Summary Report of Benefit-Risk Assessment

SPINRAZA SOLUTION FOR INJECTION 12MG/5ML

NEW DRUG APPLICATION

Active Ingredient(s)	Nusinersen sodium
Product Registrant	Zuellig Pharma Pte. Ltd.
Product Registration Number	SIN16751P
Application Route	Abridged evaluation
Date of Approval	31 March 2023

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A INTRODUCTION

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

The active substance, nusinersen sodium, is an antisense oligonucleotide (ASO) which increases the amount of full-length protein produced from survival motor neuron 2 (SMN2) gene by modulating its messenger ribonucleic acid (mRNA) splicing pattern. Nusinersen binds to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA), displaces the splicing factors, which normally suppress splicing. This leads to retention of exon 7 in the SMN2 mRNA and increases the proportion of exon 7 inclusion in SMN2 mRNA transcripts. Hence, when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein.

Spinraza is available as a solution for injection containing 12mg of nusinersen as nusinersen sodium per 5ml. Other ingredients in the vial are sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydrochloride, hydrochloric acid and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, nusinersen sodium, is manufactured at Ionis Pharmaceuticals, Inc., Carlsbad, United States of America. The drug product, Spinraza Solution for Injection 12mg/ 5ml, is manufactured at Patheon Italia S.p.A., Ferentino, Italy and Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at -20°C with a re-test period of 60 months. The packaging is double low-density polyethylene (LDPE) bags within a high-density polyethylene (HDPE) drum, and each bag is sealed with cable ties. The HDPE drum is then sealed with a tamper evident closure.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the shelf-life of 48 months when stored between 2°C-8°C, protected from light. The in-use period after opening is no more than 6 hours. The container closure system is a Type I clear glass vial with a bromobutyl rubber stopper, an aluminium over-seal and a plastic cap. Each vial contains 5ml of drug product.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of nusinersen in the treatment of 5q SMA was based primarily on two pivotal Phase III studies, Study CS3B in subjects with infantile-onset SMA and Study CS4 in subjects with later-onset SMA, as well as one Phase II study (Study SM201) in pre-symptomatic infants with genetically diagnosed SMA.

Study CS3B (Infantile-onset SMA)

Study CS3B was a Phase III, randomised, double-blind, sham-procedure controlled study in subjects with infantile-onset SMA. The main inclusion criteria were subjects ≤7 months of age with genetic documentation of 5q SMA (homozygous gene deletion, homozygous mutation, or compound heterozygote) and 2 copies of SMN2, as well as onset of clinical signs and symptoms consistent with SMA at ≤6 months of age.

Patients in the study were randomised in a 2:1 ratio to receive either an intrathecal 12mg scaled equivalent dose of nusinersen based on cerebrospinal fluid (CSF) volume scaling or a sham procedure control. Nusinersen was administered using a loading regimen (Days 1, 15, 29 and 64), followed by maintenance dosing once every 4 months (Days 183 and 302).

The primary efficacy endpoints were the proportion of motor milestone responders [Section 2 of the Hammersmith Infant Neurological Examination (HINE)] and time to death or permanent ventilation. Secondary efficacy endpoints included the proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders, survival rate, percent of subjects not requiring permanent ventilation, proportion of compound muscle action potential (CMAP) responders, as well as time to death or permanent ventilation in the subgroup of subjects below the study median disease duration and in the subgroup of subjects above the study median disease duration.

An interim analysis was planned where only the first primary efficacy endpoint based on the proportion of motor milestone responders was tested. To control the overall Type I error rate at 0.05 across the interim and final analyses, a stage-wise hierarchical strategy using independent alpha spending functions for primary and secondary endpoints was applied. The only alpha spending in the interim analysis was for the testing of the first primary efficacy endpoint at an alpha of 0.032. The second primary efficacy endpoint and all secondary efficacy

endpoints were tested in the final analysis with an alpha of 0.05 since they were not tested at the interim analysis (i.e., no alpha spending).

A total of 122 subjects were randomised and 1 subject who was randomised to receive nusinersen withdrew from the study prior to receiving study treatment. The intention-to-treat (ITT) population comprised a total of 121 subjects: 80 subjects in the nusinersen group and 41 subjects in the control group. Sixty-seven subjects (55%) were female and 54 (45%) were male. Age at first study treatment ranged from 30 to 262 days (median 175 days). Majority of subjects (86%) were White. Almost all (99%) subjects had 2 copies of the SMN2 gene. Most had achieved few or no motor milestones at baseline (81% were unable to maintain their head upright, 73% were unable to kick, 95% could not roll, 97% could not sit, and none was able to crawl, stand or walk).

The demographic and baseline disease characteristics were generally similar between the treatment groups with a few exceptions. Subjects in the nusinersen group were younger than those in the control group (median age at first dose of 165 days vs 205 days). In addition, subjects in the nusinersen group had a younger age of SMA symptom onset than the control group (median of 6.5 weeks vs 8 weeks), required more ventilatory support (26% vs 15%) and exhibited more severe symptoms of SMA such as paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), and swallowing or feeding difficulties (51% vs 29%). These imbalances suggested that SMA disease severity was greater in the nusinersen group than in the control group at study entry.

At the interim analysis, treatment with nusinersen demonstrated a statistically significant improvement in the percentage of subjects who achieved a motor milestone response as assessed by HINE Section 2 compared to the control group (41.2% vs 0%; difference = 41.2%, 95% CI: 18.2, 61.2; p<0.0001). Consistent results were observed in the final analysis, with 50.7% of subjects in the nusinersen group achieved a response compared to 0% in the control group (difference = 50.7%, 95% CI: 31.8, 66.5; p<0.0001). In the nusinersen group, 16 subjects (21.9%) achieved full head control, 6 subjects (8.2%) achieved independent sitting, and 1 subject (1.4%) achieved standing with support, whereas no subjects in the control group achieved any of these milestones. The achievement in motor milestones in nusinersen-treated subjects was clinically meaningful considering the natural history of infantile-onset SMA where patients could never achieve independent sitting or standing. The observed treatment benefit was also considered robust given that subjects in the nusinersen group had more severe SMA symptoms than subjects in the control group at baseline. Time to death or permanent ventilation was prolonged in subjects treated with nusinersen, where there was a 47% reduction in the risk of death or permanent ventilation compared to control [hazard ratio (HR) 0.53; 95% CI: 0.32, 0.89; p=0.0046].

For the secondary endpoints, a statistically significantly greater percentage of subjects achieved a CHOP INTEND response in the nusinersen group (71.2%) compared to the control group (2.7%; p<0.0001). The risk of death was 62.8% lower in nusinersen-treated subjects than in those who received the control procedure (HR 0.37, 95% CI: 0.18, 0.77; p=0.0041). The observed treatment benefit was considered robust since subjects in the nusinersen group had greater risk factors in terms of swallowing or feeding difficulties at baseline compared to the control group. There was a trend toward a lower percentage of subjects in the nusinersen group requiring permanent ventilation during the study compared with the control group (HR 0.66, 95% CI: 0.32, 1.37; p=0.1329). As statistical significance was not achieved for this endpoint, all subsequent tests of lower rank were considered exploratory.

The proportion of CMAP responders was numerically greater in the nusinersen group compared to the control group (35.6% vs 5.4%; nominal p=0.0004). In the analysis of subjects with disease duration below the median of 13.1 weeks, nusinersen-treated subjects had a 76% decrease in risk of death or permanent ventilation compared with control subjects (HR 0.24; 95% CI: 0.10, 0.58; p=0.0003). In the analysis of subjects with a disease duration greater than the median of 13.1 weeks, there was a 16% reduction in the risk of death or permanent ventilation following treatment with nusinersen (HR 0.84; 95% CI: 0.43, 1.67; p=0.3953). The results suggested that early treatment with nusinersen might be necessary for a meaningful event-free survival benefit to be observed.

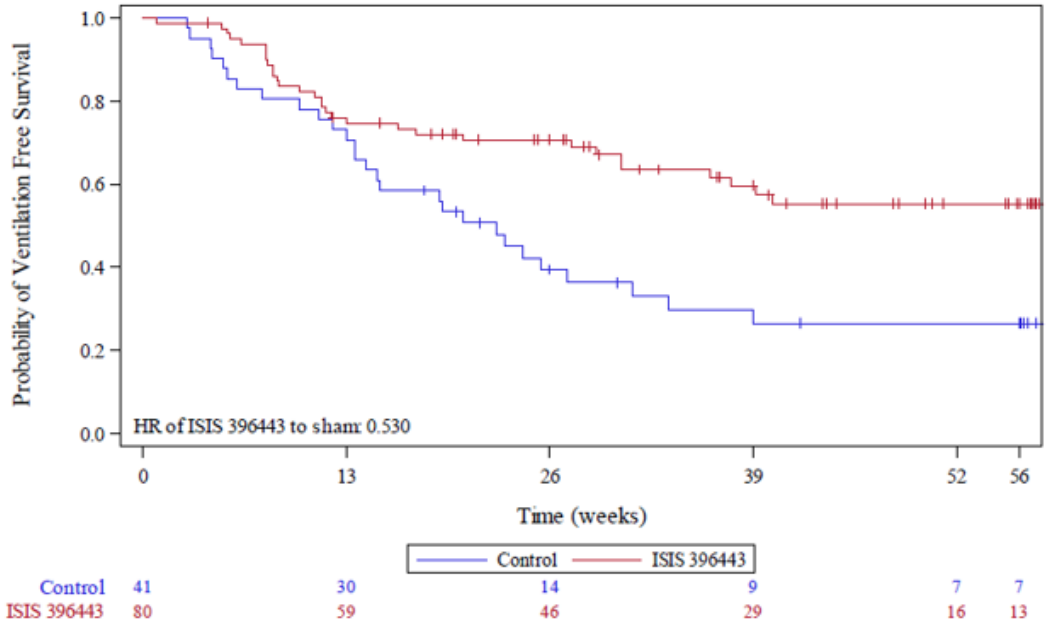
Summary of key efficacy results at final analysis (Study CS3B)

	Nusinersen	Control
Primary endpoints		
Proportion of motor milestone responders, n (%)	37/73 (50.7%)	0/37 (0%)
Difference in percentage (95% CI)	50.7% (31.8, 66.5)	
p-value[a]	<0.0001	
Time to death or permanent ventilation		
Number of events, n (%)	31/80 (38.8%)	28/41 (68.3%)
Median time to events (weeks) (95% CI)	NA (36.3, NA)	22.6 (13.6, 31.3)
Hazard ratio (95% CI)	0.53 (0.32, 0.89)	
p-value[b]	0.0046	
Secondary endpoints		
Proportion of CHOP INTEND responders, n (%)	52/73 (71.2%)	1/37 (2.7%)
Difference in percentage (95% CI)	68.5% (51.3, 82.0)	
p-value[a]	<0.0001	
Overall survival		
Number of patients who died, n (%)	13/80 (16.3%)	16/41 (39.0%)
Median OS (months) (95% CI)	NA (NA, NA)	NA (23.1, NA)
Hazard ratio (95% CI)	0.37 (0.18, 0.77)	
p-value[b]	0.0041	
Time to permanent ventilation		
Number of events, n (%)	18/80 (22.5%)	13/41 (31.7%)
Median time to events (weeks) (95% CI)	NA (NA, NA)	NA (22.6, NA)
Hazard ratio (95% CI)	0.66 (0.32, 1.37)	
p-value[b]	0.1329	
Proportion of CMAP responders, n (%)	26/73 (35.6%)	2/37 (5.4%)
Difference in percentage (95% CI)	30.2% (10.4, 48.1)	
p-value[a]	0.0004	
Time to death or permanent ventilation in the subgroup of subjects below the study median disease duration		
Number of subjects below the study median disease duration, n	39	21
Number of events, n	9	14
Median time to events (weeks) (95% CI)	NA (NA, NA)	25.4 (13.1, 40.3)
Hazard ratio (95% CI)	0.24 (0.10, 0.58)	
p-value[c]	0.0003	
Time to death or permanent ventilation in the subgroup of subjects above the study median disease duration		

Number of subjects below the study median disease duration, n	41	20
Number of events, n	22	14
Median time to events (weeks) (95% CI)	27.4 (12.0, NA)	19.0 (11.3, 27.1)
Hazard ratio (95% CI)	0.84 (0.43, 1.67)	
p-value[c]	0.3953	

[a] Based on Fisher's exact test
[b] Based on log-rank test stratified by disease duration
[c] Based on log-rank test

Kaplan-Meier curves for time to death or permanent ventilation (Study CS3B)



Study CS4 (Later-onset SMA)

Study CS4 was a Phase III, randomised, double-blind, sham-procedure controlled study in subjects with later-onset SMA. The main inclusion criteria were subjects 2 to 12 years of age with genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote) and onset of clinical signs and symptoms consistent with SMA at >6 months of age.

Patients in the study were randomised in a 2:1 ratio to receive either a 12mg dose of nusinersen intrathecally or a sham procedure control. Nusinersen was administered intrathecally using a loading regimen (Days 1, 29, and 85), followed by a maintenance dose 6 months thereafter on Day 274.

The primary efficacy endpoint was the change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) score at 15 months. The secondary efficacy endpoints included the following at 15 months: proportion of subjects who achieved a ≥3-point increase from baseline in HFMSE, proportion of subjects who achieved any new motor milestone assessed using the World Health Organization (WHO) Motor Milestone criteria, number of motor milestones achieved, change from baseline in Revised Upper Limb Module (RULM) Test, proportion of subjects achieving standing alone and proportion of subjects achieving walking with assistance.

An interim analysis was planned where only the primary efficacy endpoint was tested. To control the overall Type I error at 0.05 across the interim and final analyses, a stage-wise hierarchical strategy using independent alpha spending functions for primary and secondary endpoints was applied. The only alpha spending in the interim analysis was for the testing of the primary efficacy endpoint at an alpha of 0.025. The secondary endpoints were tested in the final analysis with an alpha of 0.05 since they were not tested at the interim analysis (i.e., no alpha spending).

A total of 126 subjects were randomised and included in the ITT Set: 84 subjects in the nusinersen group and 42 subjects in the control group. Sixty-seven subjects (53%) were female and 59 (47%) were male. Age at screening ranged from 2 to 9 years (median 3 years). The majority of subjects (84%) were <6 years of age and 16% were ≥6 years of age. Ninety-four subjects (75%) were White. The median age at symptom onset was 11 months and ranged from 6 to 20 months. Majority of subjects (88%) had 3 copies of the SMN2 gene, 8% have 2 copies, 2% have 4 copies and 2% have an unknown copy number. At baseline, all subjects had achieved independent sitting and no patients had achieved independent walking.

At the interim analysis, treatment with nusinersen resulted in a statistically significant and clinically meaningful improvement in HFMSE scores from baseline to 15 months in the nusinersen group compared with the control group [least-squares (LS) mean of 4.0 vs -1.9; difference = 5.9, 95% CI: 3.7, 8.1; p = 0.0000002]. At the final analysis, the results were consistent, showing an improvement in HFMSE scores from baseline to 15 months in the nusinersen group and a decline in the control group (LS mean of 3.9 vs -1.0; difference = 4.9, 95% CI: 3.1, 6.7; p = 0.0000001).

For the secondary endpoints, the proportion of subjects who achieved a 3-point or greater increase from baseline in HFMSE score at 15 months was statistically significantly greater in the nusinersen group compared to the control group (56.8% vs 26.3%; p = 0.0006). The proportion of subjects who achieved any new WHO motor milestone in the nusinersen and control groups was 19.7% and 5.9%, respectively (p = 0.0811). As statistical significance was not achieved for this endpoint, all subsequent tests of lower rank were considered exploratory. The number of new motor milestones achieved per subject at 15 months was 0.2 in the nusinersen group versus -0.2 in the control group (nominal p = 0.0001). Improvements were seen in the RULM Test scores from baseline to 15 months in both groups, but a numerically greater improvement was seen in the nusinersen group compared to the control group (LS mean change of 4.2 vs 0.5; nominal p = 0.0000001).

There were few subjects in either treatment group who achieved the milestones of standing alone or walking with assistance. At 15 months, there was 1 subject (1.5%) in the nusinersen group and 1 subject (2.9%) in the control group who had achieved standing alone. There was 1 subject (1.5%) in the nusinersen group and none in the control group who had achieved walking with assistance.

Summary of key efficacy results at final analysis (Study CS4)

	Nusinersen (N=84)	**Control (N=42)**
Primary endpoints		
Change from baseline in HFMSE score at 15 months		
LS mean[a] (95% CI)	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)
LS mean difference[a] (95% CI)	4.9 (3.1, 6.7)	
p-value[a]	0.0000001	
Secondary endpoints		

Proportion of subjects who achieved a 3-point or greater increase from baseline in HFMSE score at 15 months[b] (%) (95% CI)	56.8% (45.6, 68.1)	26.3% (12.4,40.2)
Difference in percentage[b] (95% CI)	30.5% (12.7, 48.3)	
p-value[c]	0.0006	
Proportion of subjects who achieved any new WHO motor milestone (%) (95% CI)	19.7% (10.9, 31.3)	5.9% (0.7, 19.7)
Difference in percentage (95% CI)	13.8 (-6.6, 34.2)	
p-value[d]	0.0811	
Number of new motor milestones achieved per subject at 15 months		
LS mean[e] (95% CI)	0.2 (0.1, 0.3)	-0.2 (-0.4, 0.0)
LS mean difference[e] (95% CI)	0.4 (0.2, 0.7)	
p-value[e]	0.0001	
Change from baseline in RULM Test at 15 months		
LS mean[f] (95% CI)	4.2 (3.4, 5.0)	0.5 (-0.6, 1.6)
LS mean difference[f] (95% CI)	3.7 (2.3, 5.0)	
p-value[f]	0.0000001	

[a] From multiple imputation (MI) procedure, based on analysis of covariance (ANCOVA) with treatment as a fixed effect and adjustment for each subject's age at screening and HFMSE at baseline
[b] The estimates are from the MI procedure and are based on binomial proportions
[c] Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline
[d] Based on Fisher's exact test
[e] Based on ANCOVA with treatment as a fixed effect and adjustment for each subject's age at screening and number of milestones at baseline
[f] From MI procedure, based on ANCOVA with treatment as a fixed effect and adjustment for each subject's age at screening and derived total score at baseline

Study SM201 (Pre-symptomatic infants)

Study SM201 was a Phase II, open-label, single-arm study in subjects ≤6 weeks of age with genetic documentation of 5q SMA, 2 or 3 copies of the SMN2 gene, CMAP ≥1 mV, and without signs or symptoms of SMA. The pre-symptomatic subjects were expected to most likely develop Type I or II SMA based on their SMN2 copy number and the clinical presentation of their siblings who also had SMA. The dose of nusinersen was originally a 12mg scaled equivalent dose based on CSF volume scaling, and was subsequently changed to a fixed dose of 12mg following a protocol amendment. Nusinersen was administered using a loading regimen on Days 1, 15, 29 and 64, followed by maintenance dosing once every 4 months beginning on Days 183. Twenty-five subjects were enrolled. Age at first dose ranged from 3 to 42 days with a median of 22.0 days. Fourteen subjects (56%) were White. Fifteen subjects had 2 SMN2 copies and 10 had 3 SMN2 copies.

As of the data cut-off date of 15 May 2018, all 25 subjects were alive. Four subjects initiated respiratory intervention and therefore met the primary endpoint of death or respiratory intervention [defined as (i) invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days, or (ii) tracheostomy]. These 4 subjects initiated respiratory intervention in the context of acute, reversible infections, and none required tracheostomy or permanent ventilation. Two of the 4 subjects improved and did not require continued respiratory support on the day of their last visit. These observations suggested favourable improvements with nusinersen, considering the natural history of SMA where improvement is rarely observed once permanent ventilation is required.

All subjects achieved and maintained the maximum score for HINE motor milestones in the category of head control, and the majority of subjects achieved the maximum score in the categories of sitting (24 of 25 subjects), kicking (24 of 25 subjects), standing (16 of 25 subjects), and walking (16 of 25 subjects) at the time of the last visit up to Day 778. Also, all subjects achieved improvements in the CHOP INTEND total score. The majority of subjects achieved the WHO motor milestones of hands-and-knees crawling (68%), standing with assistance (96%), walking with assistance (80%), standing alone (68%), and walking alone (68%) at the last observed visit. The results demonstrated that infants with pre-symptomatic SMA who received nusinersen treatment could achieve motor milestones and develop muscle strength and motor function that were expected of normal infants than symptomatic infants with SMA.

Overall, the data from studies CS3B, CS4 and SM201 in subjects with infantile-onset, later-onset and pre-symptomatic SMA, respectively, adequately supported the efficacy of nusinersen for the treatment of 5q SMA.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of nusinersen in the treatment of 5q SMA was based primarily on data from two Phase III studies, Study CS3B in subjects with infantile-onset SMA and Study CS4 in subjects with later-onset SMA. These results were supported by safety data from Phase I or II studies in subjects with pre-symptomatic SMA (Study SM201), infantile-onset SMA (Study CS3A), later-onset SMA (Studies CS1, CS2, CS10, and CS12), as well as infantile- and later-onset SMA (Studies SM202 and CS11). Across the studies, a total of 352 subjects have been exposed to nusinersen for 699 subject-years. The median time on study was 657 days.

Overview of safety profile in Study CS3B

	Nusinersen (N=80)	**Control (N=41)**
TEAE	77 (96%)	40 (98%)
Possibly related or related AE	9 (11%)	6 (15%)
SAE	61 (76%)	39 (95%)
Treatment discontinuation due to AE	13 (16%)	16 (39%)
AE with a fatal outcome	13 (16%)	16 (39%)

Overview of safety profile in Study CS4

	Nusinersen (N=84)	**Control (N=42)**
TEAE	78 (93%)	42 (100%)
Possibly related or related AE	24 (29%)	4 (10%)
SAE	14 (17%)	12 (29%)
Treatment discontinuation due to AE	0	0
AE with a fatal outcome	0	0

In studies CS3B and CS4, the most commonly reported treatment-emergent adverse events (TEAEs) were respiratory and/or infectious in nature. In Study CS3B, the incidence of TEAEs was 96% in the nusinersen group and 98% in the control group. TEAEs with an incidence at least 5% higher in the nusinersen group than in the control group were constipation (35% vs 22%), upper respiratory tract infection (30% vs 22%), pneumonia (29% vs 17%), nasopharyngitis (19% vs 10%), teething (18% vs 7%), respiratory tract infection (11% vs 5%), urinary tract infection (9% vs 0%), bronchitis (8% vs 2%), upper respiratory tract congestion (8% vs 2%), bronchitis viral (6% vs 0%) and influenza (6% vs 0%). The incidence of TEAEs

assessed by the Investigator to be possibly related to study treatment was slightly lower in the nusinersen group versus the control group (11% vs 15%). Vomiting was the only lumbar puncture-related AE observed in the study (nusinersen vs control: 5% vs 0%). Other lumbar puncture-related AEs like headache or back pain were not reported possibility because the study only recruited infants.

In Study CS4, the incidence of TEAEs was 93% in the nusinersen group and 100% in the control group. TEAEs with an incidence at least 5% higher in the nusinersen group than in the control group were pyrexia (43% vs 36%), headache (29% vs 7%), back pain (25% vs 0%), vomiting (29% vs 12%) and epistaxis (7% vs 0%). TEAEs that were considered possibly related or related were reported in 29% of subjects in the nusinersen group and 10% of subjects in the control group. This imbalance was mainly driven by AEs associated with lumbar puncture [headache (10% vs 2%), back pain (8% vs 0%), post lumbar puncture syndrome (2% vs 0%) and vomiting (2% vs 0%)]. The incidences of lumbar puncture-related AEs were higher in Study CS4 compared to Study CS3B, which could be due to better verbal communication skills in the older subjects in the later-onset SMA study CS4.

The most common serious adverse events (SAEs) in Study CS3B included respiratory distress (nusinersen vs control: 26% vs 20%), respiratory failure (25% vs 39%), pneumonia (24% vs 12%), atelectasis (18% vs 10%) and acute respiratory failure (14% vs 22%). In Study CS4, the most common SAEs were pneumonia (nusinersen vs control: 2% vs 14%), pneumonia viral (4% vs 0%), and respiratory distress (2% vs 5%). The SAEs were consistent with the complications of the underlying disease condition. No deaths were reported in subjects with later-onset SMA and subjects with pre-symptomatic SMA who received nusinersen. In Study CS3B (infantile-onset SMA), the incidence of deaths was lower in the nusinersen group compared to the control group (16% vs 39%). Most deaths were due to respiratory disorders (nusinersen vs control: 9% vs 29%), including respiratory failure, acute respiratory failure, respiratory arrest and respiratory distress, which were consistent with the causes of death typically seen in infants with Type I SMA.

The potential safety concerns with nusinersen included thrombocytopenia and coagulation abnormalities, renal toxicity and hydrocephalus. While the available data did not suggest a signal for thrombocytopenia and coagulation abnormalities as well as renal toxicity with nusinersen, the risk could not be excluded given that these events had been reported with other subcutaneous and intravenous ASOs. Relevant warnings on these risks have been included in the package insert.

During post-market surveillance, AEs associated with the administration of nusinersen by lumbar puncture such as meningitis, communicating hydrocephalus, aseptic meningitis and hypersensitivity (e.g., angioedema, urticaria, rash) have been reported. These AEs have been described in the package insert.

Overall, the AEs reported with nusinersen were generally consistent with the nature and frequency of AEs typically observed in SMA patients or lumbar puncture procedure. There were no major safety concerns identified and the safety profile of nusinersen was considered acceptable for the target population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

SMA is a rare, autosomal recessive neuromuscular disease characterised by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. SMA is the most common genetic cause of infant morbidity and has high mortality rate. Treatment option for SMA is very limited and there remains a significant unmet medical need for effective treatments for SMA patients.

The clinical benefit of nusinersen in the treatment of 5q SMA had been demonstrated in different disease phenotypes, including symptomatic infantile-onset (Study CS3B), later-onset SMA (Study CS4) and pre-symptomatic SMA (Study SM201). In infantile-onset SMA, a statistically significant greater proportion of subjects in the nusinersen group achieved a motor milestone response as assessed by HINE Section 2 compared to the control group (50.7% vs 0%; difference = 50.7%, 95% CI: 31.8, 66.5; p<0.0001). In the nusinersen group, 21.9% of subjects achieved full head control, 8.2% achieved independent sitting and 1.4% achieved standing with support, while none in the control group achieved these milestones. Time to death or permanent ventilation was also prolonged in subjects treated with nusinersen (HR 0.53; 95% CI: 0.32, 0.89; p=0.0046).

In later-onset SMA, a statistically significant and clinically meaningful improvement in HFMSE scores from baseline to 15 months in the nusinersen group compared with the control group has been demonstrated (LS mean of 4.0 vs -1.9; difference = 5.9, 95% CI: 3.7, 8.1; p = 0.0000002). Efficacy of nusinersen in later-onset SMA was further supported by improvement in motor milestone attainment and upper limb strength. Similarly in patients with pre-symptomatic SMA, treatment with nusinersen resulted in achievement of motor milestones and development of muscle strength and motor function that were expected of normal infants than symptomatic infants with SMA.

While adult-onset (Type IV) SMA has not been investigated in the clinical studies, given that the underlying cause of adult-onset SMA is the same as that of infantile-onset and later-onset SMA, nusinersen which acts by increasing the amount of full-length protein produced from the SMN2 gene for translation to SMN protein is expected to provide clinical benefit to adult-onset SMA. In addition, the clinical studies have not included patients with prenatal (Type 0) SMA who have severe SMN protein deficiency that results in profound hypotonia and respiratory failure at birth, and the package insert has included a caveat that these patients has not been studied and may not experience a clinically meaningful benefit due to severe SMN protein deficiency.

In terms of safety, the type and frequency of AEs reported with nusinersen were generally due to the complications of SMA or lumbar puncture procedure. Important potential safety risks with nusinersen such as thrombocytopenia and coagulation abnormalities, renal toxicity and hydrocephalus have been adequately described in the package insert. The safety profile of nusinersen was considered acceptable relative to benefits.

Overall, the benefit-risk profile of nusinersen in the treatment of 5q SMA was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Spinraza for the treatment of 5q SMA was deemed favourable and approval of the product registration was granted on 31 March 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

SPINRAZA
Solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Spinraza 12 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

The recommended dosage is 12 mg (5 ml) per administration.
Spinraza treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter.

Duration of treatment
Information on long term efficacy of this medicinal product is not available. 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 below.

Table 1: Recommendations for delayed or missed dose

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.	

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 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. 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.

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 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

Clinical Trial Adverse Drug Reactions

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

The safety of SPINRAZA in infants and children with SMA was assessed in three randomized, double blind, sham controlled studies, two of which were phase 3 (Study CS3B and Study CS4) and one phase 2 (Study SM202), in an open label phase 2 study in symptomatic infants (Study CS3A), an open label study in pre symptomatic infants genetically diagnosed with SMA (Study CS5) 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 CS11 enrolled infantile- and later-onset subjects, including those who completed Studies CS3B, CS4, 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 CS3B, 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 CS4, 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 CS3B and CS4 are summarized in Tables 2 and 3, respectively. Events reported across the open-label studies and the double-blind Study SM202 were consistent with those observed in Studies CS3B and CS4.

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

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

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

Table 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 later-onset SMA

System Organ Class	Preferred term	Control N=42	SPINRAZA N=84
	Any adverse event	42 (100%)	78 (93%)
General disorders and administration site conditions	Pyrexia	15 (36%)	36 (43%)
Nervous system disorders	Headache*	3 (7%)	24(29%)
Gastrointestinal disorders	Vomiting*	5 (12%)	24 (29%)
Respiratory, thoracic and mediastinal disorders	Epistaxis	0	6 (7%)
Musculoskeletal and connective tissue disorders	Back pain*	0	21 (25%)

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

Description of selected adverse events

Adverse events associated with the administration of Spinraza 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 Spinraza.

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

Immunogenicity

The immunogenic response to nusinersen was determined in 346 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADA). Overall, the incidence of ADAs was low, with 15 (4%) patients classified as ADA positive overall, of which 4 had a transient response, 5 had a persistent response, and 6 patients had responses which could not be classified as transient or persistent at the time of data cut off. The impact of immunogenicity on safety was not formally analysed as the number of patients with ADAs was low. However, individual safety data for the treatment-emergent ADA-positive cases were reviewed, and no adverse events (AEs) of interest were identified.

Post-marketing experience

Adverse events associated with the administration of Spinraza by lumbar puncture have been observed in the post-marketing setting. Serious infections associated with lumbar puncture, such as meningitis, have been observed. Communicating hydrocephalus, aseptic meningitis and hypersensitivity (e.g. angioedema, urticaria, rash) have also been reported.

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 the Health Science Authority (HSA) Adverse Event Online Reporting Form.

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.

Clinical efficacy and safety

Symptomatic patients

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 (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 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 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%).

At the final analysis, a statistically significant greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza 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 Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) score were observed in patients in the Spinraza group compared to those in the sham-control group (Table 5).

In the efficacy set, 18 patients (25%) in the Spinraza group and 12 patients (32%) 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.

Table 5 : Primary and secondary endpoints at final analysis – Study CS3B

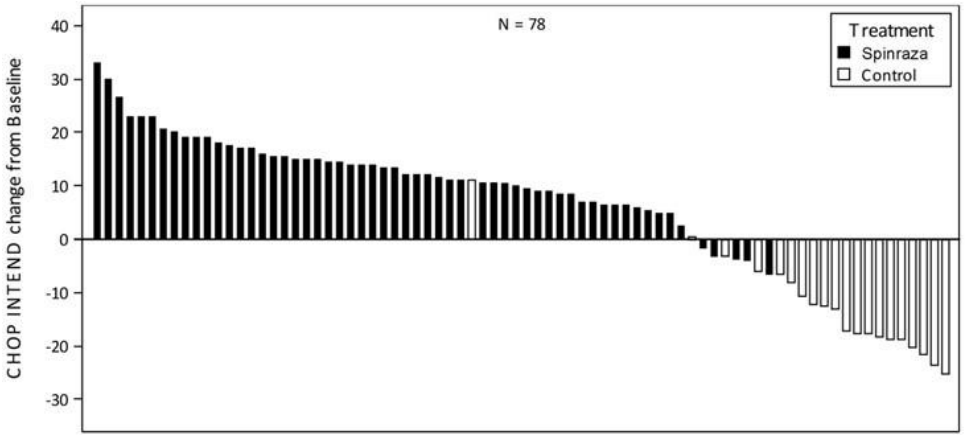
Efficacy Parameter	**Spinraza treated Patients**	**Sham-control Patients**
Survival		
Event-free survival[2] Number of patients who died or received permanent ventilation	31 (39%)	28 (68%)
Hazard ratio (95% CI) p-value[6]	0.53 (0.32 -0.89) p = 0.0046	
Overall survival[2] Number of patients who died	13 (16%)	16 (39%)
Hazard Ratio (95% CI) p-value[6]	0.37 (0.18 – 0.77) 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%)

[1]CS3B 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 group (41%) compared to the sham-control group (0%), p<0.0001)
[2]At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT Spinraza n=80; Sham-control n=41).
[3]At the final analysis, CHOP INTEND and motor milestone analyses were conducted using the Efficacy Set (Spinraza n=73; Sham-control n=37).
[4]Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
[5]According to 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.
[6]Based on log-rank test stratified by disease duration

The extent of improvement in CHOP INTEND is shown in Figure 1 (change from baseline score for each subject).

Figure 1: 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 Study CS11 all patients received Spinraza, with the length of treatment ranging from 65 to 592 days (median 289 days) at the time of interim analysis. Improvements in motor function were observed among patients continuing Spinraza from Study CS3B, as well as those who initiated Spinraza in Study CS11 (Figure 3), with the greatest benefit observed in those with earlier treatment initiation. Among patients without permanent ventilation at the baseline of Study CS11, a majority were alive and without permanent ventilation at the time of interim analysis.

In patients randomized to Spinraza in Study CS3B and including the experience in Study CS11, the median time to death or permanent ventilation was 73 weeks. At the time of a Study CS11 interim analysis, 61 out of 65 patients (94%) were alive. Of the 45 patients who had not met the definition of permanent ventilation in Study CS3B, 38 patients (84%) were alive without permanent ventilation in Study CS11 at the time of interim analysis. Further improvement in mean total motor milestone (HINE-Section 2) (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 CS11.

Patients who first initiated Spinraza treatment in Study CS11 (n=24; sham control in Study CS3B) 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 CS11. At the time of interim analysis, 22 out of 24 patients (92%) were alive. Of the twelve patients (50%) who had not met the definition of permanent ventilation in Study CS3B, 7 patients (58%) were alive without permanent ventilation in Study CS11. The median time to death or permanent ventilation was 50.9 weeks after initiation of Spinraza treatment in Study CS11. Improvement in mean total motor milestone (HINE-Section 2) (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 CS11.

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 (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 group and 29% in sham-control) or walk with support (24% of patients in the Spinraza 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 group compared to the sham-control group (Table 6 , Figure 2).
The analysis was conducted in the ITT population (Spinraza: 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 treated subjects had improvement (73% vs 41%, respectively) and a lower proportion of Spinraza 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 6 .

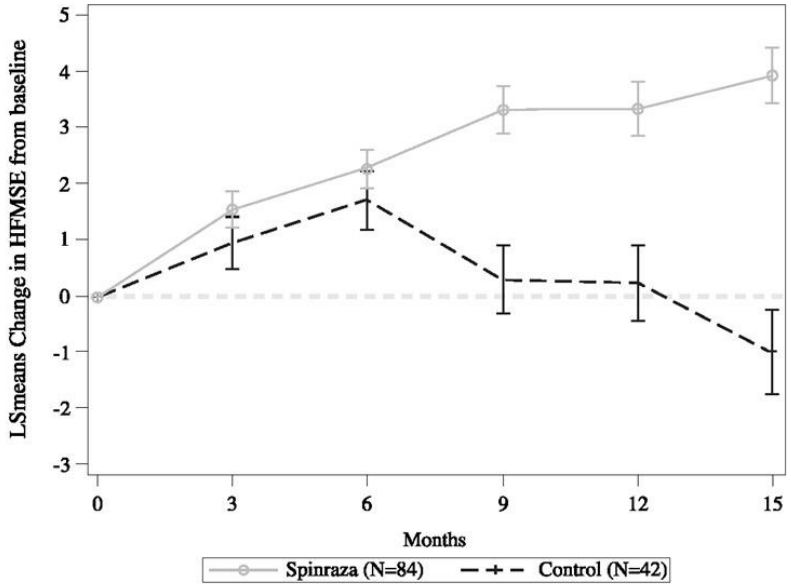
Initiation of treatment sooner after symptom onset resulted in earlier and greater improvement in motor function than those with delayed treatment initiation; however, both groups experienced benefit compared to sham-control.

Table 6 : Primary and secondary endpoints at final analysis – Study CS4[1]

	Spinraza treated Patients	Sham-control Patients
HFMSE score Change from baseline in total HFMSE score at 15 months[1,2,3]	3.9 (95% CI: 3.0, 4.9) p=0.0000001	-1.0 (95% CI: -2.5, 0.5)
Proportion of patients who achieved at least a 3 point improvement from baseline to month 15[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)

[1]CS4 was stopped following positive statistical analysis on the primary endpoint at interim analysis (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))
[2] Assessed using the Intent to Treat population (Spinraza n=84; Sham-control n=42); data for patients without a Month 15 visit were imputed using the multiple imputation method
[3]Least squares mean
[4] Assessed using the Month 15 Efficacy Set (Spinraza n=66; Sham control n=34); analyses are based on imputed data when there are missing data.
[5] Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline
[6]Nominal p value

Figure 2: Mean change from baseline in HFMSE score over time at final analysis (ITT) – Study CS4 [1,2]



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

Upon completion of Study CS4 (CHERISH) 125 patients enrolled in Study CS11 (SHINE), where all patients received Spinraza. The length of treatment ranged from 74 to 474 days (median 250 days) at the time of the interim analysis. A majority of Spinraza treated patients experienced stabilization or improvement in motor function, with the greatest benefit observed in those with earlier treatment initiation.

Of patients who initiated Spinraza treatment in Study CS4 (n=39), stabilization or additional improvements in mean HFMSE (0.2; SD 3.06) and RULM (0.7; SD 2.69) scores were observed from baseline to Study Day 265 in Study CS11.

Patients who initiated Spinraza treatment in Study CS11 (n=20) had a median age of 4.0 years (range 3 - 8 years). Of these patients, stabilization or improvement 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 CS11.

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 was13.8 (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 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 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 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 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 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).

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.

Pre-symptomatic infants

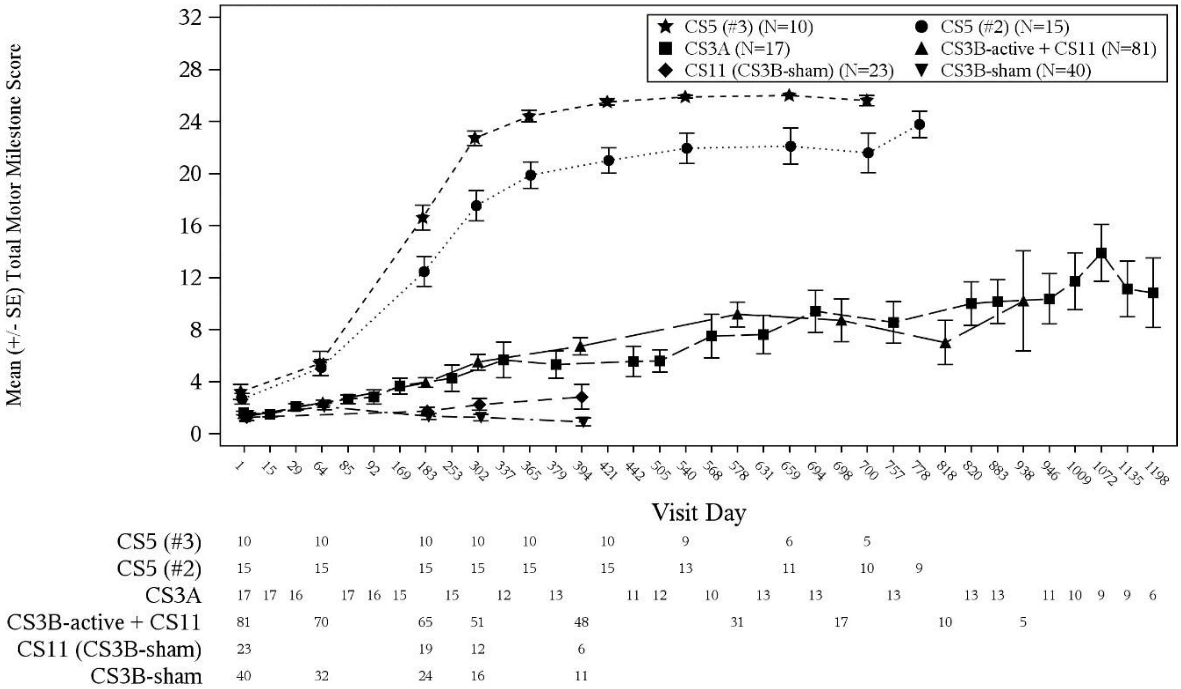
Study CS5 (NURTURE) is an open-label study in pre-symptomatic infants genetically diagnosed with SMA, who were enrolled at 6 weeks of age or younger. Patients in this study were deemed most likely to develop Type I or II SMA. Median age at first dose was 22 days.

An interim analysis was conducted when patients had been on study for 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 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, 22 (88%) patients were walking 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 patients with 2 SMN2 copies and 62.6 (58 - 64) amongst those with 3 SMN2 copies. All patients had the ability to suck and swallow at last assessment, with 22 (88%) infants achieving 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 visit at the interim analysis (n=16). 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 11 patients (64%) 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 pre-symptomatic SMA is shown in Figure 3.

Figure 3: Change in HINE Motor Milestones versus Study days for Study CS3B (treated and sham-control), CS3A, CS5 and CS11



Population used in figure: CS5 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 CS3B the data were windowed into intervals based on time from baseline.
For each study, visits with n < 5 are not plotted.

5.2 Pharmacokinetic properties

Single- and multiple-dose pharmacokinetics (PK) of nusinersen, administered via intrathecal injection, were determined in paediatric 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. Mean CSF trough concentrations of nusinersen accumulated approximately 1.4- to 3-fold after multiple loading and maintenance doses, and reached a steady state within approximately 24 months. 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 is 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 135 to 177 days. 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

Carcinogenesis

A 2-year carcinogenicity study of nusinersen was conducted in mice.

Nusinersen was administered by subcutaneous injection to mice at dose levels of 5, 15, and 50 mg/kg every 2 weeks for 104 weeks. These doses provided plasma exposure levels that were 6-fold, 20-fold, and 104-fold higher than the exposure in patients receiving 12 mg of maintenance nusinersen.

In mice, nusinersen had no effect on survival or the incidence of palpable masses, microscopic neoplasias, or non-neoplastic hyperplasias. Thus, no evidence of an oncogenic effect due to nusinersen was observed.

Mutagenesis

Nusinersen demonstrated no evidence of genotoxicity.

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 toxicity studies (14-weeks and 53-weeks) of intrathecal administration to juvenile cynomolgus monkeys, nusinersen was well tolerated. The exception was an acute, transient deficit 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 intrathecal dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours.

In the 53-week intrathecal dosing study in cynomolgus monkeys no toxicity effects were seen at levels up to 14-fold the recommended annual clinical maintenance dose.

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

4 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

5 ml in a Type I glass vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap.
Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

For single use only.

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 or waste material must be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

ZUELLIG PHARMA PTE. LTD.
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8. DATE OF REVISION OF THE TEXT

March 2023