

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{PR} **SPINRAZA**TM

(nusinersen injection)

solution for injection, 2.4 mg/mL nusinersen (as nusinersen sodium), intrathecal

Other drugs for disorders of the musculo-skeletal system

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.5 Missed Dose	05/2023
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TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS	4
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations	5
4.2 Recommended Dose and Dosage Adjustment	5
4.4 Administration.....	6
4.5 Missed Dose	7
5 OVERDOSAGE	8
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	8
7 WARNINGS AND PRECAUTIONS	9
7.1 Special Populations	11
7.1.1 Pregnant Women	11
7.1.2 Breast-feeding	11
7.1.3 Pediatrics	11
8 ADVERSE REACTIONS	11
8.1 Adverse Reaction Overview.....	11
8.2 Clinical Trial Adverse Reactions	12
8.2.1 Clinical Trial Adverse Reactions - Pediatrics	12
8.3 Less Common Clinical Trial Adverse Reactions.....	15
8.5 Post-Market Adverse Reactions	15
9 DRUG INTERACTIONS	16

9.2	Drug Interactions Overview.....	16
9.3	Drug-Behavioural Interactions	16
9.4	Drug-Drug Interactions.....	16
9.5	Drug-Food Interactions	16
9.6	Drug-Herb Interactions.....	16
9.7	Drug-Laboratory Test Interactions	16
10	CLINICAL PHARMACOLOGY	16
10.1	Mechanism of Action.....	16
10.2	Pharmacodynamics	17
10.3	Pharmacokinetics	17
11	STORAGE, STABILITY AND DISPOSAL	18
12	SPECIAL HANDLING INSTRUCTIONS.....	18
PART II: SCIENTIFIC INFORMATION.....		19
13	PHARMACEUTICAL INFORMATION.....	19
14	CLINICAL TRIALS.....	20
14.1	Clinical Trials by Indication	20
	Indication: Treatment of 5q Spinal Muscular Atrophy	20
15	MICROBIOLOGY	38
16	NON-CLINICAL TOXICOLOGY	38
PATIENT MEDICATION INFORMATION.....		39

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SPINRAZA (nusinersen) is indicated for:

- the treatment of 5q Spinal Muscular Atrophy (SMA).

There are limited data in patients over the age of 18 years. SPINRAZA has been studied in patients ranging in age from newborn to 19 years (see [14 CLINICAL TRIALS](#)).

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 [14 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.

1.1 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SPINRAZA in pediatric patients has been established (see [14 CLINICAL TRIALS](#)).

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

SPINRAZA 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- SPINRAZA 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.
- Doses of SPINRAZA should be at least 14 days apart.
- In the case of a delayed or missed dose, follow the recommended dosing schedule outlined in Table 1 (see [4.5 Missed Dose](#)).

4.2 Recommended Dose and Dosage Adjustment

- **Pediatrics (<18 years of age):** 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.
- **Adults (≥ 18 years of age):** Clinical studies of SPINRAZA have included patients from newborn up to 19 years of age. There is limited data involving the use of SPINRAZA in adults. However, no dose adjustment is required.
- **Geriatrics:** There is no data from patients over the age of 65 years.
- **Patients with Hepatic Insufficiency:** The pharmacokinetics of nusinersen in patients with hepatic impairment has not been studied. 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 [10.3 Pharmacokinetics](#)).
- **Patients with Renal Insufficiency:** The pharmacokinetics of nusinersen in patients with renal impairment has not been studied.

4.4 Administration

Preparation of dose

1. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25°C/77°F) 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 into the syringe, if the solution is not used within 6 hours, it must be discarded.

4.5 Missed Dose

Based on population pharmacokinetics, the impact of a delayed or missed dose on median nusinersen CSF exposures was found to be strongly dependent on both the duration of dosing interruption and the phase in which the interruption occurred.

If a loading or a maintenance dose is delayed or missed, SPINRAZA should be administered according to the schedule in Table 1, below.

Table 1: Dosing administration of delayed or missed dose¹

2nd or 3rd Loading Dose	Timing of Dosing Administration
any delay [†]	<ul style="list-style-type: none"> Administer the delayed or missed loading dose as soon as possible, with at least 14 days between doses; then Continue with subsequent doses on the prescribed intervals from the last dose. <p>† If the third loading dose is administered ≥ 8 months from last dose, follow the same recommendations as for the maintenance dose for the same duration of dose interruption.</p> <p>† If a loading dose is delayed ≥ 40 months from the last dose, restart the entire loading regimen on the prescribed intervals.</p>
4th Loading Dose	Timing of Dosing Administration
≤ 5 months from the 3 rd loading dose	<ul style="list-style-type: none"> Administer the delayed loading dose as soon as possible; then The first maintenance dose 4 months later; then Subsequent maintenance doses every 4 months.
> 5 to < 8 months from the 3 rd loading dose	<ul style="list-style-type: none"> Administer the delayed loading dose as soon as possible; then Reschedule the first maintenance dose to 8 months from the 3rd loading dose, with at least 14 days between doses; then Continue with subsequent maintenance doses 4 months after the last dose and repeat every 4 months.
≥ 8 to < 16 months from the 3 rd loading dose	<ul style="list-style-type: none"> Administer the missed dose as soon as possible; then The next dose 14 days later; then An additional dose 14 days later; then A maintenance dose 4 months after the last dose and repeat every 4 months.
≥ 16 to < 40 months from last dose	<ul style="list-style-type: none"> Administer the missed dose as soon as possible; then The next dose 14 days later; then An additional dose 14 days later; then A maintenance dose 4 months after the last dose and repeat every 4 months.

≥ 40 months from the 3 rd loading dose	<ul style="list-style-type: none"> Administer the entire loading regimen on the prescribed intervals (Days 0, 14, 28 and 63); then A maintenance dose 4 months after the last dose and repeat every 4 months.
Maintenance dose	Timing of Dosing Administration
> 4 to < 8 months from last dose	<ul style="list-style-type: none"> Administer the delayed maintenance dose as soon as possible; then The next maintenance dose per the original scheduled date, as long as these two doses are administered at least 14 days apart; then A maintenance dose 4 months after the last dose and repeat every 4 months.
≥ 8 to < 16 months from last dose	<ul style="list-style-type: none"> Administer the missed dose as soon as possible; then The next dose 14 days later; then A maintenance dose 4 months after the last dose and repeat every 4 months.
≥ 16 to < 40 months from last dose	<ul style="list-style-type: none"> Administer the missed dose as soon as possible; then The next dose 14 days later; then An additional dose 14 days later; then A maintenance dose 4 months after the last dose and repeat every 4 months.
≥ 40 months from last dose	<ul style="list-style-type: none"> Administer the entire loading regimen on the prescribed intervals (Days 0, 14, 28 and 63); then A maintenance dose 4 months after the last dose and repeat every 4 months.

¹ Cutoff values allow some flexibility (\pm several days) as long as closest doses are administered at least 14 days apart.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
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intrathecal by lumbar puncture	solution for intrathecal injection 2.4 mg/mL	calcium chloride dihydrate, disodium phosphate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection
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*Sodium hydroxide and hydrochloric acid may be used for pH adjustment.

SPINRAZA is a clear and colourless solution (2.4 mg/mL) with a pH of 7.2. SPINRAZA is supplied as 5mL in a single-use Type I vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap. Pack size: one vial per carton.

7 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 [4.1 Dosing Considerations](#); [8.5 Post-Market Adverse Reactions](#)).

Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY](#).

Cardiovascular

See [8.2 Clinical Trial Adverse Reactions](#).

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 [7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests](#)).

Monitoring and Laboratory Tests

Conduct the following laboratory tests at baseline and as clinically indicated:

- Platelet count (see [7 WARNINGS AND PRECAUTIONS, Hematologic](#))
- Prothrombin time; activated partial thromboplastin time (see [7 WARNINGS AND PRECAUTIONS, Hematologic](#))
- Quantitative spot urine testing (see [7 WARNINGS AND PRECAUTIONS, Renal](#))

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 [10.3 Pharmacokinetics](#)).

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.

Reproductive Health: Female and Male Potential

- **Fertility**

The effects of SPINRAZA on labor and delivery are not known.

7.1 Special Populations

7.1.1 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 [16 NON-CLINICAL TOXICOLOGY](#)).

7.1.2 Breast-feeding

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. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 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 (see [16 NON-CLINICAL TOXICOLOGY](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In sham-controlled and open-label clinical studies, a total of 346 SMA patients were treated with SPINRAZA and total time on study ranged from 6 to 2028 days (median 627 days). The experience in open-label clinical trials is consistent with the experience in the sham-controlled clinical trials.

The adverse reactions presented below are based on safety information from two phase 3 randomized, double-blind, sham-controlled clinical trials (Study 1 and Study 2). 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).

The most common adverse events (>10%) reported in the clinical trials more frequently with SPINRAZA than with sham-control were respiratory events (upper respiratory tract infection, pneumonia, nasopharyngitis, respiratory tract infection), gastrointestinal events (constipation, vomiting, teething), events considered related to the lumbar puncture procedure (headache, back pain), and pyrexia.

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

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 3: 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

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

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 4: 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

	SPINRAZA n = 84 (%)	Control n = 42 (%)
Any adverse event	78 (93%)	42 (100)
Gastrointestinal disorders		
Vomiting*	24 (29%)	3 (7%)

	SPINRAZA n = 84 (%)	Control n = 42 (%)
General disorders and administration site conditions		
Pyrexia	36 (43%)	15 (36%)
Musculoskeletal and connective tissue disorders		
Back pain*	21 (25%)	0
Nervous system disorders		
Headache*	24 (29%)	3 (7%)
Respiratory thoracic and mediastinal disorders		
Epistaxis	6 (7%)	0

* 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 247 patients 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.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent adverse events that were reported in clinical trials (for infantile-onset and later-onset SMA) with a frequency greater than 5% and not presented in Section 8.2 are summarized below by system organ class and preferred term.

Events are categorized by system organ class alphabetically with preferred terms listed in decreasing order of incidence in SPINRAZA-treated patients.

Cardiac disorders: tachycardia.

Gastrointestinal disorders: diarrhea, gastroesophageal reflux disease, dysphagia.

Infections and infestations: conjunctivitis, gastroenteritis, viral infection, bronchiolitis, pneumonia viral, rhinovirus infection, viral upper respiratory tract infection, gastroenteritis viral, otitis media.

Investigations: oxygen saturation decreased.

Respiratory, thoracic and mediastinal disorders: cough, respiratory distress, respiratory failure, atelectasis, rhinorrhea, acute respiratory failure, nasal congestion, pneumonia aspiration.

8.5 Post-Market Adverse Reactions

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 [4.1 Dosing Considerations](#); [7 WARNINGS AND PRECAUTIONS](#)). Hydrocephalus, aseptic meningitis, and hypersensitivity (e.g. angioedema, urticaria, rash) have also been observed.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

There is no data available, regarding interactions of SPINRAZA with other drugs, herbal remedies, lifestyle, food, or laboratory tests.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

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

Nusinersen is metabolized via nucleases and not by the cytochrome P450 (CYP450) system (see [10.3 Pharmacokinetics](#)).

In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism (see [10.3 Pharmacokinetics](#)).

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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.

10.3 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.

Across nusinersen studies, median CSF trough concentrations of nusinersen accumulated approximately 2-fold over the loading phase, as compared to the median trough concentration after the first dose. A steady state is reached within approximately 24 months.

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:

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

- **Pediatrics:** The pharmacokinetic properties of nusinersen have been characterized using data from clinical studies conducted in pediatric patients.
- **Geriatrics:** No assessment of SPINRAZA pharmacokinetics in patients 65 years of age was conducted.
- **Sex:** Population pharmacokinetic analysis showed that gender does not affect the pharmacokinetics of nusinersen.
- **Pregnancy and Breast-feeding:** There are no data from clinical studies on the use of SPINRAZA during pregnancy in humans. It is not known if nusinersen is present in human breast milk. There are no data on the use of SPINRAZA during lactation.
- **Ethnic Origin:** As assessed by population PK analysis, ethnic origin is unlikely to affect the pharmacokinetics of nusinersen.
- **Hepatic Insufficiency:** The pharmacokinetics of nusinersen in patients with hepatic impairment have not been studied.
- **Renal Insufficiency** The pharmacokinetics of nusinersen in patients with renal impairment have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated at 2°C to 8°C (36°F to 46°F). 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 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 25°C (77°F).

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.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling required.

PART II: SCIENTIFIC INFORMATION

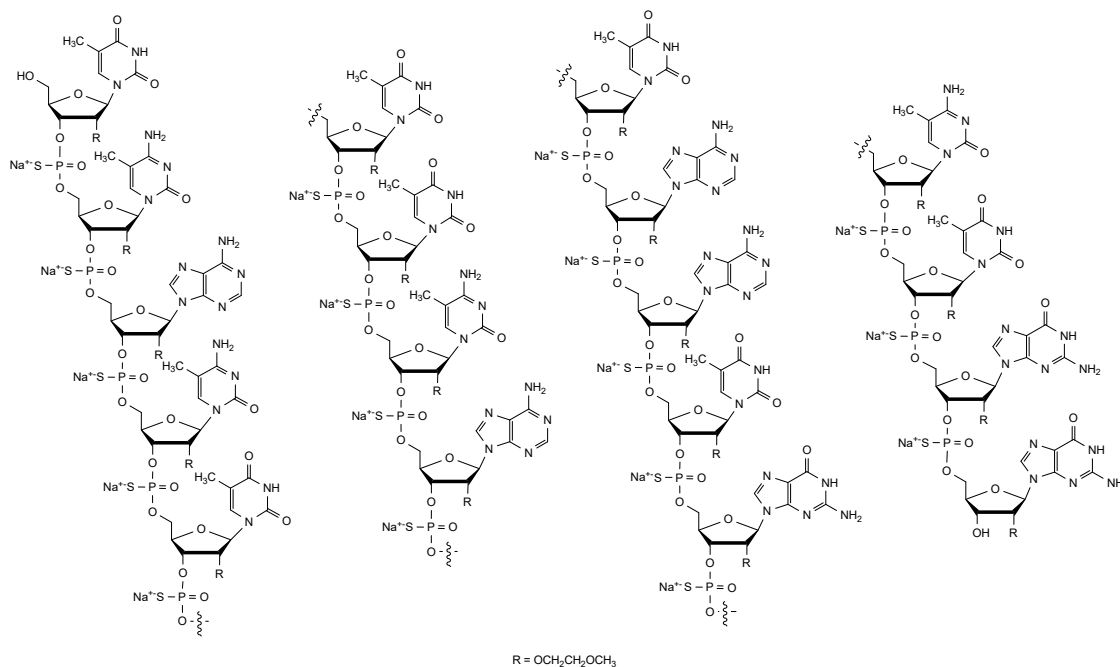
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: nusinersen sodium

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 sodium 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 free acid in artificial cerebral spinal fluid.

Each vial of SPINRAZA contains a 5 ml solution with 12 mg nusinersen free acid (2.4 mg/ml), equivalent to 12.6 mg nusinersen sodium, with an adjusted pH of approximately 7.2.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication: Treatment of 5q Spinal Muscular Atrophy

Table 5 - Summary of patient demographics for clinical trials in patients with SMA

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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 Intrathecal administration Study duration: ~13 months; study terminated early	121 Population Studied: Most likely to develop Type I SMA SMN2 gene copies: 2 (120), 3 (1)	Median age at symptom onset 8 weeks (range 1 to 20 weeks) Median age at first dose: 175 days (range 30 to 262 days)	45% male 55% female

<p>Study 2 (CHERISH ; CS4)</p>	<p>Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled in subjects with symptomatic later-onset SMA [Completed]</p>	<p>12 mg scaled equivalent dose or sham-procedure (2:1) Loading dose: Days 1, 29 and 85 Maintenance dose: Day 274 Intrathecal administration Study duration: ~15 months; study terminated early</p>	<p>126 Population Studied: SMN2 gene copies: 2 (10), 3 (111), 4 (3), unknown (2)</p>	<p>Median age at symptom onset: 11 months (range: 6 to 20 months) Median age at first dose: 3.95 years (range 2.1 to 9.2)</p>	<p>47% male 53% female</p>
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<p>Study 3 (CS3A)</p>	<p>Phase 2, open-label, multiple-dose in subjects with symptomatic infantile-onset SMA [Completed]</p>	<p>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. Intrathecal administration Study duration: ~3.7 years; study terminated early</p>	<p>20 Population Studied: Most likely to develop Type I or Type II SMA SMN2 gene copies: 2 (17), 3 (2), unknown (1)</p>	<p>Median age at symptom onset 56 days (range: 21 to 154 days) Median age at first dose: 162 days (range 37 to 223 days)</p>	<p>60% male 40% female</p>
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<p>Study 4 (NURTUR E; CS5; SM201)</p>	<p>Phase 2, open-label study in pre symptomatic infants genetically diagnosed with SMA [Ongoing]</p>	<p>12 mg scaled equivalent loading and maintenance doses of nusinersen on day 1, 15, 29, 64, 183, and every 4 months thereafter. Intrathecal administration Study duration: ~8 years</p>	<p>25 Population Studied: SMN2 gene copies: 2 (5), 3 (10)</p>	<p>Median age at first dose: 22 days (range 3 - 42 days)</p>	<p>48% male 52% female</p>
<p>Study 5 (EMBRAC E; SM202)</p>	<p>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]</p>	<p>12 mg scaled equivalent dose or sham procedure (2:1) at Days 1, 15, 29, 64, 183, and 302 Intrathecal administration Study duration: Part 1: ~13 months, study terminated early Part 2: ~28 months</p>	<p>21 Population studied: SMN2 gene copies: 2(7), 3(14)</p>	<p>Median age at symptom onset: 5.1 months (range: 1.8 to 11 months) Age at symptom onset ≤6 months: 62% > 6 months: 38% Median age at first dose: 17 months (range: 7 to 53 months)</p>	<p>52% male 48% female</p>

<p>Study 6 (SHINE; CS11)</p>	<p>Phase 3, open-label, extension in subjects who previously participated in Study CS3A, CS3B, CS4, CS12 [Ongoing]</p>	<p>12 mg scaled equivalent loading dose</p> <p>Group 1A (subjects who received sham procedure in CS3B): nusinersen on Days 1, 15, 29, and 64</p> <p>Group 1B (subjects who received nusinersen in CS3B): 3 sham procedures on Days 1, 15, and 64; and nusinersen on Day 29</p> <p>Group 2A (subjects who received sham procedure in CS4): nusinersen on Days 1, 29, and 85</p> <p>Group 2B (subjects who received nusinersen in CS4): nusinersen on Days 1 and 85, and sham procedure on Day 29</p> <p>Day 1 of maintenance dose of nusinersen for</p>	<p>100 infantile- and 170 later-onset</p> <p>Population studied: SMN2 gene copies: Infantile-onset: 2 (97), 3 (3) Later-onset: 2 (10), 3 (147), 4 (10), unknown (3)</p>	<p>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)</p> <p>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)</p>	<p>Infantile-onset: 43% male 57% female</p> <p>Later-onset: 47% male 53% female</p>
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		<p>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.</p> <p>Intrathecal administration</p> <p>Study duration: ~5 years after Day 1 of maintenance dose.</p>			
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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.

Study Results

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 \leq 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).

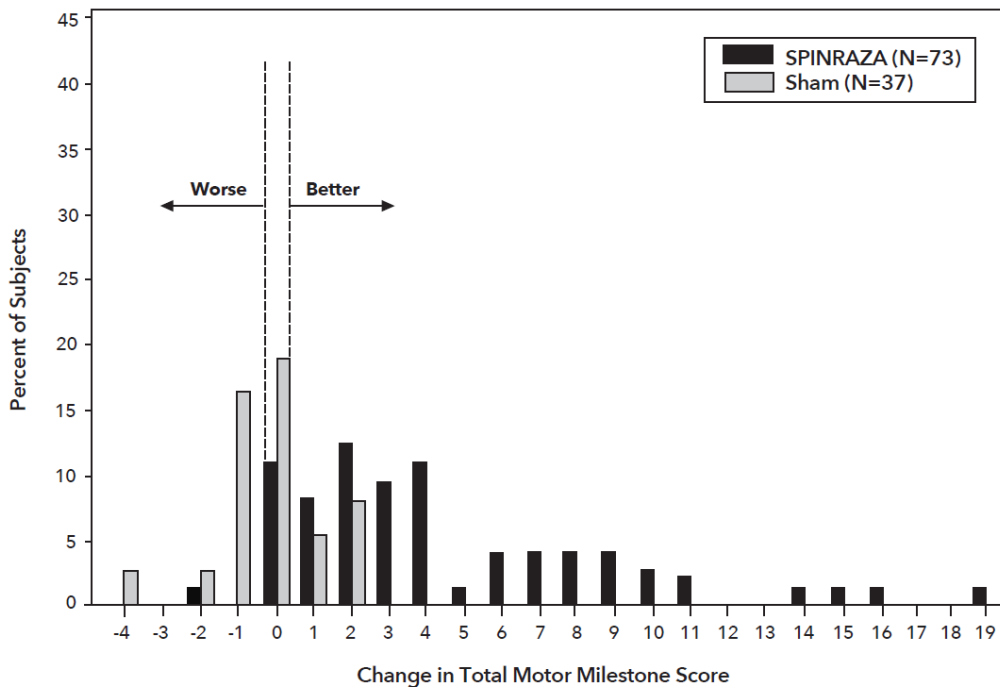
In the efficacy set, 51% of patients in the SPINRAZA group achieved the definition of motor milestone responder compared to 0% in the sham control group at the final analysis ($p < 0.0001$). The proportion of responders increased over time in patients in the SPINRAZA group with 41% responders at 6 months (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 6 - Primary and secondary endpoints at final analysis – Study 1

Efficacy Parameter	SPINRAZA, 12 mg	Sham-control Patients
Survival		
Event-free survival¹ (Number of patients who died or received permanent ventilation)	31 (39%)	28 (68%)
Hazard ratio (95% CI) p-value ²	0.53 (0.32, -0.89) P = 0.0046	
Overall survival¹ Number of patients who died	13 (16%)	16 (39%)
Hazard Ratio (95% CI) p-value ²	0.37 (0.18 – 0.77) p=0.0041	
Motor Function		
Motor milestones³ (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-INTEND³		
Proportion achieving a 4-point improvement	52 (71%) P< 0.0001	1 (3%)
Proportion achieving a 4-point worsening	2 (3%)	14(46%)
Proportion with any improvement	53 (73%)	1 (3%)
Proportion with any worsening	5(7%)	18 (49%)

¹At 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).

²Based on log-rank test stratified by disease duration

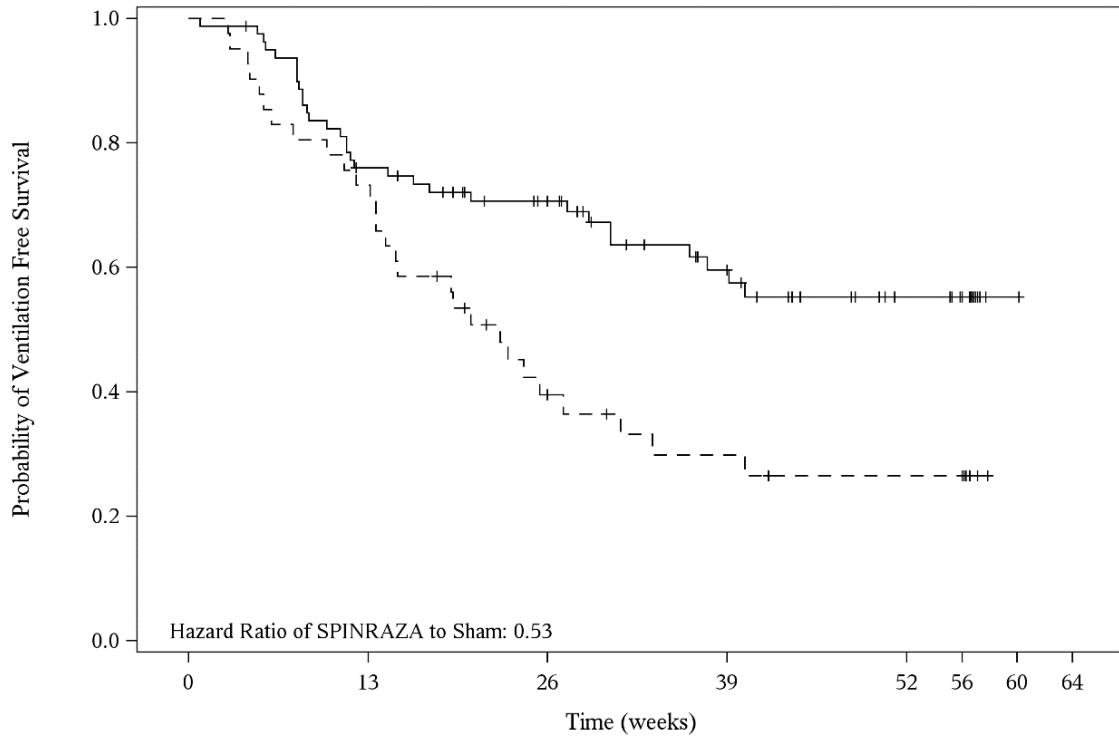
³At the final analysis, CHOP-INTEND and motor milestone analyses were conducted using the Efficacy Set (SPINRAZA n=73; Sham-control n=37).

⁴Assessed at the later of Day 183, Day 302, and Day 394 Study Visit

⁵According 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.

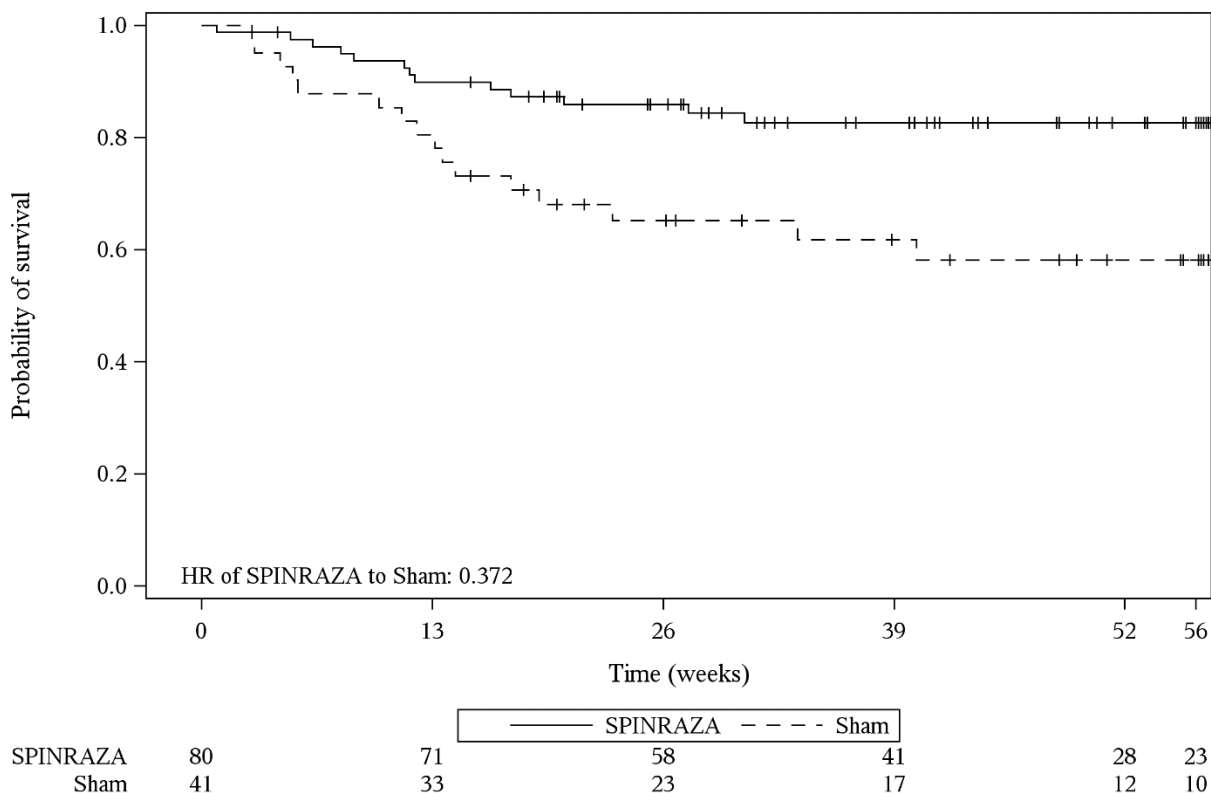
⁶The proportion of motor milestones responders at Day 183, Day 302, and Day 394 are based on efficacy sets at those visits

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



	0	13	26	39	52	56	60	64
SPINRAZA	80	59	46	29	16	13	1	0
Sham	41	30	14	9	7	7	0	

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.

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.

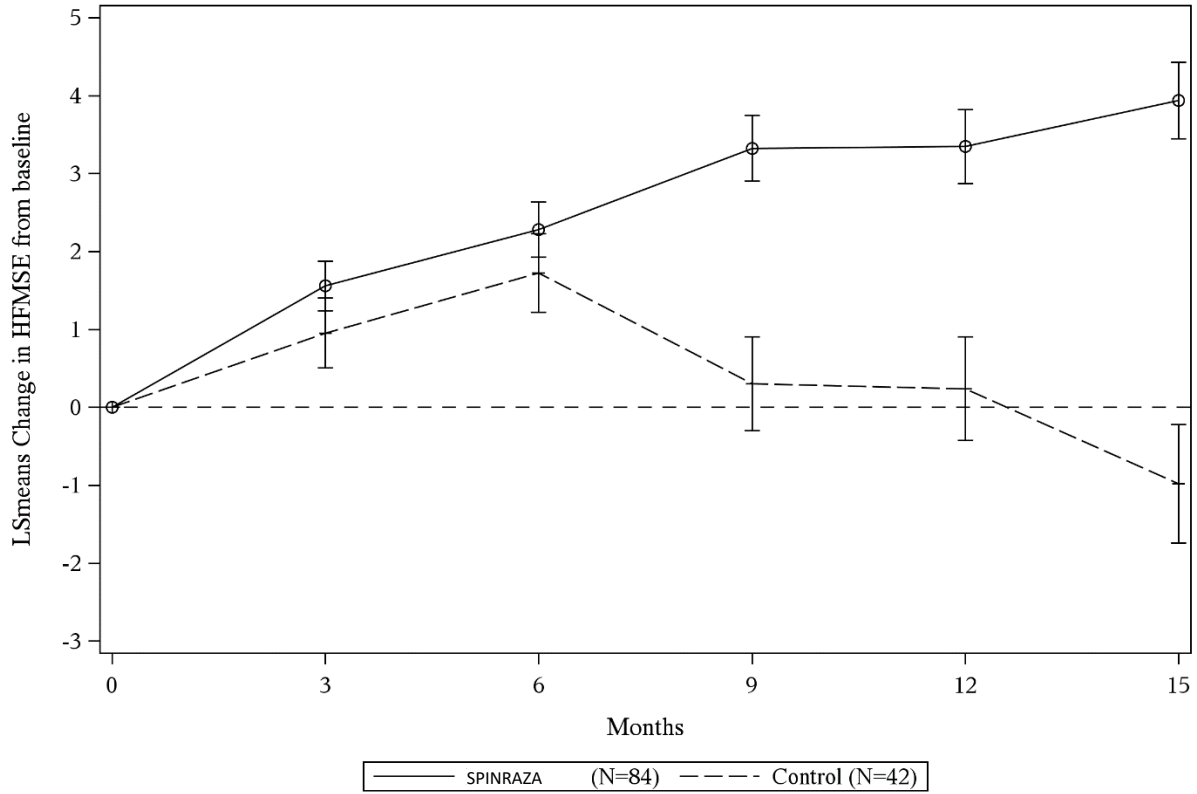
The proportion of subjects achieving new WHO motor milestones (without worsening in any baseline motor milestones) in the SPINRAZA group and sham-control groups was 19.7% and 5.9%, respectively, for a difference of 13.8% (p =0.0811). At 15 months, 1 of the 66 (2%) subjects in the SPINRAZA group compared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



¹Data for patients without a Month 15 visit were imputed using the multiple imputation method

²Error bars denote +/- standard error

Table 7 – Primary and secondary endpoints at final analysis – Study 2

	SPINRAZA, 12 mg	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)
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

¹Assessed 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

²Least squares mean

³Negative value indicates worsening, positive value indicates improvement.

⁴Assessed using the Month 15 Efficacy Set (SPINRAZA n=66; Sham control n=34; analyses are based on imputed data when there are missing data.

⁵Based 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=25, 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 [7.1.3 Pediatrics](#)).

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

Carcinogenicity: Nusinersen did not demonstrate significant carcinogenic potential in a 2-year mouse carcinogenicity study in which the drug was administered by subcutaneous injection at dose levels of 5, 15, and 50 mg/kg every 2 weeks for 104 weeks. Nusinersen had no effect on survival or the incidence of palpable masses, or microscopic neoplasias. Slight increases in the incidence of uterine hemangiomas were noted in females receiving mid to high doses. Myocardial infiltration and/or fibrosis was observed in male animals and some females.

Reproductive and Developmental Toxicology: 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.

Juvenile Toxicity: No juvenile toxicity studies were conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSPINRAZA

nusinersen injection

Read this carefully before you or your child start receiving **SPINRAZA** and each time you receive a 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**.

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 belongs to 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:

Solution for intrathecal (lower spinal cord) injection: 2.4 mg/mL

Do not use SPINRAZA if:

- You or your child are allergic to nusinersen or to any of the other ingredients in SPINRAZA or its container.

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

- have known reasons why you or your child should not have a lumbar puncture (lower spinal cord injection). These may include:
 - a skin infection near the site of the lumbar puncture;
 - increased pressure within the skull;
 - uncontrolled problems with blood clotting;
 - recent injury or damage to the spinal cord.
- have a ventriculo-peritoneal shunt (a small tube that helps drain extra cerebrospinal fluid from the brain). It is used to treat hydrocephalus (buildup of fluid in the brain).
- have been told by a healthcare professional that you/your child have low levels of platelets in the blood.
- have kidney problems.
- are pregnant, think you might be pregnant or are planning to have a baby.
- are breastfeeding or are planning to breastfeed.

Other warnings you should know about:

SPINRAZA can cause serious side effects, including:

- **Blood clotting problems and risk of bleeding:** After receiving medicines similar to SPINRAZA, some patients had:
 - low levels of platelets (blood cells that help stop bleeding) that came and went without affecting blood clotting;
 - severely low levels of platelets;
 - abnormal blood clotting.You or you child may be at risk of bleeding complications during treatment with SPINRAZA.
- **Hydrocephalus** (buildup of fluid in the brain): In patients treated with SPINRAZA there have been reports of hydrocephalus that were not due to bleeding or meningitis (inflammation of the protective membranes of the brain and spinal cord). If you or your child experience signs or symptoms of hydrocephalus during treatment with SPINRAZA, **seek immediate medical attention**. You/your child may require treatment with a ventriculo-peritoneal shunt (a small tube that helps drain extra cerebrospinal fluid from the brain).
- **Kidney toxicity** (damage to the kidneys): 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.

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.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Pregnancy: It is not known if SPINRAZA can harm an unborn baby. Therefore, SPINRAZA is not recommended during pregnancy. If you discover that you are pregnant while taking SPINRAZA, tell your healthcare professional **right away**.

Breastfeeding: It is not known if SPINRAZA can pass into breast milk and harm a breastfed baby. Talk to your healthcare professional about other ways to feed your baby during your treatment with SPINRAZA.

Check-ups and testing: Your healthcare professional will do tests before you or your child start receiving SPINRAZA and during treatment if needed. These tests may include:

- blood tests to monitor:
 - the level of platelets in the blood.
 - your or your child’s blood clotting.
- urine tests to monitor the health of your or your child’s kidneys.

Tell your healthcare professional about all the medicines you or your child 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 medicines 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 (intrathecal). It should not be injected anywhere else, or taken any other way;
 - will be given by a healthcare professional experienced in doing lumbar punctures and will be done in a healthcare setting;
 - 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.
- Your healthcare professional will tell you how long you or your child need to keep receiving SPINRAZA. Don’t stop treatment with SPINRAZA unless your healthcare professional tells you to.
- Ask your healthcare professional if you have any questions about how SPINRAZA is given.

Usual dose:

The recommended 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:

If you think you, or a person you are caring for, have been given too much SPINRAZA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child were unable to receive SPINRAZA on the planned date, contact your healthcare professional **right away**. SPINRAZA should be given as soon as possible after a missed dose.

What are possible side effects from using SPINRAZA?

These are not all the possible side effects you may have when receiving SPINRAZA. If you experience any side effects not listed here, tell your healthcare professional.

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

For the side effects that were likely a result of the lumbar puncture, see the **Serious side effects and what to do about them** table (under **Injection site/lumbar puncture reactions**).

Tell your healthcare professional if you or your child experience any of the side effects listed above. Do not treat them yourself. **Contact your healthcare professional if you or your child have any side effects that bother you/your child or that do not go away.**

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN FREQUENCY			
Allergic reaction / Angioedema: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): confusion, fever, nausea, sudden headache or stiffness of your neck, sensitivity to light, vomiting		√	
Blood clotting problems and risk of bleeding: bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	
Hydrocephalus (buildup of fluid in the brain): increase in head size or bulging soft spot on top of the head (fontanel) in infants, decreased consciousness, persistent nausea, vomiting or headache		√	
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		√	
Injection site/ lumbar puncture reactions: back pain, dizziness, feeling nauseous or throwing up, headache, pain during the injection, serious infections		√	
Kidney toxicity (damage to the kidneys): back and abdominal pain, change in the colour of urine (pale or dark) decrease in amount of urine produced, pain or discomfort when urinating, swelling of the legs and ankles		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) 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 2°C to 8°C.
- May be stored at up to 30°C 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.biogen.ca or by calling 1-844-483-3360.

This leaflet was prepared by Biogen Canada Inc.

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