

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spinraza 12 mg solution for injection
Spinraza 28 mg solution for injection
Spinraza 50 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spinraza 12 mg

Each 5 ml single use vial contains nusinersen sodium equivalent to 12 mg nusinersen.
Each ml contains 2.4 mg of nusinersen.

Spinraza 28 mg

Each 5 ml single use vial contains nusinersen sodium equivalent to 28 mg nusinersen.
Each ml contains 5.6 mg of nusinersen.

Spinraza 50 mg

Each 5 ml single use vial contains nusinersen sodium equivalent to 50 mg nusinersen.
Each ml contains 10 mg of nusinersen.

Excipients with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution with pH of approximately 7.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.

4.2 Posology and method of administration

Treatment with Spinraza should only be initiated by a physician with experience in the management of spinal muscular atrophy (SMA).

The decision to treat should be based on an individualised expert evaluation of the expected benefits of treatment for that individual, balanced against the potential risk of treatment with Spinraza. Patients with profound hypotonia and respiratory failure at birth, where Spinraza has not been studied, may not experience a clinically meaningful benefit due to severe survival motor neuron (SMN) protein deficiency.

Posology

Two dosing regimens are available. A low dose regimen of 12 mg, and a high dose regimen of 50/28 mg. Spinraza treatment should be initiated as early as possible after diagnosis.

Low dose regimen

This regimen is administered with a loading dose of 12 mg on Day 0, 14, 28 and 63, and a maintenance dose of 12 mg once every 4 months thereafter.

High dose regimen

A 50 mg loading dose should be administered on Day 0 and on Day 14. A maintenance dose of 28 mg should be administered once every 4 months thereafter.

Switching low dose regimen to the high dose regimen

Patients currently treated with Spinraza 12 mg may be transitioned to the 50/28 mg dosing regimen with one loading dose of 50 mg administered at least 4 months (+/- 14 days) after the last dose of 12 mg. The maintenance dose of 28 mg should be administered once every 4 months thereafter.

Duration of treatment

The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy.

Missed or delayed doses

If a loading or a maintenance dose is delayed or missed, Spinraza should be administered according to the schedule in Table 1 and Table 2 below for the 12 mg and 50/28 mg dosing regimens, respectively.

Table 1: Recommendations for delayed or missed dose for 12 mg dosing regimen

Delayed or Missed dose	Timing of Dosing Administration
Loading dose	
Administer the delayed or missed loading dose as soon as possible with at least 14 days between doses; continue with subsequent doses on the prescribed intervals from the last dose. e.g. if the third loading dose is administered 30 days late at Day 58 (instead of the original schedule at Day 28), then the fourth loading dose should be administered 35 days later at Day 93 (instead of the original schedule at Day 63) with a maintenance dose 4 months thereafter.	
Maintenance dose	Timing of Dosing Administration
> 4 to < 8 months from last dose	- 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*;
≥ 8 to < 16 months from last dose	Administer the missed dose as soon as possible and then the next dose 14 days later*;
≥ 16 to < 40 months from last dose	Administer the missed dose as soon as possible and then the next dose 14 days later, followed by a third dose 14 days later*;
≥ 40 months from last dose	Administer the entire loading regimen on the prescribed intervals (Days 0, 14, 28 and 63)*;
* Then subsequently to the above recommendations, a maintenance dose 4 months after the last dose should be administered and repeated every 4 months.	

Table 2: Recommendations for delayed or missed dose for 50/28 mg dosing regimen

Delayed or Missed Dose	Timing of Dosing Administration
Second loading dose	
- If time since last dose is less than 4.5 months, administer the missed 50 mg loading dose as soon as possible; administer the 28 mg maintenance dose per the original scheduled date, as long as these two doses are administered at least 14 days apart; then administer 28 mg every 4 months thereafter. - If time since last dose is 4.5 months to less than 8.5 months, administer the missed 50 mg loading dose as soon as possible; followed by the 28 mg maintenance dose 14 days later, then administer the next 28 mg maintenance dose 4 months thereafter. - If time since last dose exceeds 8.5 months, restart regimen.	
Maintenance dose	
<8 months from last dose	- Administer the missed dose as soon as possible; then - Administer the next maintenance dose per the original scheduled date, as long as these two doses are administered at least 14 days apart; then - Administer next maintenance doses every 4 months thereafter.
8 months to <12 months from last dose	- Administer the delayed dose as soon as possible; then - Administer one additional maintenance dose 14 days later; then - Administer next maintenance doses every 4 months thereafter
≥12 months from last dose	Restart regimen

Special populations

Renal impairment

Nusinersen has not been studied in patients with renal impairment. The safety and efficacy in patients with renal impairment has not been established and they should be closely observed.

Hepatic impairment

Nusinersen has not been studied in patients with hepatic impairment. Nusinersen is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment (see sections 4.5 and 5.2).

Method of administration

Spinraza is for intrathecal use by lumbar puncture.

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

Spinraza is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anaesthesia needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid (CSF), equivalent to the volume of Spinraza to be injected, is removed from the patient prior to administration of Spinraza.

Sedation may be required to administer Spinraza, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of Spinraza, particularly in younger patients and in patients with scoliosis; see instructions for use in section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lumbar puncture procedure

There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. arachnoiditis, headache, back pain, vomiting; see section 4.8). Potential difficulties with this route of administration may be seen in very young patients and those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration of Spinraza, can be considered at the physician's discretion. Should arachnoiditis be suspected, an MRI should be performed to confirm arachnoiditis and the extent of the inflammation. Identification of arachnoiditis precludes the use of the injection site until local inflammation has been ruled out.

Thrombocytopenia and coagulation abnormalities

Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides. If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of Spinraza.

Renal toxicity

Renal toxicity has been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.

Hydrocephalus

There have been reports of communicating hydrocephalus not related to meningitis or bleeding in patients treated with nusinersen 12 mg 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.

Excipients

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml vial, that is to say essentially 'sodium-free'.

Potassium

This medicinal product contains potassium, less than 1 mmol (39 mg) per 5 ml vial, i.e. essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. *In vitro* studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism. *In vitro* studies indicate that the likelihood for

interactions with nusinersen due to competition for plasma protein binding, or competition with or inhibition of transporters is low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of nusinersen in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of nusinersen during pregnancy.

Breast-feeding

It is unknown whether nusinersen/metabolites are excreted in human milk.

A risk to the newborn/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from nusinersen therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In toxicity studies in animals no effects on male or female fertility were observed (see section 5.3). There are no data available on the potential effects on fertility in humans.

4.7 Effects on ability to drive and use machines

Nusinersen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions (ADRs) associated with the administration of nusinersen by lumbar puncture were headache, vomiting, and back pain.

Experience from administering 12 mg dosing regimen

The safety of Spinraza 12 mg was assessed in clinical trials based on two Phase 3 clinical studies in infants (CS3B) and children (CS4) with SMA, together with one Phase 2 study in infants and children with SMA (CS7) and open-label studies including presymptomatic infants (CS5) genetically diagnosed with SMA and infants and children with SMA. Study CS11 enrolled infantile and later-onset patients including those who had completed studies CS3B, CS4 and CS12.

A total of 385 SMA patients were treated with Spinraza 12 mg or lower and total time on study ranged from 1 to 3940 days (>10 years) (median 2388 days).

Experience from administering 50/28 mg dosing regimen

The safety of Spinraza at 50/28 mg in infants, children and adults with SMA was assessed in study SM203 and study SM302 in symptomatic SMA patients who ranged in age from 14 days to 65 years at the time of first study dose.

A total of 128 SMA patients were treated with Spinraza 50 mg or 28 mg and total time on study ranged from 13 to 1521 days (>4 years) (median 740.5 days).

Tabulated list of adverse reactions

The safety assessment of nusinersen is based on data from patients from clinical trials and from post-marketing surveillance. The ADRs associated with nusinersen administration are summarised in Table 3.

The assessment of undesirable effects is based on the following frequency data:

Very common ($\geq 1/10$)

Not known (cannot be estimated from the available data)

Table 3: Adverse reactions related to Spinraza administration

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Meningitis	Not known
Immune system disorders	Hypersensitivity*	Not known
Nervous system disorders	Headache**	Very common
	Aseptic meningitis	Not known
	Arachnoiditis	Not known
Gastrointestinal disorders	Vomiting**	Very common
Musculoskeletal and connective tissue disorders	Back pain**	Very common
General Disorders and Administration Site Conditions	Pyrexia	Very common

*e.g. angioedema, urticaria and rash.

** Adverse reactions considered related to the lumbar puncture procedure. These reactions can be considered manifestations of post-lumbar puncture syndrome. These adverse reactions were reported in CS4 (later onset SMA) with an incidence at least 5% higher in patients treated with Spinraza 12 mg (n=84) compared to Sham control.

Events of communicating hydrocephalus have been observed in the post-marketing setting (see section 4.4).

Description of selected adverse reactions

Adverse reactions associated with the administration of nusinersen by lumbar puncture have been observed. The majority of these are reported within 72 hours of the procedure. The incidence and severity of these events were consistent with events expected to occur with lumbar puncture. No serious complications of lumbar puncture, such as serious infections, have been observed in the clinical trials of nusinersen.

Some adverse reactions commonly associated with lumbar puncture (e.g. headache and back pain) could not be assessed in the infant population exposed to nusinersen due to the limited communication appropriate for that age group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

Malta

ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

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

In the event of an overdose, supportive medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX07

Mechanism of action

Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein.

SMA is a progressive neuromuscular disease resulting from mutations in chromosome 5q in the SMN1 gene. A second gene SMN2, located near SMN1, is responsible for a small amount of SMN protein production. SMA is a clinical spectrum of disease with disease severity linked to fewer numbers of SMN2 gene copies and younger age of symptom onset.

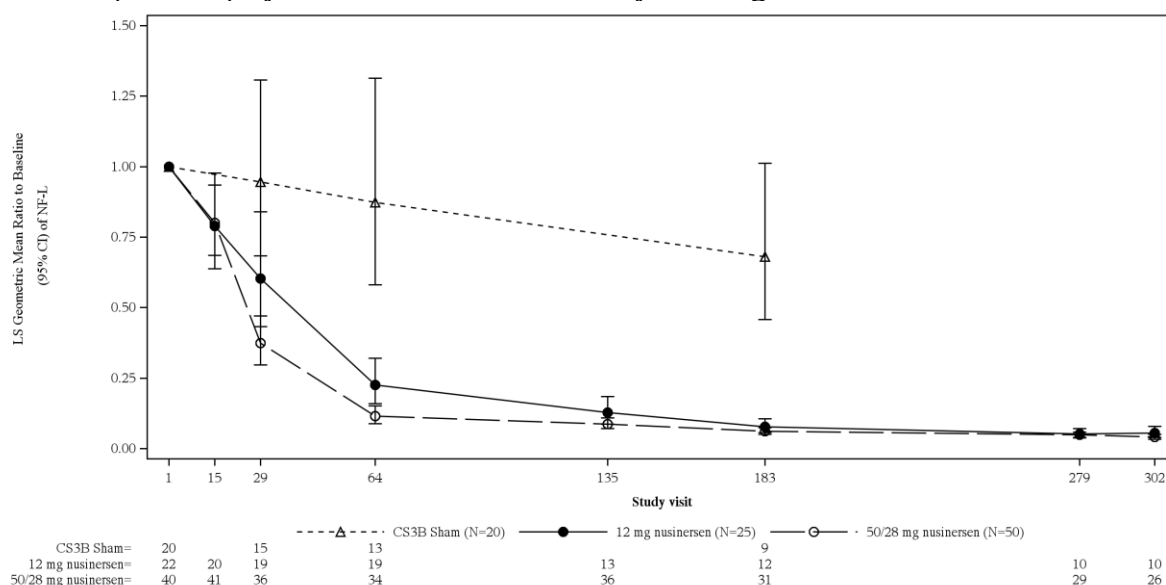
Plasma neurofilament light chain (Nf-L)

Levels of plasma neurofilament light chain (Nf-L), a blood-based marker of axonal injury were measured at baseline and at several timepoints in study SM203 assessing the 50/28 mg dosing regimen in patients with infantile-onset and later-onset SMA.

Levels of plasma Nf-L were reduced more rapidly in the 50/28 mg group compared to the 12 mg group with an 88% reduction from baseline to Day 64 in the 50/28 mg group, compared to a 77% reduction in the 12 mg group (difference in geometric mean ratios for 50/28 mg group to 12 mg group: 49%; ($p = 0.0035$)) (Figure 1).

Similarly, treatment naïve patients with later-onset SMA experienced reductions of 62% in plasma Nf-L levels in the 50/28 mg group from baseline to Day 64, as compared to a 34% reduction in the 12 mg group (difference in geometric mean ratios for 50/28 mg group to 12 mg group: 42%; ($p = 0.0047$)).

Figure 1: Study SM203 Part B Infantile-Onset SMA Plasma NfL LS mean ratio to baseline (95% CI) by visit from ANCOVA analysis using MI: ITT, Matched Sham Set



Day 64 is the secondary endpoint for comparison of 12 mg versus 50/28 mg

Day 183 is the secondary endpoint for comparison of matched sham versus 50/28 mg

Immunogenicity

The presence of ADAs appeared to decrease Spinraza plasma clearance. No discernible effects of ADAs on plasma Nf-L or measures of clinical function have been observed in Spinraza 12 mg and 50/28 mg dosing regimens. ADAs had no effect on safety as measured by incidence of adverse events (AEs) including hypersensitivity, anaphylactic reaction, and angio-oedema.

Clinical efficacy and safety

Symptomatic patients treated with Spinraza 50/28 mg regimen

Study SM203 Part B was a randomized, double-blind evaluation of the safety and efficacy of 50/28 mg nusinersen in treatment-naïve infantile-onset and later-onset patients. Part B was powered to assess efficacy in infantile-onset patients for the 50/28 mg group vs. a prespecified matched sham group from Study CS3B. The 12 mg dosing regimen in Study SM203 Part B provided supportive evidence but the study was not sufficiently powered to detect statistically significant treatment differences between those randomized to 50/28 mg and 12 mg nusinersen. Part C was an open-label, safety and efficacy evaluation in children and adults with infantile-onset or later-onset SMA who had transitioned from the 12 mg to the 50/28 mg regimen.

Infantile onset

In Study SM203 Part B, patients with infantile-onset SMA (2 *SMN2* copies; symptom onset before 6 months of age) were randomized 2:1 to receive the 50/28 mg or 12 mg regimen. Prespecified analyses matched 20 of 37 sham patients from Study CS3B based on similarities in both baseline disease duration and Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) score. The primary endpoint was change in CHOP INTEND at Day 183 in infantile-onset patients in the 50/28 mg group compared to this matched sham group from Study CS3B.

In the infantile-onset cohort in Study SM203, participants were stratified by age when randomized to create balanced 50/28 mg and 12 mg groups. Key baseline demographic characteristics (age at first dose, age at screening, age at symptom onset, *SMN2* copy number, and baseline motor function) were

balanced between the 50/28 mg group, the 12 mg group and the matched sham group. Relative to the infantile-onset population in Study CS3B, patients enrolled in Study SM203 were progressing more quickly and were further into their disease course, these patients had shorter disease duration (time from symptom onset to screening) and lower baseline CHOP INTEND scores. Prespecified matching to a subgroup of the Study CS3B sham control group helped minimize some of this imbalance; however, baseline mean (SD) disease duration remained shorter and baseline CHOP INTEND remained lower in the 50/28 mg and 12 mg groups relative to the matched sham group of study CS3B (Table 4). Other key baseline demographic characteristics (age at first dose, age at screening, age at symptom onset, *SMN2* copy number, and baseline motor function) were balanced between the 50/28 mg group, the 12 mg group and the matched sham group.

Table 4: Patient baseline characteristics in study SM203 Part B

Patient Characteristics	Spinraza 50/28 mg (n = 50)	Spinraza 12 mg (n = 25)	CS3B matched-sham (n = 20)
Baselines median (range) age at first dose (weeks)	18.4 (2 to 33)	15.9 (3 to 31)	22.2 (4 to 34)
Baseline mean (SD) age at symptom- onset (weeks)	7.5 (5.26)	5.8 (4.44)	8.8 (5.11)
Baseline mean (SD) disease duration (time from symptom-onset to screening) (weeks)	9.6 (5.29)	9.2 (6.11)	11.1 (4.92)
Baseline mean (SD) CHOP INTEND (points)	20.9 (10.23)	19.9 (9.63)	23.6 (5.84)

The primary endpoint, the mean change in CHOP INTEND from baseline to Day 183 was statistically significantly greater in the 50/28 group (15.1-point improvement) compared to the matched sham group (11.1-point worsening) (LS mean difference: 26.19 points [95% CI: 20.7, 31.7] $p < 0.0001$).

The change in CHOP INTEND from baseline to Day 302 was numerically higher in the 50/28 mg group than the 12 mg group based on the difference in ranks, but this difference was not statistically significant based on the JRT (LS mean difference in ranks (1.00 (95%CI: -9.290, 11.299); JRT $p = 0.8484$). The LS mean change from baseline to Day 302 based on ANCOVA with MI was numerically higher in the 12 mg group; 50/28 mg group (19.6 points improvement), 12 mg group (21.6 points improvement; [95%CI; 16.5, 22.8]) (LS mean difference -1.94 [7.77, 3.88]).

In a supplementary analysis similar to the primary endpoint in study CS3B, 60% of patients in the 50/28 mg group and 44% of patients in the 12 mg group met the HINE section 2 (HINE-2) responder definition at Day 302. The change in HINE-2 motor milestone from baseline to Day 302 was numerically greater in the 50/28 mg group (5.9 points improvement) compared to the 12 mg group (5.3 points improvement) (LS mean difference 0.58 (1.89, 3.04)), but these differences were not statistically significant.

When compared to sham, a statistically significantly greater proportion of patients in the 50/28 mg group met the HINE section 2 (HINE-2) responder definition at Day 183 (58% vs. 0%; $p < 0.0001$) (Table 5).

Table 5: Motor outcomes in 50/28 mg group vs 12 mg group and 50/28 mg group vs matched-sham group - Study SM203 Part B Infantile-onset

Efficacy Parameter	Spinraza 50/28 mg group (n = 50)	Matched Sham from Study CS3B (n = 20)	Differences between arms (95% CI)
CHOP-INTEND			
LS mean (95% CI) for ranked score of change from baseline to Day 183	42.9 (38.7, 47.2)	16.9 (10.1, 23.7)	26.06 (17.94, 34.17) p<0.0001 ³
LS mean change (95% CI) from baseline to Day 183 ^{1,2}	15.1 (12.4, 17.8)	-11.1 (-15.9, -6.2)	26.1 (20.7, 31.7) ²
HINE-2 Responder⁵			
Proportion achieving motor milestone responder criteria at Day 183	29 (58%)	0 (0%)	58% (39.5, 71.8) ⁴ p<0.0001
HINE-2 Total Score			
LS Mean (95% CI) for ranked score of change from baseline to Day 183	43.1 (39.0, 47.2)	16.5 (9.9, 23.0)	26.67 (18.81, 35.53) p<0.0001 ³
LS mean change (95% CI) from baseline to Day 183 in HINE-2 total score ^{1,2}	3.7 (3.0, 4.4)	-0.2 (-1.5, 1.0)	3.94 (2.46, 5.42) ²

¹ANCOVA and Multiple Imputation applied

²Least Square Mean difference

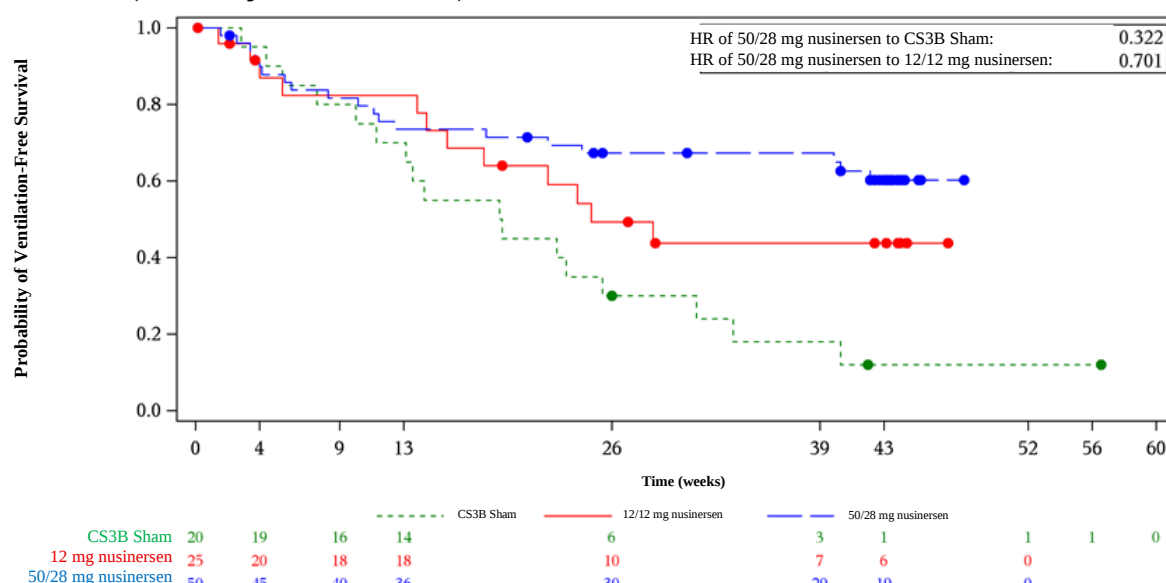
³Joint Rank Test

⁴Fisher Exact Test

⁵Definition of Responder: ≥ 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.

The 50/28 mg group experienced a 29.9% reduction relative to the 12 mg group ($p = 0.2775$) and a nominally statistically significant 68% reduction in the risk of death or permanent ventilation relative to the matched sham group ($p = 0.0006$). The median time to death or permanent ventilation was not reached in the 50/28 mg group, was 24.7 weeks in the 12 mg group, and 19.1 weeks in the matched sham group. Similar observations were seen for overall survival (Figure 2).

Figure 2 Part B: Infantile-Onset SMA: Kaplan-Meier Curves for Time to Death or Permanent Ventilation (EAC-Adjudicated Events): ITT, Matched Sham Set



Later Onset

Study SM203 Part B included 24 patients with later-onset SMA (the majority with 3 *SMN2* copies; symptom onset after 6 months of age) were randomized 2:1 to receive the 50/28 mg regimen (n = 16) or 12 mg regimen (n = 8). Analyses were prespecified to compare the 50/28 mg regimen to matched sham from Study CS4 group. Analyses were not powered to detect significant differences between treatment groups.

The baseline demographic characteristics of the 50/28 mg, matched treatment and matched sham group were generally balanced with the exception of age at first dose. The mean (SD) age at first dose was 6.1 (3.0) years for the 50/28 mg group, 5.7 (3.0) years for the 12 mg group, and 5.13 (1.8) years for the matched sham.

The change from baseline to Day 302 in HFMSE score (LS mean [95% CI]) was numerically higher in the 50/28 mg group (3.3 [1.5, 5.0]) than the 12 mg group (2.6 [0.2, 5.1]) (LS mean difference: 0.63 (-2.5, 3.8; p = 0.70). The change from baseline to Day 279 in HFMSE score was also numerically higher in the 50/28 mg group than the matched sham group from Study CS4 (LS mean difference: 3.2 (0.2, 6.2); p = 0.037).

The change from baseline to Day 302 in revised upper limb module (RULM) score (LS mean [95% CI]) was numerically higher in the 50/28 mg group (2.5 [0.7, 4.2]) than the 12 mg group (1.8 [-0.8, 4.4]), but the difference was not statistically significant (p = 0.66). The change from baseline to Day 279 in RULM score was also numerically higher in the 50/28 mg group than the matched sham group from Study CS4 (LS mean difference: 1.7 (-0.2, 3.5); p = 0.076).

Study SM203 Part C was an open-label cohort that enrolled 40 patients aged 4-65 years with 1-4 *SMN2* copies who had transitioned from the 12 mg to the 50/28 mg regimen. Patients received one 50 mg dose followed by two 28 mg maintenance doses (4 months apart).

Two patients (5%) were infantile-onset and 38 (95%) patients were later-onset. Sixteen patients were younger than 18 years old and 24 patients were older than 18 years at the time of their 50 mg loading dose. The median age (range) at SMA symptom onset was 24 (4 to 192) months. The median time (range) on the 12 mg Spinraza therapy regimen was 3.9 years (1, 5). Twenty-one patients (53%) could ambulate 15 steps independently at baseline.

Participants experienced a mean improvement on HFMSE of 1.8 points [SD 3.99] from baseline to

Day 302, with a 2.3-point [SD 3.95] mean improvement in the adult subgroup (n = 24). Overall, 53% of patients (n = 38) experienced an increase in HFMSE score from baseline to Day 302.

On RULM, participants experienced a mean improvement of 1.2 points [SD 2.14] from baseline to Day 302, with a 0.9-point [SD 1.89] improvement in the adult subgroup. Of those with an opportunity to improve (a score below the maximum possible at baseline; n = 26), 62% experienced an increase in RULM score from baseline to Day 302.

Symptomatic patients treated with Spinraza 12 mg regimen

Infantile onset

Study CS3B (ENDEAR) was a Phase 3, randomized, double-blind, sham-procedure controlled study conducted in 121 symptomatic infants ≤ 7 months of age, diagnosed with SMA (symptom onset before 6 months of age). CS3B was designed to assess the effect of Spinraza on motor function and survival. Patients were randomized 2:1 to either Spinraza 12 mg (as per the approved dosing regimen) or sham-control, with a length of treatment ranging from 6 to 442 days.

The median age of onset of clinical signs and symptoms of SMA was 6.5 weeks and 8 weeks for Spinraza 12 mg treated versus sham-control patients respectively, with 99% of patients having 2 copies of the SMN2 gene and therefore deemed most likely to develop Type I SMA. The median age when patients received their first dose was 164.5 days for treated patients, and 205 days for sham-control. Baseline disease characteristics were largely similar in the Spinraza 12 mg treated patients and sham-control patients except that Spinraza 12 mg 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%).

At the final analysis, a statistically significant greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza 12 mg group (51%) compared to the sham-control group (0%) ($p < 0.0001$). 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 12 mg group compared to those in the sham-control group (Table 6).

In the efficacy set, 18 patients (25%) in the Spinraza 12 mg group and 12 patients (32%) in the sham-control group required permanent ventilation. Of these patients, 6 (33%) in the Spinraza 12 mg group and 0 (0%) in the sham-control group met the protocol-defined criteria for a motor-milestone responder.

Table 6: Primary and secondary endpoints at final analysis – Study CS3B

Efficacy Parameter	Spinraza 12 mg treated Patients	Sham-control Patients
Survival		
Event-free survival²		
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 ⁶	p = 0.0046	
Overall survival²		
Number of patients who died	13 (16%)	16 (39%)
Hazard Ratio (95% CI)	0.37 (0.18 – 0.77)	

Efficacy Parameter	Spinraza 12 mg treated Patients	Sham-control Patients
p-value ⁶	p=0.0041	
Motor function		
Motor milestones ³		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2) ^{4,5}	37 (51%) ¹ p<0.0001	0 (0%)
Proportion at Day 183	41%	5%
Proportion at Day 302	45%	0%
Proportion at Day 394	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%)

¹CS3B was stopped following positive statistical analysis on the primary endpoint at interim analysis (statistically significantly greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza 12mg group (41%) compared to the sham-control group (0%), p<0.0001)

²At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT Spinraza 12 mg n=80; Sham-control n=41).

³At the final analysis, CHOP INTEND and motor milestone analyses were conducted using the Efficacy Set (Spinraza 12 mg n=73; Sham-control n=37).

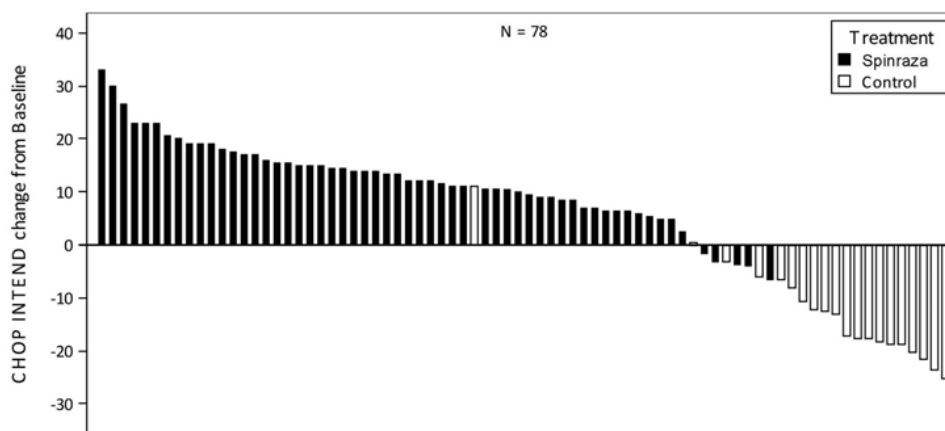
⁴Assessed at the later of Day 183, Day 302, and Day 394 Study Visit

⁵According to Hammersmith Infant Neurological Examination (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.

⁶Based on log-rank test stratified by disease duration

The extent of improvement in CHOP INTEND is shown in Figure 3 (change from baseline score for each subject).

Figure 3: Change in CHOP INTEND from Baseline to Later of Day 183, Day 302, and Day 394 Study Visit – Endear Study /CS3B (Efficacy Set, ES)



Note 1: Shortest bars at 0 line indicate 0 value.

Note 2: Out of the 110 patients in the efficacy set, 29 died (13 (18%) for Spinraza and 16 (43%) for Control) and 3 withdrew for reason other than death (2 (3%) for Spinraza and 1 (3%) for Control) and were therefore not included in this analysis of the ES.

To allow for long term follow up of these patients, at the end of Study CS3B, 89 patients (Spinraza: n=65; sham-control: n=24) enrolled in Study CS11 (SHINE). Study CS11 is an open-label extension study for SMA patients who previously participated in the other Spinraza clinical studies. In patients randomised to Spinraza in Study CS3B and including the extension of treatment with Spinraza in Study CS11, patients received the medication for 6 to 3043 days (median 2443 days). In patients randomised to sham in Study CS3B and initiating Spinraza in Study CS11, patients received the medication for 65 to 2520 days (median 2090 days).

Improvements in motor function were observed among patients continuing Spinraza from Study CS3B, as well as those who initiated Spinraza in Study CS11 (Figure 5), with the greatest benefit observed in those with earlier treatment initiation. The majority of patients were alive at their last visit after initiating treatment with Spinraza in either Study CS3B or Study CS11.

Patients initiating Spinraza in Study CS3B were of median age 5.5 months (range 1.7 to 14.9 months). From Spinraza initiation and including extension of treatment in Study CS11, the median time to death or permanent ventilation was 1.4 years. At the end of Study CS11, 60 out of 81 patients (74%) were alive and 41 out of 81 patients (51%) were alive and had not met the Study CS11 definition of permanent ventilation. Mean HINE-2 total motor milestone score increased by 5.3 (SD 4.6; n=52) and CHOP INTEND score increased by 18.4 (SD 14.7; n=38) points from initiation of Spinraza to follow up visit day 394 and 2198 respectively.

Patients randomised to sham in Study CS3B and initiating Spinraza in Study CS11 were of a median age of 17.8 months (range 10.1 to 23.0 months). Prior to Spinraza initiation 12 out of 24 patients (50%) had met the Study CS11 definition of permanent ventilation. The median time to death or permanent ventilation was 2.76 years after initiation of Spinraza in Study CS11. At the end of Study CS11, 19 out of 24 patients (79%) were alive and 6 out of 12 patients (50%) were alive without permanent ventilation. Improvement in mean total motor milestone score of 1.4 (SD 1.8; n=12) and CHOP INTEND score of 11.5 (SD 12.2, n=10) scores were observed from Study CS11 baseline to follow up visit day 394 or 2198 respectively.

These results are supported by an open-label Phase 2 study in symptomatic patients diagnosed with SMA (CS3A). Median age of onset of clinical signs and symptoms was 56 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. The median age at first dose was 162 days.

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%) in the study met the primary endpoint with improvement in mean motor milestone achievement over time. An improvement in mean CHOP INTEND score over time 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 the last study visit. Of the 20 subjects enrolled, 11 (55%) were alive and free of permanent ventilation at the last visit. Four patients met the criteria for permanent ventilation and five patients died during the study.

Later onset

Study CS4 (CHERISH) was a Phase 3, randomised, double-blind, sham-procedure controlled study conducted in 126 symptomatic patients with later-onset SMA (symptom onset after 6 months of age). Patients were randomized 2:1 to either Spinraza 12 mg (dosed with 3 loading doses and maintenance doses every 6 months) or sham-control, with a length of treatment ranging from 324 to 482 days. The median age at screening was 3 years, and the median age of onset of clinical signs and symptoms of SMA was 11 months. 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 Hammersmith Functional Motor Scale Expanded (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 with the exception of an imbalance in the proportion of patients who had ever achieved the ability to stand without support (13% of patients in the Spinraza 12 mg group and 29% in sham-control) or walk with support (24% of patients in the Spinraza 12 mg group and 33% in sham-control).

At the final analysis, a statistically significant improvement in HFMSE score from baseline to Month 15 was seen in the Spinraza 12 mg group compared to the sham-control group (Table 7, Figure 4). The analysis was conducted in the ITT population (Spinraza 12 mg: n=84; sham-control: n=42), and post-baseline HFMSE data for patients without a Month 15 visit were imputed using the multiple imputation method. 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 12 mg treated subjects had improvement (73% vs 41%, respectively) and a lower proportion of Spinraza 12 mg treated subjects had worsening (23% vs 44%, respectively) in total HFMSE score compared to sham-control. Secondary endpoints including functional measures and WHO motor milestone achievement were formally statistically tested and are described in Table 7.

Initiation of treatment sooner after symptom onset resulted in earlier and greater improvement in motor function than those with delayed treatment initiation; however, both groups experienced benefit compared to sham control.

Table 7: Primary and secondary endpoints at final analysis – Study CS4¹

	Spinraza 12 mg 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 ²	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 ^{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)

¹CS4 was stopped following positive statistical analysis on the primary endpoint at interim analysis (statistically significant improvement from baseline HFMSE score was observed in Spinraza 12 mg treated patients compared to the sham-control patients (Spinraza 12 mg vs. sham-control: 4.0 vs. -1.9; p=0.0000002))

² Assessed using the Intent to Treat population (Spinraza 12 mg n=84; Sham-control n=42); data for patients without a Month 15 visit were imputed using the multiple imputation method

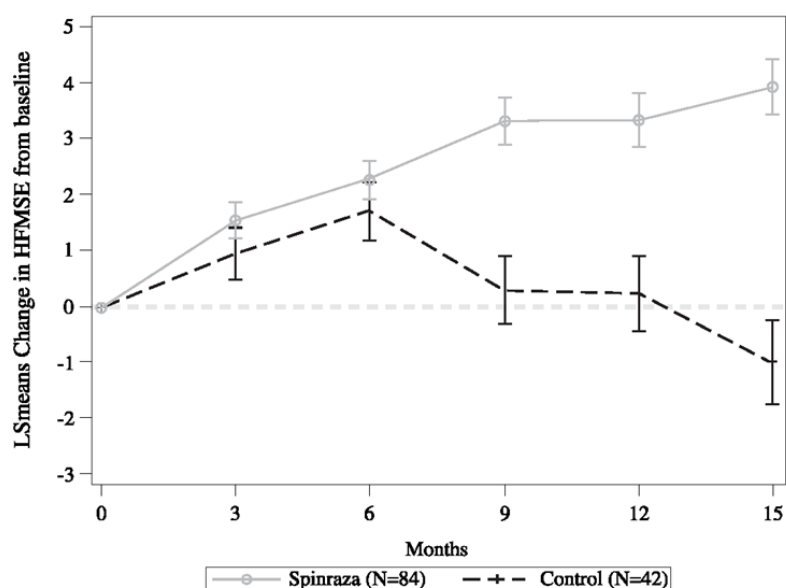
³Least squares mean

⁴ Assessed using the Month 15 Efficacy Set (Spinraza 12 mg n=66; Sham control n=34); analyses are based on imputed data when there are missing data.

⁵ Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline

⁶Nominal p value

Figure 4: Mean change from baseline in HFMSE score over time at final analysis (ITT) – Study CS4^{1,2}



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

²Error bars denote +/- standard error

Upon completion of Study CS4 (CHERISH), 125 (83 Spinraza and 42 sham) patients enrolled in Study CS11 (SHINE) where all patients received Spinraza 12 mg. The majority of Spinraza 12 mg treated patients experienced stabilization or improvement in motor function, with the greatest benefit observed in those with earlier treatment initiation.

Patients initiating Spinraza in Study CS4 were of a median age 4.1 years (range 2.1 to 9.2 years). From Spinraza initiation and including extension of treatment in Study CS11, patients received the medication for a median time of 7.2 years (range 1.3 to 8.4 years). HFMSE mean score increased 1.3 (SD 9.4 n=54) and RULM mean score increased by 6.4 (SD 6.5 n=54) at follow up visit day 2070.

Patients randomised to sham in Study CS4, initiated treatment with Spinraza in Study CS11 at a median age of 4.9 years (range 3.3 to 9.0 years). From Spinraza initiation in Study CS11, patients received the medication for a median time of 5.8 years (range 2.7 to 6.7 years). HFMSE mean score decreased by 1.3 (SD 9.3 n=22) and RULM, score increased by 4.2 (SD 4.4 n=23) points at follow up visit day 2070.

In contrast, the natural disease course of untreated patients of similar age and clinical characteristics shows a progressive loss of motor function over time, with an estimated mean decline in HFMSE of 6.6 points over a similar period of 5 years.

These results are supported by 2 open label studies (study CS2 and study CS12). The analysis included 28 patients who received their first dose in study CS2, and then transferred to the extension phase, study CS12. The studies enrolled patients who were between 2 to 15 years of age at first dose. Of the 28 patients, 3 were at least 18 years of age at their last study visit. 1 out of 28 patients had 2 SMN2 gene copies, 21 had 3 copies, and 6 had 4 copies.

Patients were assessed over a 3 year treatment period. A sustained improvement was seen in patients with Type II SMA who experienced a mean improvement from baseline HFMSE score of 5.1 (SD 4.05, n=11) at Day 253, and 9.1 (SD 6.61, n=9) at Day 1050. The mean total score was 26.4 (SD 11.91) at Day 253 and 31.3 (SD 13.02) at Day 1050, no plateau was observed. Patients with Type III SMA demonstrated a mean improvement from baseline HFMSE score of 1.3 (SD 1.87, n=16)

at Day 253 and 1.2 (SD 4.64, n=11) at Day 1050. The mean total score was 49.8 (SD 12.46) at Day 253 and 52.6 (SD 12.78) at 1050 days.

In patients with Type II SMA the Upper Limb Module test was conducted with mean improvement of 1.9 (SD 2.68, n=11) at Day 253 and 3.5 (SD 3.32, n=9) at Day 1050. The mean total score was 13.8 (SD 3.09) at Day 253 and 15.7 (SD 1.92) at Day 1050.

The 6MWT (six-minute walk test) was conducted for ambulatory patients only. In these patients, a mean improvement of 28.6 meters (SD 47.22, n=12) at Day 253 and 86.5 metres (SD 40.58, n=8) at Day 1050. The mean 6MWT distance was 278.5 meters (SD 206.46) at Day 253 and 333.6 metres (SD 176.47) at Day 1050. Two previously non-independent ambulatory patients (Type III) achieved independent walking, and one non-ambulatory patient (Type II) achieved independent walking.

An additional clinical study, CS7 (EMBRACE) was opened for patients not eligible for participation in Study CS3B or Study CS4 due to screening age or SMN2 copy number. CS7 is a phase 2, randomized, double-blind, sham-procedure study in symptomatic patients diagnosed with infantile-onset SMA (≤ 6 months) or later-onset SMA (> 6 months) and 2 or 3 copies of SMN2 (Part 1), followed by a long-term open-label extension phase (Part 2). In Part 1 of the study, patients were followed for a median of 302 days.

All patients who received Spinraza 12 mg 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 12 mg or sham-control group required the use of permanent ventilation. Of the 13 patients with infantile-onset SMA, 7 of out 9 patients (78%; 95%CI: 45, 94) in the Spinraza 12 mg group and 0 out of 4 patients (0%; 95%CI: 0, 60) in the sham group met the criteria for motor milestone response (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). Of the 8 patients with later-onset SMA, 4 out of 5 patients (80%; 95% CI: 38, 96) in the Spinraza 12 mg group and 2 out of 3 (67%; 95% CI: 21, 94) in the sham-control group met this definition of response.

Adult

Real world clinical findings support the effectiveness of nusinersen to stabilize or improve motor function in some SMA adult Type II and III patients.

By month 14 of nusinersen 12 mg treatment, the number of patients with a clinically meaningful improvement from baseline on HFMSE (≥ 3 points) was 53 out of 129 patients, the number of patients with clinically meaningful improvement on the RULM (≥ 2 points) was 28 out of 70 and among walkers 25 out of 49 for the 6MWT (≥ 30 meters).

Part C of Study SM203 assessing the efficacy and safety of patients who had transitioned to the Spinraza 50/28 mg dosing regimen included 24 adults (≥ 18 years of age) who had been treated for a median of 3.9 years with 12 mg. Post transition, participants experienced a 2.3-point [SD 3.95] mean improvement on HFMSE in the adult subgroup (n = 24). On RULM, participants experienced a 0.9-point [SD 1.89] improvement in the adult subgroup. Furthermore, 14 of 23 (61%) adults experienced improvement from baseline on HFMSE at Day 302 and 8 of 12 (67%) adults who had not achieved a maximum RULM score at baseline, improved at Day 302.

The safety data in the adult population are consistent with the known safety profile of nusinersen and with co-morbidities associated with the underlying disease of SMA.

Presymptomatic infants

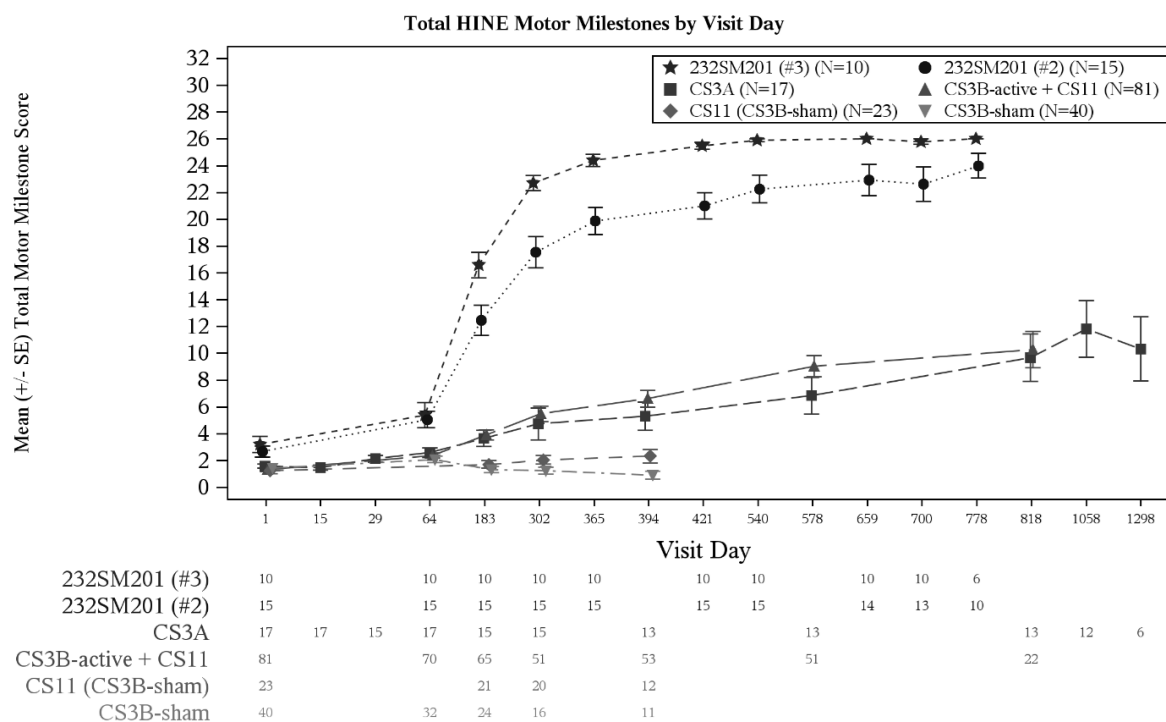
Study CS5 (NURTURE) is an open-label study in presymptomatic infants genetically diagnosed with SMA, who were enrolled at 6 weeks of age or younger. Patients in this study were deemed most likely to develop Type I or II SMA. Median age at first dose was 22 days.

An interim analysis was conducted when patients had been on study for a median of 48.3 months (36.6 to 57.1 months) and were of a median age at last visit of 46.0 months (34.0 to 57.1 months). At the interim analysis, all 25 patients (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 non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days or tracheostomy), could not be estimated as there were too few events. Four patients (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 and more consistent with normal development. At the interim analysis, all 25 (100%) patients had achieved the WHO motor milestone of sitting without support, 23 (92%) patients were walking with assistance and 22 (88%) had achieved walking alone. Twentyone (84%) patients achieved the maximum attainable CHOP INTEND score of 64. All patients had the ability to suck and swallow at last visit (Day 788), with 22 (88%) infants achieving a maximal score on the HINE Section 1.

Patients developing clinically manifested SMA was assessed at Day 700 visit. 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 out of 15 patients (47%) with 2 SMN2 gene copies and 0 out of 5 patients (0%) with 3 SMN2 copies, met the protocol-defined criteria of clinically manifested SMA, however, these patients were gaining weight and achieving WHO milestones, inconsistent with Type I SMA. A comparison of motor milestone achievement among the patients with symptomatic infantile-onset SMA and presymptomatic SMA is shown in Figure 5.

Figure 5: Change in HINE Motor Milestones versus Study days for Study CS3B (treated and sham-control), CS3A, CS5 and CS11



Population used in figure: 232SM201 subjects in the ITT set with SMN2 copy number denoted in parentheses, CS3A: SMN2 2 copy subjects, CS3B: Subjects with SMN2 2 copy in ITT set.

For CS3A and CS3B the data were windowed into intervals based on time from baseline.

For 232SM201 and CS3A, visits with $n < 5$ are not plotted. For the remaining groups visits with $n < 10$ are not plotted.

SOURCE: ISIS396443/ISS/CDS-UPDATE-2024/F-HMOTOR-BYVIS-GRA-CLN.SAS

DATE: 18MAR2024

5.2 Pharmacokinetic properties

Single- and multiple-dose pharmacokinetics (PK) of nusinersen, administered via intrathecal injection, were determined in paediatric and adult patients diagnosed with SMA.

Absorption

Intrathecal injection of nusinersen into the CSF allows nusinersen to be fully available for distribution from the CSF to the target central nervous system (CNS) tissues.

Cumulative CSF PK data evaluated in the long-term exposure study CS11 in the 12 mg dosing regimen indicated that in infantile and later onset SMA patients, CSF concentrations continued to accumulate over approximately 9 years.

A similar trend in accumulation of CSF concentration was also observed for the 50/28 mg dosing regimen in Study SM203 and Study SM302 from CSF PK collected over the entire duration of data.

Following intrathecal administration trough plasma concentrations of nusinersen were relatively low compared to the trough CSF concentration. Median plasma T_{max} values ranged from 1.7 to 6.0 hours. Mean plasma C_{max} and AUC values increased approximately dose proportionally over the evaluated dose range. There was no accumulation in plasma exposure measures (C_{max} and AUC) after multiple doses.

Distribution

Autopsy data from patients ($n=3$) show that nusinersen administered intrathecally is broadly distributed within the CNS achieving therapeutic levels in the target spinal cord tissues. Presence of

nusinersen was also demonstrated in neurons and other cell types in the spinal cord and brain, and peripheral tissues such as skeletal muscle, liver, and kidney.

Biotransformation

Nusinersen is metabolized slowly and predominantly 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 in CSF is estimated at approximately 20 months. The primary route of elimination is expected via urinary excretion of nusinersen and its metabolites.

Interactions

In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism and therefore should not interfere with other medicinal products for these metabolic pathways. Nusinersen is not a substrate or inhibitor of human BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or BSEP transporters.

Characteristics in specific patient populations

Renal and hepatic impairment

The pharmacokinetics of nusinersen in patients with renal or hepatic impairment has not been studied. The effect of hepatic or renal insufficiency as covariates could not be thoroughly evaluated in the population PK model given the rarity of patients displaying clinically relevant liver or kidney insufficiencies. Population PK analyses revealed no apparent correlation between hepatic and renal clinical chemistry markers and inter-subject variability.

Race

The majority of patients studied were Caucasian. The population PK analysis suggests that race is unlikely to affect the PK of nusinersen.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

Nusinersen demonstrated no evidence of genotoxicity.

In a carcinogenicity study, nusinersen was administered to male and female mice by subcutaneous injection at 0, 5, 15, or 50 mg/kg, once every two weeks for 2 years. An increase in the incidence of vascular tumours (combined hemangioma and hemangiosarcoma) was observed at the 50 mg/kg dose. No evidence of oncogenic effects due to nusinersen was observed at dose levels up to 15 mg/kg. On an annual dose basis this dose was associated with a serum AUC₀₋₂₄ that is 30-fold clinical serum exposure at 28 mg maintenance dose.

Reproductive toxicity

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

Toxicology

In repeat-dose (combined 6-weeks and 13-weeks, 14 weeks, and 53 weeks) toxicity studies in juvenile cynomolgus monkeys, intrathecal administration of nusinersen did not produce any adverse toxic effects at the doses evaluated.

Acute, transient deficit in lower spinal reflexes, limited use of limbs, and/or uncoordinated movement occurred in some individual monkeys. These effects were observed within several hours post dose and resolved within 48 hours and were not considered adverse.

In the 53-week juvenile monkey toxicology study, nusinersen was tested at dose levels up to 4 mg per dose, equivalent to 40 mg per intrathecal dose in patients and resulting in a cumulative dose, over one year, 6.2-fold higher than the nusinersen clinical maintenance dose of 28 mg (three maintenance doses per year).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium phosphate
Sodium chloride
Potassium chloride
Calcium chloride dihydrate
Magnesium chloride hexahydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in a refrigerator (2°C 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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 should not exceed 30 hours, at a temperature that does not exceed 25°C.

6.5 Nature and contents of container

Spinraza 12 mg

Single-use Type I glass vial with bromobutyl grey rubber stopper and an aluminium over-seal and plastic cap containing 12 mg nusinersen in 5 mL of artificial cerebral spinal fluid.

Pack size of one vial per carton.

Spinraza 28 mg

Single-use Type I glass vial with bromobutyl grey rubber stopper and a red aluminium over-seal and plastic cap containing 28 mg nusinersen in 5 mL of artificial cerebral spinal fluid.

Pack size of one vial per carton.

Spinraza 50 mg

Single-use Type I glass vial with bromobutyl grey rubber stopper and a blue aluminium over-seal and plastic cap containing 50 mg nusinersen in 5 mL of artificial cerebral spinal fluid.
Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

For single use in one patient only. Do not dilute.

Instructions for preparation of the medicinal product before administration

1. The Spinraza vial should be inspected for particles prior to administration. If particles are observed and/or the liquid in the vial is not clear and colourless, the vial must not be used.
2. Aseptic technique should be used when preparing Spinraza solution for intrathecal administration.
3. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25°C) without using external heat sources, prior to administration.
4. If the vial remains unopened and the solution is not used, it should be returned back to the refrigerator (see section 6.4).
5. Just prior to administration, remove the plastic cap and insert the syringe needle into the vial through the centre of the over-seal to remove the appropriate volume. Spinraza must not be diluted. The use of external filters is not required.
6. Once drawn into the syringe, if the solution is not used within 6 hours, it must be discarded.
7. Any unused product in the vial should be discarded and waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1188/001
EU/1/17/1188/002
EU/1/17/1188/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 May 2017

Date of latest renewal: 31 January 2022

10. DATE OF REVISION OF THE TEXT

07/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.