOSAGE AND ADMINISTRATION). Hydrocephalus, aseptic meningitis, and hypersensitivity (e.g. angioedema, urticaria, rash) have also been observed.

DRUG INTERACTIONS

No clinical studies of interactions with other medicines have been performed.

Nusinersen is metabolized via nucleases and not by the cytochrome P450 (CYP450) system.

In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism.

In vitro studies indicated that the likelihood for interactions with nusinersen due to competition with or inhibition of transporters is low.

The co-administration of other intrathecal agents with SPINRAZA has not been evaluated and the safety of these combinations is not known.

DOSAGE AND ADMINISTRATION

Dosing Considerations

SPINRAZA (nusinersen) is only for intrathecal use by lumbar puncture. SPINRAZA should not be administered by intravenous, intramuscular, subcutaneous or epidural routes.

Treatment should be administered by health care professionals experienced in performing lumbar punctures.

SPINRAZA has not been studied in patients with renal impairment.

SPINRAZA has not been studied in patients with hepatic impairment. SPINRAZA is not metabolized via the cytochrome P450 enzyme system in the liver, therefore dosage adjustment is unlikely to be required in patients with hepatic impairment (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Recommended Dose

The recommended dose is 12 mg (5 mL).

Loading doses

Initiate treatment as early as possible after diagnosis with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals (e.g., Day 0, Day 14, Day 28). The fourth loading dose should be administered approximately 30 days after the third loading dose (e.g., Day 63).

Maintenance doses

Following the fourth loading dose, a maintenance dose should be administered once every 4 months.

Missed Dose

If a loading dose is delayed or missed SPINRAZA should be administered as soon as possible, with at least 14 days between doses, and dosing should continue at the prescribed frequency.

If a maintenance dose is delayed or missed SPINRAZA should be administered as soon as possible and dosing should continue at the prescribed frequency.

Administration

Preparation of dose

1. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25ºC/77ºF) without using external heat sources, prior to administration. The solution must be visually inspected prior to use. Only clear and colorless solutions, free from particles, can be used. Do not administer SPINRAZA if visible particles are observed or if the solution in the vial is discolored. Use of external filters is not required.
2. Aseptic technique must be used when preparing and administering SPINRAZA.
3. Just prior to administration insert the syringe needle into the vial through the center of the over-seal and withdraw 12 mg (5 mL) of SPINRAZA from the vial into the syringe. SPINRAZA must not be diluted. If a vial remains unopened and the solution has not been used, it should be returned back to the refrigerator.

Administration of dose

1. Sedation may be required to administer SPINRAZA, as indicated by the clinical condition of the patient.
2. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of SPINRAZA, particularly in younger patients.
3. Prior to administration, removal of 5 mL of cerebral spinal fluid is recommended.
4. Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation.
5. Once drawn in to the syringe, if the solution is not used within 6 hours, it must be discarded.

OVERDOSAGE

No cases of overdose associated with adverse reactions were reported in clinical studies.

In case of overdose with SPINRAZA the patient should be advised to seek medical attention if they experience any signs or symptoms of adverse reactions.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SPINRAZA (nusinersen) is an antisense oligonucleotide (ASO) specifically designed to treat SMA, an autosomal recessive progressive neuromuscular disease, caused by mutations in the chromosome 5q. These mutations lead to loss of function of the survival motor neuron 1 (SMN1) gene, resulting in deficiency of SMN protein. The SMN2 gene also produces SMN protein but at low levels. In patients with SMA, fewer SMN2 gene copies are associated with earlier age of onset and increased severity of symptoms.

SPINRAZA binds to a specific site in the SMN2 pre-messenger ribonucleic acid (pre-mRNA) to increase the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts made, which can be translated into the functional full length SMN protein.

Pharmacodynamics
Autopsy samples from treated infants had higher levels of SMN2 mRNA containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.

Pharmacokinetics
Single- and multiple-dose pharmacokinetics of nusinersen, administered via intrathecal injection, were determined in pediatric patients diagnosed with SMA.

Absorption: Intrathecal injection of nusinersen 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 Tmax values ranged from 1.7 to 6.0 hours. Mean plasma Cmax and AUC values increased approximately dose proportionally over the evaluated dose range up to 12 mg. There is no accumulation in plasma exposure measures (Cmax and AUC) after multiple doses.

Distribution: Autopsy data from patients (n=3) showed that following intrathecal administration, nusinersen was broadly distributed within the CNS and peripheral tissues such as skeletal muscle, liver, and kidney.

Metabolism/Biotransformation: Nusinersen is metabolized slowly via exonuclease (3'- and 5') mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes.

Elimination: The mean terminal elimination half-life is estimated at 135 to 177 days in CSF and 63 to 87 days in plasma. Following slow metabolism in tissues, the primary route of elimination is likely by urinary excretion of nusinersen and its chain-shortened metabolites. During the first 24 hours after dosing, only 0.5% of the administered dose was recovered in urine.

Special Populations and Conditions:

Gender: Population pharmacokinetic analysis showed that gender does not affect the pharmacokinetics of nusinersen.

Renal and Hepatic Insufficiency: The pharmacokinetics of nusinersen in patients with renal impairment or hepatic impairment have not been studied.

STORAGE AND STABILITY

Store refrigerated at 2ºC to 8ºC (36ºF to 46ºF). 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 30ºC 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 and secondary packaging should not exceed 30 hours, at a temperature that does not exceed 25ºC (77ºF).

Once in the syringe, if the solution is not used within 6 hours, it must be discarded.

Discard any unused solution left in a vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Single-use solution for intrathecal injection containing 5 mL of a 2.4 mg/mL clear and colorless solution of nusinersen.

Composition
SPINRAZA is formulated at a pH of approximately 7.2 and contains:

Artificial cerebral spinal fluid contents per 5 mL;
Sodium dihydrogen phosphate dihydrate (0.25 mg),
Disodium phosphate (0.49 mg),
Sodium chloride (45.83 mg),
Potassium chloride (1.12 mg),
Calcium chloride dihydrate (1.03 mg),
Magnesium chloride hexahydrate (0.82 mg)
Water for injection

Sodium hydroxide and hydrochloric acid may be used for pH adjustment.

Packaging
SPINRAZA is supplied as 5mL in a Type I vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap. Pack size: one vial per carton.

PART II: SCIENTIFIC INFORMATION

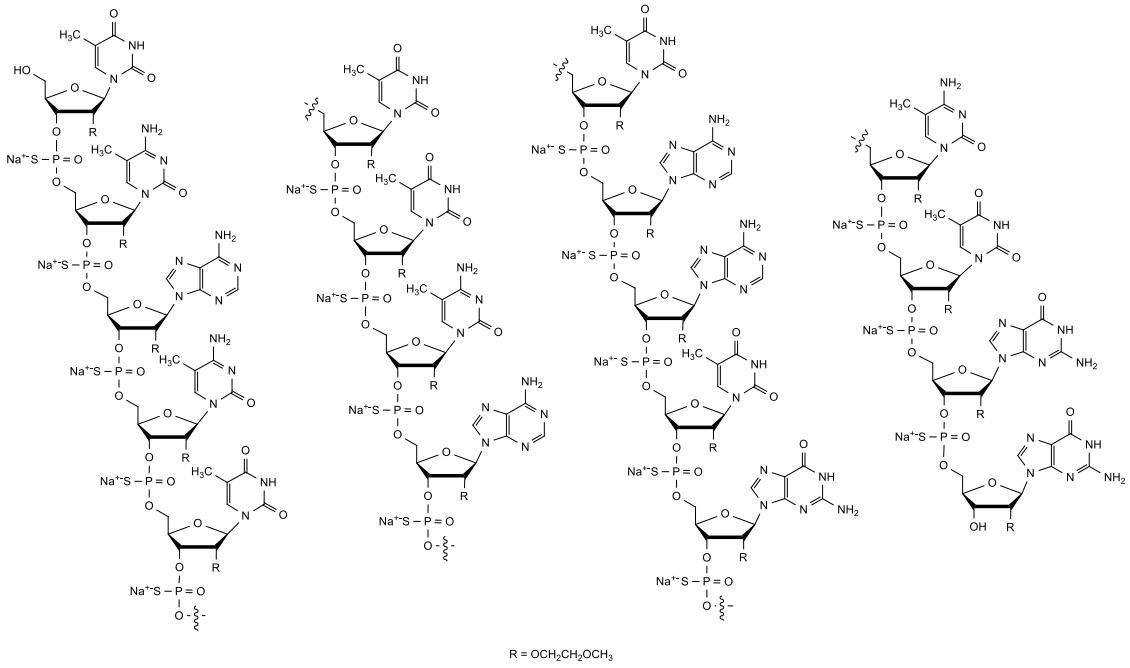
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: nusinersen

Molecular formula and molecular mass: 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 amu

Structural formula:



Physicochemical properties: Nusinersen is a fully modified 2′-O-2-methoxyethyl antisense oligonucleotide designed to bind to a specific sequence in the intron downstream of Exon 7 of the SMN2 transcript. SPINRAZA is a sterile, preservative-free solution that contains 2.4 mg/mL nusinersen in artificial cerebral spinal fluid. SPINRAZA contains 12.6 mg nusinersen sodium equivalent to 12 mg nusinersen free acid in 5 mL per vial.

pH of approximately 7.2.

CLINICAL TRIALS
Study demographics and trial design

Table 3 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage and duration[1]	Study subjects (n = number)	Population studied
Study 1 (ENDEAR; CS3B)	Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled in subjects with symptomatic infantile-onset SMA [Completed]	12 mg scaled equivalent dose or sham-procedure (2:1) Loading dose: Days 1, 15, 29, 64 Maintenance dose: Days 183 and 302 Study duration: ~13 months; study terminated early	121	Most likely to develop Type I SMA Median age at symptom onset 8 weeks (range 1 to 20 weeks) SMN2 gene copies: 2 (120), 3 (1) Median age at first dose: 175 days (range 30 to 262 days) Gender: - 45% male - 55% female
Study 2 (CHERISH; CS4)	Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled in subjects with symptomatic later-onset SMA [Completed]	12 mg scaled equivalent dose or sham-procedure (2:1) Loading dose: Days 1, 29 and 85 Maintenance dose: Day 274 Study duration: ~15 months; study terminated early	126	Median age at symptom onset: 11 months (range: 6 to 20 months) SMN2 gene copies: 2 (10), 3 (111), 4 (3), unknown (2) Median age at first dose: 3.95 years (range 2.1 to 9.2) Gender: - 47% male - 53% female

Study #	Trial design	Dosage and duration[1]	Study subjects (n = number)	Population studied
Study 3 (CS3A)	Phase 2, open-label, multiple-dose in subjects with symptomatic infantile-onset SMA [Completed]	Cohort 1: 6 mg scaled equivalent loading dose and 12 mg maintenance dose Cohort 2: 12 mg scaled equivalent loading dose and 12 mg maintenance dose Loading dose: Days 1, 15, and 85 Maintenance dose: Day 253 and every 4 months thereafter. Study duration: ~3.7 years; study terminated early	20	Most likely to develop Type I or Type II SMA Median age at symptom onset 56 days (range: 21 to 154 days) SMN2 gene copies: 2 (17), 3 (2), unknown (1) Median age at first dose: 162 days (range 37 to 223 days) Gender: - 60% male - 40% female
Study 4 (NURTURE ; CS5; SM201)	Phase 2, open-label study in pre symptomatic infants genetically diagnosed with SMA [Ongoing]	12 mg scaled equivalent loading and maintenance doses of nusinersen on day 1, 15, 29, 64, 183, and every 4 months thereafter. Study duration: ~8 years	25	Most likely to develop Type I or II SMA. SMN2 gene copies: 2 (5), 3 (10) Median age at first dose: 22 days (range 3 - 42 days) Gender: - 48% male - 52% female
Study 5 (EMBRACE ; SM202)	Phase 2, randomized, double-blind, multiple-dose, sham-procedure controlled in subjects with symptomatic infantile- or late-onset SMA who were not eligible to participate in Study CS3B or CS4 [Part 1 has been completed and Part 2 is ongoing]	12 mg scaled equivalent dose or sham procedure (2:1) at Days 1, 15, 29, 64, 183, and 302 Study duration: Part 1: ~13 months, study terminated early Part 2: ~28 months	21	Part 1 Median age at symptom onset: 5.1 months (range: 1.8 to 11 months) Age at symptom onset - <=6 months: 62% - > 6 months: 38% SMN2 gene copies: 2(7), 3(14) Median age at first dose: 17 months (range: 7 to 53 months) Gender: - 52% male - 48% female

Study #	Trial design	Dosage and duration[1]	Study subjects (n = number)	Population studied
Study 6 (SHINE; CS11)	Phase 3, open-label, extension in subjects who previously participated in Study CS3A, CS3B, CS4, CS12 [Ongoing]	12 mg scaled equivalent loading dose Group 1A (subjects who received sham procedure in CS3B): nusinersen on Days 1, 15, 29, and 64 Group 1B (subjects who received nusinersen in CS3B): 3 sham procedures on Days 1, 15, and 64; and nusinersen on Day 29 Group 2A (subjects who received sham procedure in CS4): nusinersen on Days 1, 29, and 85 Group 2B (subjects who received nusinersen in CS4): nusinersen on Days 1 and 85, and sham procedure on Day 29 Day 1 of maintenance dose of nusinersen for Groups 1A, 1B, 2A, 2B, 3 (subjects from CS12), and 4 (subjects from CS3A) was 120 days after last dosing visit and every 4 months thereafter. Study duration: ~5 years after Day 1 of maintenance dose.	100 infantile- and 170 later- onset	Median age at symptom onset: Infantile-onset: 1.8 months (range: 0 to 5 months) Later onset: 12.0 months (range: 5 to 60 months) SMN2 gene copies: Infantile-onset: 2 (97), 3 (3) Later-onset: 2 (10), 3 (147), 4 (10), unknown (3) Median age at first dose: Infantile-onset: 16.7 months (range: 8 to 54 months) Later-onset: 5.8 years (range: 3 to 19 years) Gender: Infantile-onset: - 43% male - 57% female Later-onset: - 47% male - 53% female

[1]Intrathecal administration
In addition to the studies noted in the table above, data from Phase 1 open label studies in SMA type II or III [study numbers CS2, CS12, CS1, CS10 (n= 56)] are included in the integrated data presented below.

The efficacy of SPINRAZA (nusinersen) was demonstrated in three, randomized, double-blind, sham-procedure controlled clinical trials, one in symptomatic patients with infantile-onset SMA (Study 1), one in later-onset SMA (Study 2), and another in symptomatic patients who were not eligible to participate in Study 1 or Study 2 (Study 5). This is further supported by ongoing and completed open-label clinical trials conducted in patients with infantile-onset SMA, patients with

later-onset SMA, and patients with presymptomatic genetically diagnosed SMA (Study 3, 4, and 6).

Clinical Trials in Infantile-Onset SMA

This study was a phase 3, multicenter, randomized, double-blind, sham-procedure controlled study conducted in 121 symptomatic infants ≤ 7 months of age at the time of first dose or sham procedure, diagnosed with SMA (symptom onset before 6 months of age). The median age of onset of clinical signs and symptoms of SMA was 6.5 weeks (range 2-18) and 8 weeks (range 1-20) for SPINRAZA treated versus sham control patients respectively. Patients in this study were deemed most likely to develop type I SMA. At baseline, the mean total motor milestone score was 1.37 (range 0-6), the median CHOP INTEND score was 28 (range 8-50.5), and the median CMAP amplitudes were 0.20 (range 0.00-0.87) and 0.30 (range 0.00-1.50) for the ulnar nerve and peroneal nerves, respectively. The median age when patients received their first dose was 164.5 days (range 52-242) for treated patients, and 205 days (range 30-262) for sham control. Patients were randomized 2:1 to either SPINRAZA or sham-control, with a length of treatment ranging from 6 to 442 days (median 258). Patients randomized to the SPINRAZA group received 4 loading doses of 12 mg nusinersen intrathecal injection, administered by lumbar puncture, on Days 1, 15, 29 and 64, followed by maintenance doses administered at 4-month intervals on Days 183 and 302. In the sham-control group patients received a dermal puncture at all scheduled dosing visits.

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%).

A planned interim analysis was conducted based on patients with the opportunity to reach a 6 month evaluation. The primary endpoint assessed at the interim analysis was the proportion of motor milestone responders: patients achieving a pre-defined level of improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE). A treatment responder was defined as any patient with at least 2 point increase [or maximal score of 4] in ability to kick, or at least a 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking. To be classified as a responder, patients needed to exhibit improvement in more categories of motor milestones than worsening. Of the 78 patients who were eligible for the interim analysis, a statistically significantly greater proportion of patients achieved the definition of a motor milestone responder in the SPINRAZA group (41%) compared to the sham-control group (0%), $p<0.0001$.

At the final analysis, time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy) was assessed as the primary endpoint. Statistically significant effects on event-free survival, overall survival, the proportion of patients achieving the definition of a motor milestone responder, and the percentage of patients with at least a 4 point improvement from baseline in CHOP-INTEND score were observed in patients in the SPINRAZA group compared to those in the sham-control group (Table 4).

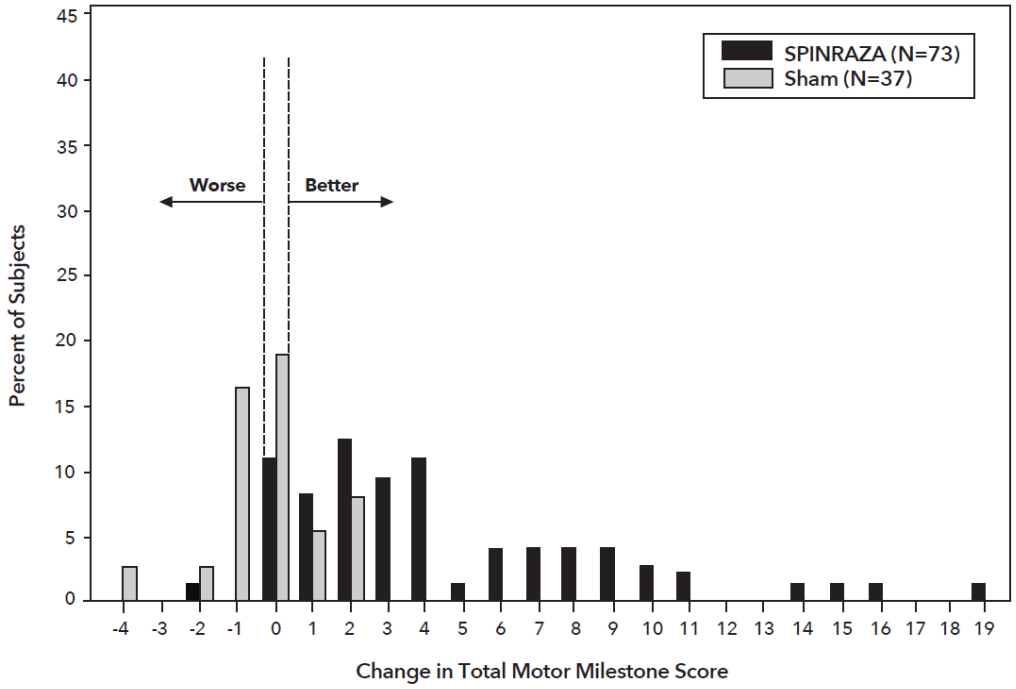
A 47% reduction in the risk of death or permanent ventilation was observed in the ITT population ($p=0.0046$). Median time to death or permanent ventilation was not reached in

SPINRAZA group, and was 22.6 weeks in the sham-control group. A statistically significant 62.8% reduction in the risk of death was also observed (p=0.0041) (Figure 3).

In the efficacy set, 51% of patients in the SPINRAZA group achieved the definition of motor milestone responder compared to 0% in the sham control group at the final analysis (p<0.0001). The proportion of responders increased over time in patients in the SPINRAZA group with 41% responders at 6 months (compared to 5% in sham-control), 45% at 10 months (compared to 0% in sham-control), and 54% at 13 months (compared to 0% in sham-control). Overall, 49 (67%) of SPINRAZA compared to 5 (14%) of sham-control patients experienced improvement, and 1(1%) of SPINRAZA compared to 8 (22%) of sham-control patients experienced worsening in total motor milestone score (Figure 1).

In the efficacy set (ES), 18 (25%) patients in the SPINRAZA group and 12 (32%) patients in the sham-control group required permanent ventilation. Of these patients, 6 (33%) in the SPINRAZA group and 0 (0%) in the sham-control group met the protocol-defined criteria for a motor milestone responder. Eleven (61%) patients in the SPINRAZA group and 3 (25%) patients in the sham-control group experienced at least a 1 point improvement in total motor milestone score. Zero (0%) patients in the SPINRAZA group and 3 (25%) patients in the sham-control group experienced at least a 1 point worsening in total motor milestone score.
A statistically significant greater percentage of patients in the ES receiving SPINRAZA (71%) compared to sham-control (3%) achieved a least a 4 point improvement from baseline in CHOP-INTEND score (p<0.0001). Consistently, 3% of patients receiving SPINRAZA and 46% of patients receiving sham-control experienced at least a 4 point worsening from baseline in CHOP-INTEND score.

Figure 1. Distribution of the net change from baseline in HINE total motor milestone score by percent of patients in the Efficacy Set



*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.

Table 4: Primary and secondary endpoints at final analysis – Study 1

Efficacy Parameter	SPINRAZA-treated Patients	Sham-control Patients
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 = 0.0046	
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=0.0041	
Motor function		
Motor milestones[3]		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)[4,5]	37 (51%) P<0.0001	0 (0%)
Proportion at Day 183[6]	41%	5%
Proportion at Day 302[6]	45%	0%
Proportion at Day 394[6]	54%	0%
Proportion with improvement in total motor milestone score	49 (67%)	5 (14%)
Proportion with worsening in total motor milestone score	1 (1%)	8 (22%)
CHOP-INTEND[3]		
Proportion achieving a 4-point improvement	52 (71%) P<0.0001	1 (3%)
Proportion achieving a 4-point worsening	2 (3%)	17 (46%)
Proportion with any improvement	53 (73%)	1 (3%)
Proportion with any worsening	5 (7%)	18 (49%)

[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
[3]At the final analysis, CHOP-INTEND and motor milestone analyses were conducted using the Efficacy Set (SPINRAZA n=73; Sham-control n=37).
[4]Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
[5]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.
[6]The proportion of motor milestones responders at Day 183, Day 302, and Day 394 are based on efficacy sets at those visits

Figure 2: Event-Free Survival in the Intent to Treat Set – Study 1

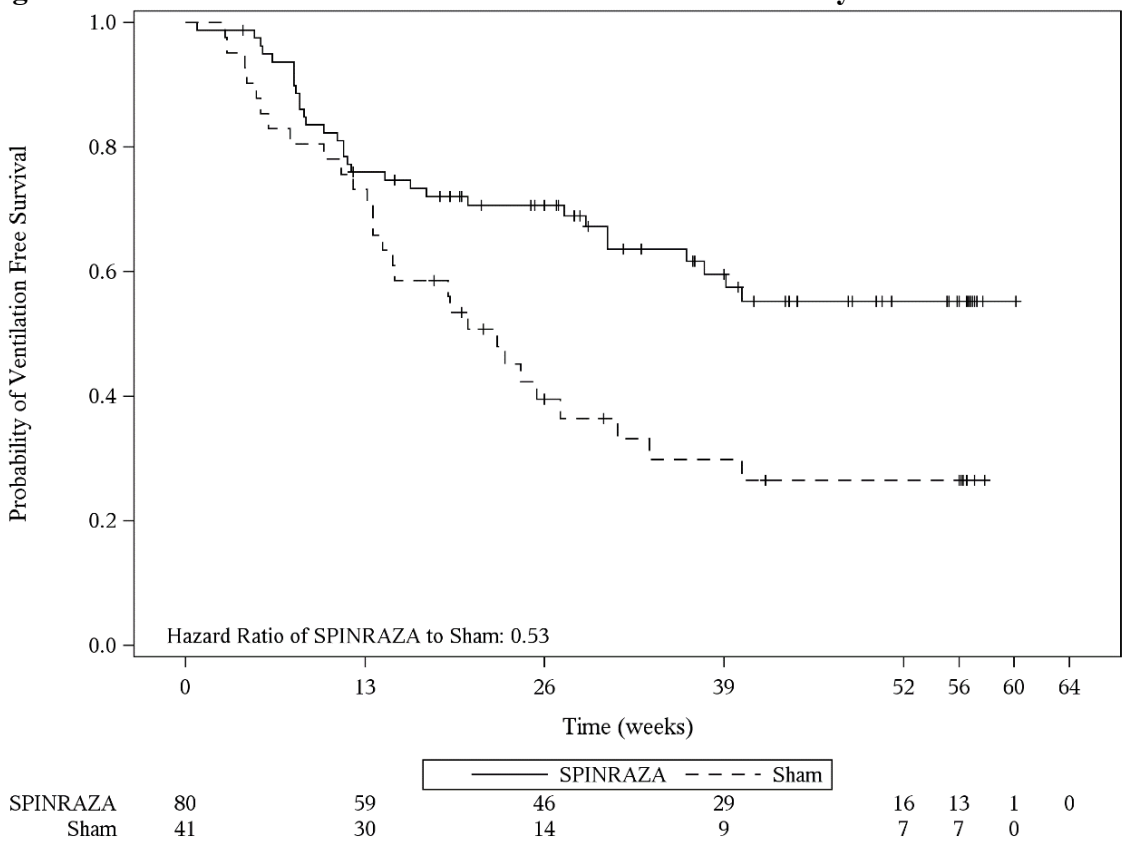
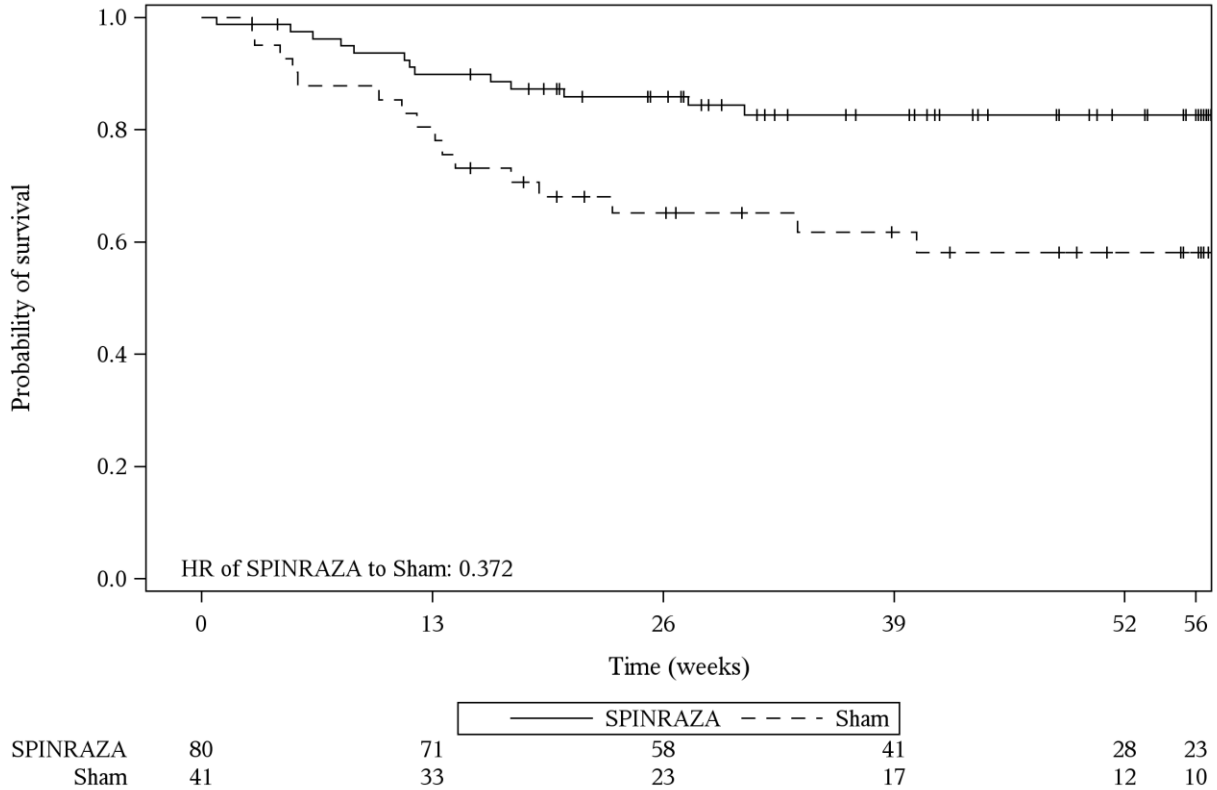


Figure 3: Overall Survival (ITT) – Study 1



Upon completion of Study 1, 89 patients (65 [SPINRAZA] and 24 [sham]) enrolled in the ongoing open-label extension study (Study 6) where all patients received SPINRAZA for 65 to 592 days (median 289 days) at the time of the interim analysis. Improvements in motor function were observed among patients continuing SPINRAZA from Study 1 as well as patients who initiated SPINRAZA in Study 6, with the greatest benefit observed in those with earlier treatment initiation. Among subjects without permanent ventilation at the baseline of Study 6, a majority were alive and without permanent ventilation at the interim analysis.

In patients randomized to SPINRAZA in Study 1 and including the experience in Study 6, the median time to death or permanent ventilation was 73 weeks. At the time of the Study 6 interim analysis, 61/65 (94%) patients were alive. Of the 45/65 subjects who had not met the definition of permanent ventilation in Study 1, 38/45 (84%) were alive without permanent ventilation in Study 6 at the interim analysis. Further improvement in mean total motor milestone (2.1; SD 4.36; n=22) and CHOP INTEND (4.68; SD 3.993, n=22) scores were observed from baseline to Study Day 304 in Study 6.

Patients who initiated treatment with SPINRAZA in Study 6 (n=24; assigned to sham in Study 1) were of a median age of 17.8 months (range 10 - 23 months) and had a mean CHOP INTEND score of 17.25 (range 2.0-46.0) at baseline in Study 6. As of the interim analysis 22/24 (92%) patients were alive. Of the 12/24 patients (50%) who had not met the definition of permanent ventilation in Study 1, 7/12 (58%) were alive without permanent ventilation in Study 6 at the interim analysis. The median time to death or permanent ventilation was 50.9 weeks after initiation of SPINRAZA in Study 6. Improvement in mean total motor milestone (1.2; SD 1.8; n=12) and CHOP INTEND (3.58; SD 7.051, n=12) scores were observed from baseline to Study Day 304 in Study 6.

Clinical Trial in Later-Onset SMA

Study 2 was a phase 3, 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 or sham-control, with a length of treatment ranging from 324 to 482 days (median 450). No patients in either treatment group discontinued treatment.

The median age at screening was 3 years (range 2-9), and the median age of onset of clinical signs and symptoms of SMA was 11 months (range 6-20). The majority of patients (88%) have 3 copies of the SMN2 gene (8% have 2 copies, 2% have 4 copies, and 2% have an unknown copy number). At baseline, patients had a mean HFMSE score of 21.6, a mean Revised Upper Limb Module (RULM) of 19.1, all had achieved independent sitting, and no patients had achieved independent walking. Patients in this study were deemed most likely to develop type II or III SMA.

Baseline disease characteristics were generally similar except for an imbalance in the proportion of patients who had ever achieved the ability to stand without support (13% of patients in the SPINRAZA group and 29% in sham-control) or walk with support (24% of patients in the SPINRAZA group and 33% in sham-control).

A planned interim analysis was conducted when all patients had completed their Month 6 assessment and at least 39 patients had completed their Month 15 assessment. The primary endpoint assessed at the time of interim analysis was change from baseline score at Month 15 on the HFMSE. The primary analysis was conducted in the ITT population which included all

subjects who were randomized and received at least 1 dose of SPINRAZA or at least 1 sham procedure (SPINRAZA: n=84; sham-control: n=42). Post-baseline HFMSE data for patients without a Month 15 visit were imputed using the multiple imputation method. A statistically significant improvement from baseline HFMSE score was observed in SPINRAZA treated patients compared to the sham-control patients (SPINRAZA vs. sham-control: 4.0 vs. -1.9; p=0.0000002).

Results from the final analysis are consistent with those from the interim analysis, showing a statistically significant improvement in HFMSE scores from baseline to Month 15 in the SPINRAZA group compared to the sham-control group (3.9 vs. -1.0; p=0.0000001) (Table 5, Figure 4).

An analysis of the subset of patients in the ITT population who had observed values at Month 15 demonstrated consistent, statistically significant results. Of those with observed values at Month 15 a higher proportion of SPINRAZA-treated subjects had improvement (73% vs 41%, respectively) and a lower proportion had worsening (23% vs 44%, respectively) in total HFMSE scores compared to sham-control treated subjects.

Among patients in the ITT population, 56.8% of patients in the SPINRAZA group achieved a 3-point or greater increase from baseline in the HFMSE score at baseline compared to 26.3% in the sham-control group, for a difference of 30.5% in favor of the SPINRAZA group (p=0.0006).

At the final analysis, all secondary endpoints including functional measures and WHO motor milestone achievement were formally statistically tested and are described in Table 5.

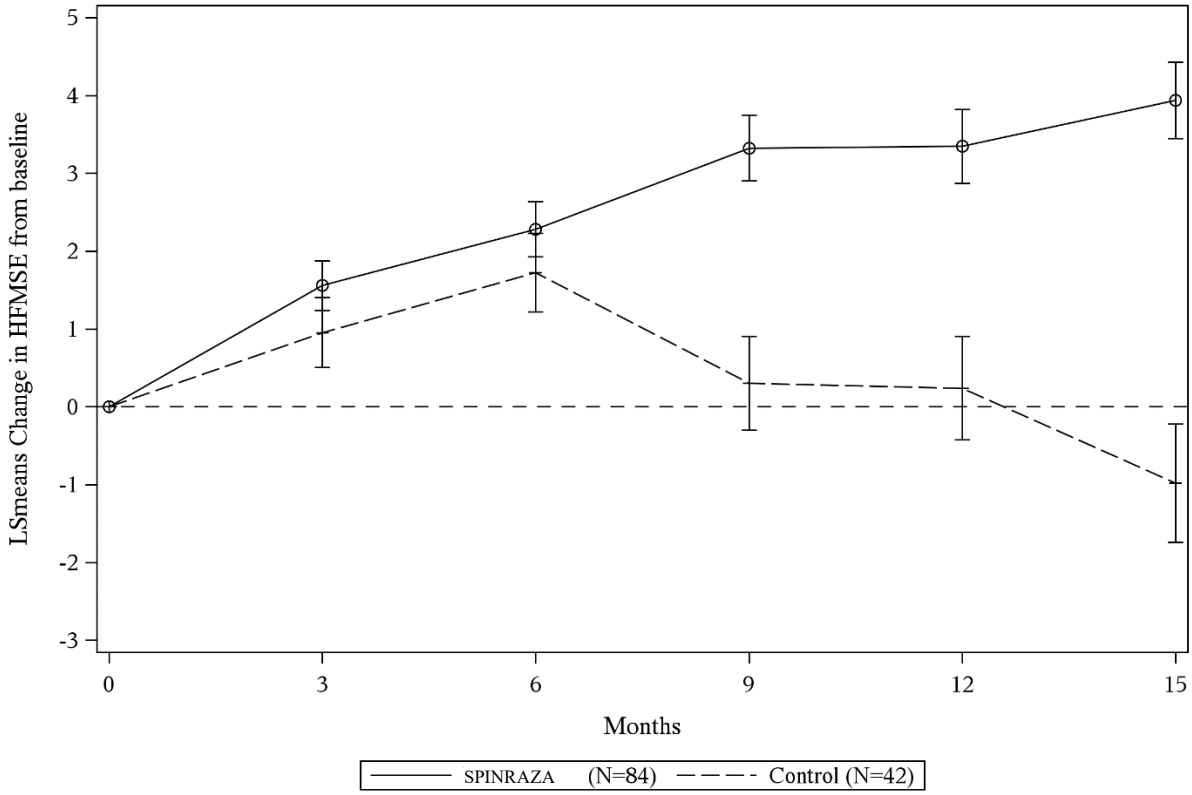
The proportion of subjects achieving new WHO motor milestones (without worsening in any baseline motor milestones) in the SPINRAZA group and sham-control groups was 19.7% and 5.9%, respectively, for a difference of 13.8% (p =0.0811). At 15 months, 1 of the 66 (2%) subjects in the SPINRAZA group compared to 9 of 34 (26%) subjects in the sham-control group had lost at least 1 motor milestone.

The number of new motor milestones achieved per subject at Month 15 was higher in the SPINRAZA group, with a least squares mean difference of 0.4 between the 2 groups (nominal p = 0.0001).

Although SPINRAZA-treated patients with a longer time from symptom onset to initiation of treatment experienced benefit compared to sham-controlled patients, initiation of treatment sooner after symptom onset resulted in earlier and greater improvement in motor function.

There was a greater improvement in Revised Upper Limb Module (RULM) Test scores from baseline to Month 15 in the SPINRAZA group (least squares mean change of 4.2) than in the sham-control group (least squares mean change of 0.5), with a least squares mean difference of 3.7 between the 2 groups (nominal p = 0.0000001). Among patients with observed values at Month 15, a higher proportion of SPINRAZA treated subjects had improvement (79% vs 68%, respectively) and a lower proportion had worsening (14% vs 21%, respectively) in RULM score compared to sham-control.

Figure 4: Mean change from baseline in HFMSE score over time at final analysis (ITT) – Study 2[1,2]



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

Table 5: Primary and secondary endpoints at final analysis – Study 2

	SPINRAZA-treated Patients	Sham-control Patients
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[5]	26.3% (95% CI: 12.4, 40.2)
RULM		
Mean change from baseline to month 15 in total RULM score[1,2,3]	4.2(95% CI: 3.4, 5.0) p=0.0000001[6]	0.5 (95% CI: -0.6, 1.6)
WHO motor milestones		
Proportion of patients who achieved new motor milestones at 15 months[4]	19.7% (95% CI: 10.9, 31.3) p=0.0811	5.9% (95% CI: 0.7, 19.7)

	SPINRAZA-treated Patients	Sham-control Patients
Mean number of new motor milestones attained[2,3,4]	0.2 (range -1 to 2, 95% CI: 0.1, 0.3) p=0.0001[6]	-0.2 (range -1 to 1, 95% CI: -0.4, 0.0)[3]

[1]Assessed using the Intent to Treat population (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]Assessed using the Month 15 Efficacy Set (SPINRAZA n=66; Sham control n=34; analyses are based on imputed data when there are missing data.
[5]Based on logistic regression with adjustment for each subject's age at screening and HFMSE score at baseline
[6] Nominal p value

Upon completion of Study 2, 125 patients enrolled in an ongoing open-label extension study (Study 6) where they received SPINRAZA for 74 to 474 days (median 250 days) at the time of the interim analysis. Subjects treated with SPINRAZA experienced stabilization or improvement in motor function, with the greatest benefit observed in those who initiated treatment with SPINRAZA in Study 2, as compared to those who initiated treatment in Study 6.

Of the patients who initiated treatment with SPINRAZA in Study 2 (n=39), stabilization or additional improvements in mean HFMSE (0.2; SD 3.6) and RULM (0.7; SD 2.69) scores were observed from baseline to Study Day 265 in Study 6.

Patients who did not receive SPINRAZA in Study 2 but initiated treatment in Study 6 (n=20) had a median age of 4.0 years (range 3, 8 years). Of these patients, stabilization or improvements in mean HFMSE (1.4; SD 4.02) and RULM (2.1; SD 2.56) scores were observed from baseline to Study Day 265 in Study 6.

Ongoing and completed open-label clinical trials
The results of the controlled trial in infantile-onset SMA patients were supported by data from completed and ongoing phase 1 and phase 2 open-label, uncontrolled trials conducted in symptomatic patients with infantile-onset SMA (n=20, age range 37 days to 223 days at first dose); in patients with later-onset SMA (n=56, age range 2 to 15 years at first dose); and, in presymptomatic genetically diagnosed patients (n=20, age range 3 to 42 days at first dose). Most of the patients included in these studies had or were likely to develop type I, type II or type III SMA. Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected, when considering the number of SMN2 gene copies of patients enrolled in the studies and the disease natural history.

Study 3 was an open-label phase 2 study in symptomatic patients diagnosed with SMA. Median age of onset of clinical signs and symptoms was 56 days (range 21 to 154 days) and patients had either 2 SMN2 gene copies (n=17) or 3 SMN2 gene copies (n=2) (SMN2 gene copy number unknown for 1 patient). Patients in this study were deemed most likely to develop type I SMA. Median age at first dose was 162 days (range 37-223). At screening, the median number of motor milestones (HINE section 2) achieved was 2 (range 1 to 12), median CHOP INTEND total score was 27 (range 17 to 64).

As of the study closure date, 15 of 20 patients (75%) were alive and 5 patients had died (aged 5.13 to 36.28 months). 11 (55%) were alive and free of permanent ventilation (4 patients were on permanent ventilation aged 6.28 to 39.97 months). Of the 15 patients alive all were at least 14 months of age (median 43.5 months, range 14.1 to 54 months), with 6 at >45 months and 2 at >50 months of age.

The primary endpoint was the proportion of patients who improved in one or more categories in motor milestones (according to HINE section 2: ≥2-point increase [or maximal score] in ability to kick or voluntary grasp OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking). Twelve out of 20 patients (60%) had met the primary endpoint, with a sustained improvement in mean motor milestone achievement over time. 8 of 20 patients (40%) developed the ability to sit independently, 4 of 20 patients (20%) gained the ability to stand with support or independently, 2 of 20 patients (10%) gained the ability to walk with support or independently.

A sustained improvement in mean CHOP INTEND score was observed from baseline to day 1072 (mean change 21.30). Overall, 11 out of 20 patients (55%) met the endpoint of an increase in total CHOP INTEND score of ≥4 points as of their last study visit prior to data cut-off.

When treatment with SPINRAZA was initiated prior to symptom onset in patients with genetically diagnosed SMA (study 4), patients achieved milestones unexpected in Type I or Type II SMA. Median age at first dose was 22 days (range 3-42 days). At baseline, the median number of motor milestones achieved was 3 (range 0-7), the median CHOP INTEND total score was 50.0 (range 25-60), and the median ulnar CMAP amplitude was 2.65 mV (1.0-6.7).

Analysis was conducted when subjects had been on study for a median of 27.1 months (15.1 – 35.5 months) and were of a median age at last visit of 26.0 months (14.0 – 34.3 months). At the time of the interim analysis of Study 4, all 25 of the patients composing the Efficacy Set (2 SMN2 gene copies, n=15; 3 SMN2 gene copies, n=10) were alive without permanent ventilation. The primary endpoint, time to death or respiratory intervention (defined as invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days OR tracheostomy), could not be estimated as there were too few events. Four subjects (2 SMN2 copies) required respiratory intervention >6 hours/day continuously for ≥7 days, all of whom initiated ventilatory support during an acute reversible illness.

Patients achieved milestones unexpected in Type I or II SMA. At interim analysis, all 25 (100%) subjects had achieved the WHO motor milestone of sitting without support, and 22 (88%) had achieved the ability to walk with assistance. Among patients older than the WHO defined window for expected age of achievement (95th percentile), 17 of 22 (77%) had achieved walking alone. The mean CHOP INTEND score at last assessment was 61.0 (46-64) amongst subjects with 2 SMN2 copies and 62.6 (58-64) amongst those with 3 SMN2 copies. All subjects had the ability to suck and swallow at last assessment, with 22/25 (88%) infants achieved a maximal score on the HINE Section 1.

The proportion of patients developing clinically manifested SMA was assessed amongst patients who reached the Day 700 (n=16) visit as of the interim analysis. The protocol-defined criteria for clinically manifested SMA included age-adjusted weight below the fifth WHO percentile, a decrease of 2 or more major weight growth curve percentiles, the placement of a percutaneous gastric tube, and/or the inability to achieve expected age-appropriate WHO milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance,

standing alone and walking alone). At Day 700, 7/11 (64%) of subjects with 2 SMN2 copies and 0/5 subjects with 3 SMN2 copies met the protocol-defined criteria for clinically manifested SMA; however, these patients were gaining weight, and achieving WHO milestones, inconsistent with Type I SMA.

Study 5 is a phase 2, two-part study of which Part 1 was randomized, double-blind, and sham procedure-controlled and Part 2 was an open label extension. The study enrolled symptomatic patients diagnosed with infantile-onset SMA (≤6 months) or later-onset SMA (>6 months) and 2 or 3 copies of SMN2 who were not eligible for participation in Study 1 or Study 2 due to screening age or SMN2 copy number. Subjects were followed for a median of 302 days in Part 1 of the study.

All patients treated with SPINRAZA were alive as of the early termination of Part 1, however, one patient in the control arm died at Study day 289. In addition, no patients in the SPINRAZA group or sham-control group required the use of permanent ventilation. Of the 13 patients with infantile-onset SMA, 7/9 (78%; 95%CI: 45, 94) of the SPINRAZA group and 0/4 (0%; 95%CI: 0, 60) of the sham group met the criteria for motor milestone response (HINE Section 2). Of the 8 patients with later-onset SMA, 4/5 (80%; 95% CI: 38, 96) of the SPINRAZA group and 2/3 (67%; 95% CI: 21, 94) of the sham-control group met this definition of response.

It is not known whether ongoing, continuous treatment with SPINRAZA will be required to maintain or prevent loss of motor function that is achieved during treatment.

TOXICOLOGY

In repeat-dose toxicity studies (14-weeks and 53-weeks) intrathecal administration of nusinersen to juvenile cynomolgus monkeys resulted in transient deficits in lower spinal reflexes which occurred at the highest dose levels in each study (3 or 4 mg per dose; equivalent to 30 or 40 mg per IT dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours. Neuronal vacuolation and necrosis/cellular debris in the hippocampus were also observed at the mid- and high doses (see WARNINGS AND PRECAUTIONS, Pediatrics).

Reproductive toxicology studies were conducted using subcutaneous administration of SPINRAZA in mice and rabbits. No impact on male or female fertility, embryo-fetal development, or pre/post-natal development was observed.

Carcinogenicity and Mutagenicity

Long-term carcinogenicity studies have not been conducted.

SPINRAZA demonstrated no evidence of genotoxicity, in *in vitro* assays (Ames and chromosomal aberration in CHO cells) or in *in vivo* assays (mouse micronucleus).

REFERENCES

1. 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): e2492-506.

2. De Vivo, DC, Bertini, E, Swoboda, KJ, et al. 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): 842-56.

3. Finkel RS. Electrophysiological and motor function scale association in a pre-symptomatic infant with spinal muscular atrophy type I. Neuromuscul Disord. 2013;23(2):112-5.

4. 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): 1723-32.

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):155-61.

6. 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):1499-507.

7. 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): 625-35.

8. Rigo F, Hua Y, Krainer AR, et al. Antisense-based therapy for the treatment of spinal muscular atrophy. J Cell Biol. 2012;199(1):21-5.

9. Sivo S, Mazzone E, Antonaci L, et al. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. Neuromuscul Disord. 2015;25(3):212-5.

10. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol. 2005;57(5):704-12.

11. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007;22(8):1027-49.

12. Young SD, Montes J, Kramer SS, et al. Six-Minute Walk Test is Reliable and Valid in Spinal Muscular Atrophy. Muscle Nerve. 2016.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION
SPINRAZA
nusinersen injection

Read this carefully before you or your child start receiving **SPINRAZA** and before each dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about you or your child's medical condition and treatment and ask if there is any new information about **SPINRAZA**. Keep this leaflet. You may need to read it again.

What is SPINRAZA used for?
SPINRAZA is used to treat a genetic disease called 5q Spinal Muscular Atrophy (SMA). SMA is caused by a problem with the 5q chromosome. This problem leads to a shortage of a particular protein called survival motor neuron (SMN). The shortage of SMN protein results in the loss of nerve cells in the spine that leads to weakness of the muscles in the shoulders, hips, thighs and upper back. It may also weaken the muscles used for breathing and swallowing.

SPINRAZA may be given to children, adolescents or adults:
- There is limited experience of SPINRAZA in people over 18 years of age.
- There is no experience of SPINRAZA in people over 65 years of age.

How does SPINRAZA work?
SPINRAZA is one of a group of medicines called anti-sense oligonucleotides (ASO). SPINRAZA works by helping the body to produce more of the SMN protein that people with SMA need. This may reduce the loss of nerve cells and improve muscle strength.

What are the ingredients in SPINRAZA?
Medicinal ingredients: nusinersen
Non-medicinal ingredients: calcium chloride dihydrate, disodium phosphate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection. Sodium hydroxide and hydrochloric acid may be used for pH adjustment.

SPINRAZA comes in the following dosage forms:
Single-use solution in a vial for intrathecal injection containing 5 mL of a 12 mg / 5 mL (2.4 mg / mL) clear and colorless solution of nusinersen. Pack size: one vial per carton.

Do not use SPINRAZA if:
- You or your child has or may have an allergy or hypersensitivity to nusinersen or to any of the ingredients in the formulation or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given SPINRAZA. Talk about any health conditions or problems you may have.

Warnings you should know about:

Lumbar puncture

- There are known reasons why you or your child should not have a lumbar puncture. These may include:
    - a skin infection near site of lumbar puncture
    - the possibility that you or your child has a brain tumour and increased pressure in the skull
    - uncontrolled problems with blood clotting
    - injury or damage to the spinal cord (only short duration and not ongoing)

Pregnancy, breastfeeding and fertility

There is no experience of the use of SPINRAZA in pregnant women. Ask your doctor for advice about taking SPINRAZA if you:

- are pregnant
- breast-feeding
- think you may be pregnant or are planning to have a baby.

Blood clotting problems and risk of bleeding

After receiving medicines similar to SPINRAZA, some patients had:

- abnormal blood clotting
- abnormal and/or severely low levels of platelets (blood cells responsible for stopping bleeding.

In a SPINRAZA clinical trial, some patients had lower than normal levels of platelets. The lower levels of platelets came and went and the patients did not have abnormal blood clotting.

You may be at risk of bleeding complications while you are taking SPINRAZA. Your doctor will monitor your blood clotting by testing your blood. You will be tested before starting treatment with SPINRAZA and any other time your doctor thinks is necessary.

Risk of kidney damage

After receiving medicines similar to SPINRAZA, some patients had:

- higher levels of protein in their urine
- an increased risk of toxicity in the kidneys
- inflammation of the kidneys, which has caused death.

In a SPINRAZA clinical trial, some patients had higher levels of protein in their urine. SPINRAZA was also found in high concentrations in the kidneys. SPINRAZA leaves the body (is excreted) through the kidneys. It is important that your kidneys work well while you are taking SPINRAZA.

Your doctor will monitor how your kidneys are working by testing your urine. Your urine will be tested before you start treatment with SPINRAZA and any other time your doctor thinks is necessary.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

At this time, there are no known medicines that interact with SPINRAZA. It is unknown if

SPINRAZA can be used safely with other drugs that are administered into the spine (intrathecal).

How SPINRAZA is given:

- SPINRAZA is given by injection to the lower back.
- This injection is called a lumbar puncture and is done by inserting a needle in the space around the spinal cord.
- This will be done by a healthcare provider experienced in doing lumbar punctures.
- The injection will take 1 to 3 minutes
- You or your child may also be given a medicine to make you relax or sleep during the injection.
- Ask your health care provider, if you have any questions about how SPINRAZA is given.

Your doctor will tell you how long you or your child needs to keep receiving SPINRAZA. Don't stop treatment with SPINRAZA unless your doctor tells you to.

Usual dose:
The dose of SPINRAZA is 12 mg. You or your child will receive SPINRAZA based on the schedule below:

- The first 3 doses of SPINRAZA will be administered 14 days apart: on Day 0, Day 14 and Day 28.
- The 4th dose will be administered about a month later, for example on Day 63.
- And then once every 4 months.

Overdose:
There is no experience with overdose with SPINRAZA.

If you think you have been given too much SPINRAZA, contact your healthcare professional immediately, even if there are no symptoms.

Missed Dose:
If you or your child is unable to receive SPINRAZA as planned, speak with your doctor to ensure that SPINRAZA can be given as soon as possible.

What are possible side effects from using SPINRAZA?

Like all medicines, SPINRAZA can cause side effects, although not everybody gets them. Contact your doctor or nurse if you notice any of these side effects. Do not try to treat them yourself.

When SPINRAZA was tested in clinical trials, most side effects seemed to be:

- continued symptoms of the disease (SMA), such as:
    - breathing problems, muscle weakness, joint and bone problems, or digestive problems
    - sinus and/or throat infections, colds
    - lung infections like bronchitis and pneumonia
- side effects of the lumbar puncture:
    - experienced during or within a few days after SPINRAZA is given

The side effects reported that were likely continued symptoms of the disease included:

- Chest infections (such as pneumonia)
    - wheezing, shortness of breath, chest pain, feeling tired, coughing - sometimes with mucus
- Constipation
- Cough
- Curving of the back or spine (scoliosis)
- Diarrhea
- Difficulty breathing or being unable to breathe
    - signs may include rapid or shallow breathing, an increase in heart rate, and a bluish-tinge of the skin, fingertips or lips
    - may be caused by a collapsed lung or part of a lung
- Difficulty swallowing or being unable to swallow
- Ear infection leading to pain or loss of balance
- Feeling nauseous or throwing up
- Fever
- Heart-burn
- Infections of the nose, throat or upper airways
    - blocked, stuffy or runny nose, sneezing and coughing, a sore or scratchy throat and watery or itchy eyes
- Nose bleed (epistaxis)
- Pain
- Permanent shortening of a muscle or joint
- Rash on forearms, legs, feet, hands
- Reduction in growth
- Stiffness of muscles or joints
- Stomach flu
- Yeast / fungus infection in mouth (oral thrush)
    - White patches usually on tongue or inner cheeks

The side effects that were likely a result of the lumbar puncture included:

- Back-pain
- Dizziness
- Feeling nauseous or throwing up
- Headache
- Pain during the injection
- Serious infections

Additional side effects included:

- Hydrocephalus (a buildup of too much fluid around the brain)
    - symptoms may include increase in head size or bulging soft spot on top of the head (fontanel) in infants, decreased consciousness, persistent nausea, vomiting or headache
- Aseptic meningitis (meningitis that is not caused by an infection)
    - symptoms may include headache, photophobia, neck stiffness, nausea, vomiting

- Hypersensitivity (an allergic or allergic-like reaction that may include swelling, rash, or itching)

Tell your doctor if you experience any of the side effects listed above. **Contact your doctor if you or your child has any side effect that bothers you or that does not go away.**

These are not all the possible side effects you may feel when taking SPINRAZA. If you experience any side effects not listed here, or have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, contact your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
SPINRAZA will be managed and stored by healthcare professionals. Below are some of the guidelines for storing SPINRAZA:

- Refrigerate at 2ºC to 8ºC.
- May be stored at up to 30ºC for up to 14 days.
- Protect from freezing.
- Protect SPINRAZA from light and keep it in the original carton until it is needed.
- Keep out of reach and sight of children.

If you want more information about SPINRAZA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website www.biogen.ca.

This leaflet was prepared by Biogen Canada Inc.
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