31 May 2018
EMA/286159/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Spinraza

nusinersen

Procedure no: EMEA/H/C/004312/P46/007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

On 14 February 2018, the MAH submitted a completed paediatric study for Patients with Infantile-Onset Spinal Muscular Atrophy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that ISIS 396443-CS3A: A Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Nusinersen (ISIS 396443) Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The drug was administered in two configurations, a 2-Vial configuration and a Ready to Use (RTU) 1 vial configuration. Bioequivalence studies were not conducted because the administered drug product for both the 2-vial configuration (used in early clinical studies) and the RTU configuration (used in the most recent clinical studies and intended for commercial use) is nearly identical. [JL1]

Throughout the clinical study, two types of formulation configurations were used: a 2-Vial configuration and a Ready to Use (RTU) 1 vial configuration. Minor differences in the amounts of the ingredients existed, but overall, the two formulations can be considered as similar. This RTU formulation is the same as that which is currently approved in the European Union MAA.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- ISIS 396443-CS3A: A Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Nusinersen (ISIS 396443) Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy

This was a Phase 2, open-label study of ISIS 396443 conducted at 3 centres in the United States and 1 center in Canada. As the first study of nusinersen for treatment of infantile-onset spinal muscular atrophy (SMA), it was originally designed as a pilot study to evaluate the clinical efficacy, safety, tolerability, and pharmacokinetics (PK) of multiple doses of nusinersen administered as intrathecal (IT) injections by lumbar puncture (LP) to subjects with infantile-onset SMA. The first study subject started treatment in May 2013. As study subjects continued to exhibit increased survival duration, achievement of new motor milestones, and improvement in muscle function, the study was amended to increase the number of subjects and formally capture efficacy endpoints as well as extend the duration of treatment and observation. An interim analysis based on study data as of January 2016

showed that the majority of subjects had clinically significant improvements in motor function and electrophysiological activity and that survival exceeded what would be expected based on the natural history of the disease. The clinical study report (CSR) for this interim analysis was submitted to the European Medicines Agency within the marketing authorisation application (MAA) on 07 October 2016 (ISIS 396443-CS3A Interim CSR). The final CSR, completed in December 2017, confirmed the interim results and showed consistent and sustained improvements in the achievement of motor milestones and other measures of motor function and electrophysiological activity, as well as prolongation of survival and event free survival, all in clear contrast to the natural history of Type I SMA.

2.3.2. Clinical study

ISIS 396443-CS3A: A Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Nusinersen (ISIS 396443) Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy

Description

Methods

Objective(s)

The objectives of this study were to evaluate the clinical efficacy, safety, tolerability, and PK of multiple doses of nusinersen administered IT to subjects with infantile-onset SMA.

The primary objective was to examine the clinical efficacy of multiple doses of nusinersen administered IT to subjects with infantile-onset SMA.

The secondary objectives were to examine the safety and tolerability and to analyze the cerebrospinal fluid (CSF) and plasma PK of multiple doses of nusinersen administered IT to subjects with infantile-onset SMA.

Study design

Study CS3A was a Phase 2, open-label study of nusinersen conducted at 3 centres in the United States and 1 centre in Canada.

The study consisted of a Screening Period, a Treatment Period (including loading and maintenance dosing), and a Post-Treatment Follow-Up Period. The total duration of participation in the study was approximately 3.7 years. Subjects were enrolled sequentially into the 6-mg loading dose cohort (Cohort 1) and the 12-mg loading dose cohort (Cohort 2). The treatment period included a loading phase and a maintenance phase.

Study population /Sample size

Twenty-one subjects were enrolled in the study, and 20 subjects received at least 1 dose of study treatment and were included in the efficacy, safety, and PK analyses.

The study population was composed of subjects with infantile-onset SMA (onset of symptoms at ≥21 days to ≤6 months of age). The clinical phenotype of infantile-onset SMA is generally equivalent to that of Type I SMA; therefore, the subjects enrolled in this study were expected to have a severe and

rapidly progressive disease with permanent ventilatory support or death from respiratory failure occurring during infancy.

Treatments

Subjects who met the eligibility criteria were admitted to the study center on Study Day 1, underwent pre-dose evaluations, and then received an LP injection of study treatment (ISIS 396443). Following the LP injection of study treatment on Study Day 1, subjects remained at the study center for at least 24 hours for safety monitoring. Subjects were to return to the study center on Study Days 15, 85, 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261 for follow-up evaluations and subsequent injections.

Following LP injections on these dosing days, subjects were monitored for at least 6 hours post injection before leaving the study center. A CSF sample was taken pre-dose on each injection day for safety and PK analyses.

During the treatment period, the study center was to monitor the subject's condition through safety monitoring visits on Study Days 16, 29, 86, 92, 169, 254, 337, 442, 568, 694, 820, 946, 1072, and 1198 and by telephone contact approximately every 3 weeks, except for the weeks when dosing or safety monitoring visits had occurred. Telephone contacts were also made the day after dose administration.

The drug product lot numbers of ISIS 396443 that were used in this study were as follows:

- ISIS 396443 Injection 20 mg/mL, 2.5 mL; 6 or 12 mg IT; multiple injections. One lot was used: CP396443-001.
- Artificial CSF Diluent for Injection, 20 mL Exact Fill. One lot was used: CPPLAC-014.
- ISIS 396443 Injection 2.4 mg/mL, 5.0 mL Ready-To-Use vials. One lot was used: CP396443-005.

Outcomes/endpoints

Pharmacokinetics/Pharmacodynamics:

Non-compartmental PK analysis of ISIS 396443 were carried out on individual subject data, and plasma PK parameters for each subject (when applicable) were determined. Plasma PK parameters (if applicable) were summarized using descriptive statistics.

ISIS 396443 CSF concentration versus time (actual) profiles from Day 1 to Day 673, for each subject, as well as the mean (±SE) CSF concentration versus time (scheduled) profiles for each treatment cohort, are presented graphically.

All subjects enrolled in this study were to receive an IT bolus (over 1 to 3 minutes) of nusinersen through an LP injection for a total of 12 injections, starting on Day 1 and ending on Day 1261. During the loading phase (dosing on Days 1, 15, and 85), 2 dose levels (adjusted based on subject age and CSF volume to be equivalent to either a 6-mg or 12-mg dose for subjects aged 24 months or younger) were evaluated sequentially. The initial dose level of 6 mg was studied in a cohort of 4 subjects, and the 12-mg dose level was studied in approximately 16 subjects. Following the loading phase, all subjects were to receive maintenance dosing with nusinersen 12 mg on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261.

Endpoints

Primary endpoint:

The primary endpoint was the proportion of subjects who achieved improvement in motor milestones as evaluated by Section 2 of the Hammersmith Infant Neurological Examination (HINE).

Secondary efficacy endpoints:

- Event-free survival determined by the proportion of subjects who were alive and did not require permanent ventilatory support (defined as tracheostomy or the need for ≥16 hours ventilation/day continuously for at least 2 weeks in the absence of an acute reversible illness)
- Improvement in motor function as measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND)
- Improvement in neuromuscular electrophysiology measured by the compound muscle action potential (CMAP) of the ulnar and peroneal nerves

Statistical Methods

Pharmacokinetics:

In general, descriptive summary statistics has been used to summarize data; results are presented by cohort and for both cohorts combined.

Clinical Efficacy / safety:

The primary analysis assessed the proportion of subjects in the Safety Population who achieved improvement in motor milestones as of their last available visit. Improvement was defined as any of the following:

1. An increase from baseline of 2 milestones or more, or the achievement of pincer grasp in the voluntary grasp category
2. An increase from baseline of 2 milestones or more, or achievement of touching toes in the ability to kick category
3. An increase from baseline of 1 milestone or more in any of the remaining 6 categories: head control, rolling, sitting, crawling, standing, or walking.

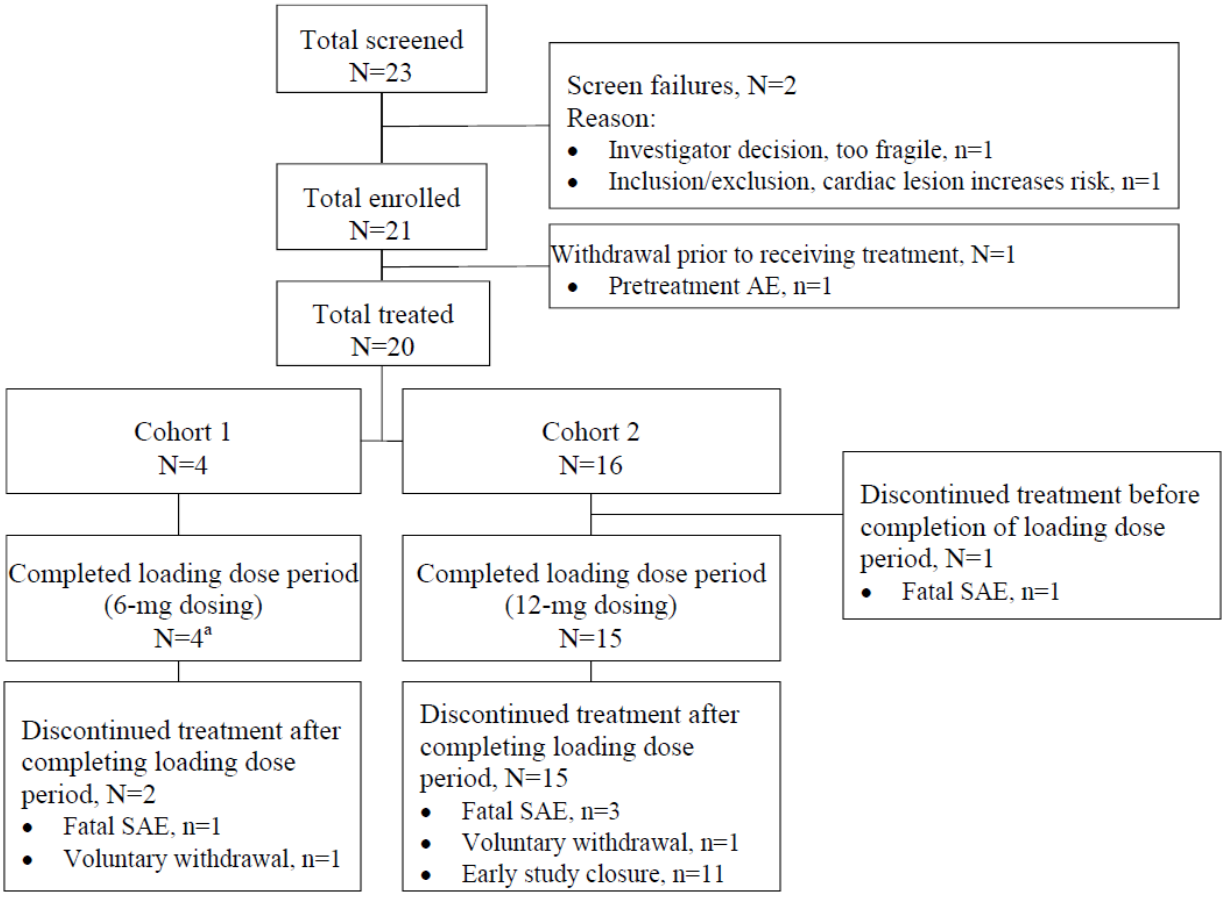
Secondary efficacy analyses assessed event-free survival, CHOP-INTEND Infant Motor Function Scale, and CMAP of ulnar and peroneal nerves. Event-free survival was estimated using Kaplan-Meier methodology.

Results

Recruitment / Number analysed

Of 23 screened pts, 21 were enrolled and 20 received treatment, as per figure below.

Figure: Subject Disposition



AE = adverse event; SAE = serious adverse event; [a] Two subjects completed the study. Subjects were recruited at 4 sites in the USA and Canada, with Site 1833 recruiting 9 subjects and the 3 remaining sites recruiting 3 or 4 subjects each (Table 36).

Twenty-three subjects were screened, of whom 21 subjects were enrolled. Of the 2 subjects who failed screening, 1 subject was considered too fragile to participate due to respiratory difficulties (Investigator decision) and 1 was found to have cardiac anomalies that violated inclusion/exclusion criteria.

Of the 21 subjects enrolled, 1 was withdrawn from the study due to respiratory failure prior to receiving the first dose of study treatment. Of the 20 subjects who received study treatment, 4 were enrolled in Cohort 1 and 16 were enrolled in Cohort 2. These 20 subjects comprise the Safety Population. Of the 20 subjects in the Safety Population, 4 subjects (100%) in Cohort 1, and 15 of 16 subjects (93.8%) in Cohort 2 received their 3 loading doses. One subject in Cohort 2 died due to a metapneumovirus infection prior to receiving all loading doses.

Of the 20 subjects in the Safety Population:

- 1 subject in Cohort 1 voluntarily withdrew from the study after receiving 4 doses of study treatment. The subject's mother did not give a reason for withdrawal.
- 1 subject in Cohort 1 withdrew from the study during the post-treatment observation period due to a fatal SAE that occurred on Day 263 (see Section 12.2.1 for additional information about the death).

- 4 subjects in Cohort 2 discontinued study treatment and withdrew from the study due to fatal SAEs, and 1 subject in Cohort 2 voluntarily withdrew. The subject's mother did not give a reason for withdrawal.
- 11 subjects (all in Cohort 2; 11 of 16 [68.8%]) terminated study treatment due to early study closure.

Of the 5 subjects who died, 4 were receiving study treatment and were considered to have discontinued study treatment at the time of death and withdrawn from the study due to the SAEs that led to their deaths, and 1 had completed study treatment under a previous version of the protocol (Protocol Amendment 2) and was considered to have withdrawn from the study due to the SAEs that led to his death. There were no other discontinuations or withdrawals due to AEs.

Baseline data

Given that this was a multiple-dose study in which subjects were enrolled sequentially into 2 dose cohorts, that no randomization was involved, and that the number of subjects in each cohort was small and the cohorts were of different size, some imbalance in the dose cohorts with respect to demographic and baseline disease characteristics was to be expected.

Overall, 12 subjects (60%) were male, and 16 subjects (80%) were White. Age at enrollment ranged from 36 to 210 days (median: 155 days). Weight ranged from 5.07 to 9.25 kg (median: 6.58 kg), with the median weight for age at the 37th percentile.

Age at onset of SMA symptoms ranged from 21 to 154 days (median: 56 days), with 16 subjects having symptom onset at ≤12 weeks of age. Time between symptom onset and enrollment ranged from 15 to 151 days (median: 75 days). Age at diagnosis of SMA ranged from 0 to 154 days (median: 81 days). The subject diagnosed at age of 0 day was diagnosed in utero. Time between diagnosis and enrollment ranged from 4 to 165 days (median: 64 days). Overall, 17 of 20 subjects (85%) were documented to have 2 copies of the SMN2 gene: all 4 subjects in Cohort 1 and 13 of 16 subjects (81%) in Cohort 2. In Cohort 2, 2 subjects (13%) had 3 copies of the SMN2 gene; for 1 subject (6%), the SMN2 gene evaluation was unavailable because the subject died before the test was performed. A total of 4 subjects (20%) had received gastrostomy tube or nasogastric tube feedings within 30 days prior to first dose.

Motor Milestones at Baseline
Motor milestones were assessed using Section 2 of the HINE, which evaluates neuromuscular development in 8 motor milestone categories. At baseline, the majority of subjects (≥80%) were at the lowest level, i.e., had not achieved any milestones for 6 of 8 categories:

- For Head Control, 16 subjects (80%) could not maintain their head upright, 3 (15%) maintained with wobble, and 1 (5%) maintained all the time.
- For Sitting, 19 subjects (95%) could not sit and 1 (5%) could sit with support at the hips.
- For Rolling, 19 subjects (95%) had no rolling and 1 (5%) could roll from prone to supine.
- For Crawling, 18 subjects (90%) could not lift their head, 1 (5%) could get on their elbow, and 1 (5%) could get on their outstretched hand.
- For Standing, 19 subjects (95%) could not support weight and 1 (5%) could support weight.
- For Walking, 19 subjects (95%) could not walk and 1 (5%) could bounce.

For voluntary grasp, 3 subjects (15%) had no grasp but 17 (85%) could grasp with the whole hand. For ability to kick, 6 (30%) could not kick, 13 (65%) could kick horizontally, and 1 (5%) could kick vertically.

The subject who could sit with support at the hips, roll from prone to supine, crawl on outstretched hand, who could support his weight when standing, and who could bounce when attempting to walk was almost 4 months old at Screening and had 3 copies of the SMN2 gene. Six of the subjects were very young and would not be expected to achieve many motor milestones, but the remainder would be expected to have achieved some level of rolling, sitting, crawling, and standing, if not for their SMA disease.

CHOP INTEND Scores at Baseline

Baseline CHOP INTEND total score ranged from 17 to 64, with a median of 27 (64 is the maximum possible score). In Cohort 1, scores ranged from 22 to 34, with a median of 26. In Cohort 2, scores ranged from 17 to 64, with a median of 28 (Table 38). Twelve of the 16 subjects (75%) in Cohort 2 had baseline scores in the 20 to 39 range while the 2 subjects with 3 copies of the SMN2 gene had baseline scores of 42 and 64.

CMAP Measurements at Baseline

Baseline ulnar CMAP amplitude ranged from 0 to 3.2 mV, with a median of 0.24 mV. Baseline ulnar CMAP area ranged from 0 to 8.8 mVms, with a median of 0.58 mVms.

Baseline peroneal CMAP amplitude ranged from 0 to 2.7 mV, with a median of 0.35 mV.

Baseline peroneal CMAP area ranged from 0 to 10.7 mVms with a median of 1.19 mVms.

Weight for Age Percentiles at Baseline

Weight for age is a key measure for growth assessment. Weight for age percentiles were based on WHO Child Growth Standards, 2006 [WHO 2006]. Overall, baseline weight for age percentiles ranged from the 3rd percentile (3.14) to the 84th percentile (83.89), with the median weight for age at the 37th percentile (37.10). At baseline, there were 3 subjects below the 5th percentile and no subjects above the 95th percentile.

Figure: Summary of Subject Demographics and Baseline Disease Characteristics, Safety Population (N = 20)

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Age (day)			
N	4	16	20
Mean (SD, SEM)	145 (67, 34)	140 (60, 15)	141 (60, 13)
Median (P25, P75)	152 (89, 201)	155 (89, 194)	155 (89, 198)
Min, Max	67, 207	36, 210	36, 210
Gender			
Male	3 (75.0%)	9 (56.3%)	12 (60.0%)
Female	1 (25.0%)	7 (43.8%)	8 (40.0%)
Ethnicity			
Hispanic or Latino	0 (0.0%)	1 (6.3%)	1 (5.0%)
Not Hispanic or Latino	4 (100.0%)	15 (93.8%)	19 (95.0%)
Race			
White	3 (75.0%)	13 (81.3%)	16 (80.0%)
Black	0 (0.0%)	1 (6.3%)	1 (5.0%)
Asian	0 (0.0%)	1 (6.3%)	1 (5.0%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple Race	1 (25.0%)	0 (0.0%)	1 (5.0%)
Other	0 (0.0%)	1 (6.3%)	1 (5.0%)

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Weight (kg)			
N	4	16	20
Mean (SD, SEM)	7.068 (1.889, 0.944)	6.704 (1.197, 0.299)	6.777 (1.310, 0.293)
Median (P25, P75)	7.075 (5.450, 8.685)	6.580 (5.625, 7.437)	6.580 (5.585, 7.900)
Min, Max	5.200, 8.920	5.070, 9.250	5.070, 9.250
Weight for Age Percentiles (%)			
N	4	16	20
Mean (SD, SEM)	43.90 (41.16, 20.58)	39.00 (25.75, 6.44)	39.98 (28.20, 6.30)
Median (P25, P75)	44.05 (8.58, 79.21)	37.10 (17.36, 62.36)	37.10 (15.46, 66.39)
Min, Max	3.59, 83.89	3.14, 81.06	3.14, 83.89
Length (cm)			
N	4	16	20
Mean (SD, SEM)	66.60 (9.73, 4.87)	64.18 (3.94, 0.99)	64.67 (5.31, 1.19)
Median (P25, P75)	69.30 (59.20, 74.00)	65.10 (61.65, 66.15)	65.10 (61.65, 66.90)
Min, Max	53.50, 74.30	56.40, 70.90	53.50, 74.30
Age at Symptom Onset (day)			
N	4	16	20
Mean (SD, SEM)	47 (19, 10)	63 (42, 11)	60 (39, 9)
Median (P25, P75)	46 (32, 63)	60 (25, 88)	56 (28, 81)
Min, Max	28, 70	21, 154	21, 154

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Time between Symptom Onset and Enrollment (day)[1]			
N	4	16	20
Mean (SD, SEM)	97 (50, 25)	77 (38, 10)	81 (40, 9)
Median (P25, P75)	100 (57, 138)	74 (43, 114)	75 (47, 121)
Min, Max	39, 151	15, 130	15, 151
Age at Diagnosis (day)			
N	4	16	20
Mean (SD, SEM)	74 (27, 14)	80 (49, 12)	78 (45, 10)
Median (P25, P75)	74 (53, 95)	81 (32, 123)	81 (39, 116)
Min, Max	42, 105	0, 154	0, 154
Time between Diagnosis and Enrollment (day)[2]			
N	4	16	20
Mean (SD, SEM)	71 (50, 25)	61 (38, 10)	63 (40, 9)
Median (P25, P75)	79 (36, 106)	58 (38, 77)	64 (38, 86)
Min, Max	4, 123	7, 165	4, 165
SMN2 Copy #			
2 copies	4 (100.0%)	13 (81.3%)	17 (85.0%)
3 copies	0 (0.0%)	2 (12.5%)	2 (10.0%)
Missing	0 (0.0%)	1 (6.3%)	1 (5.0%)
Subtype of SMA			
Type IB	4 (100.0%)	12 (75.0%)	16 (80.0%)
Type IC	0 (0.0%)	4 (25.0%)	4 (20.0%)

Note: Baseline is defined as the last non-missing value prior to the first dose of ISIS 396443.
[1]Time between symptom onset and enrollment (day)=Age(day) - Age at symptom onset(week) *7.
[2]Time between diagnosis and enrollment (day)=Age(day) - Age SMA diagnosed(week) *7.

SMA history included hypotonia (19 subjects, 95%), limb weakness (19 subjects, 95%), delayed motor development (17 subjects, 85%), history of pneumonia or respiratory symptoms (9 subjects, 45%), and swallowing or feeding difficulties (9 subjects, 45%). One subject (5%) had a history of areflexia of the knees that progressed to generalized areflexia.

Statistical Methods:

Populations:

Safety Population: All subjects who were registered and received at least 1 dose of ISIS 396443.

Efficacy Evaluable Population: All subjects who were registered, received all scheduled loading doses of study treatment, and completed visits through at least Day 92.

PK Population: All subjects who were registered and for which there is at least 1 evaluable post-dose PK sample.

2 SMN2 Copy Set: Those subjects in the Evaluable Population who haves 2 copies of the SMN2 gene.

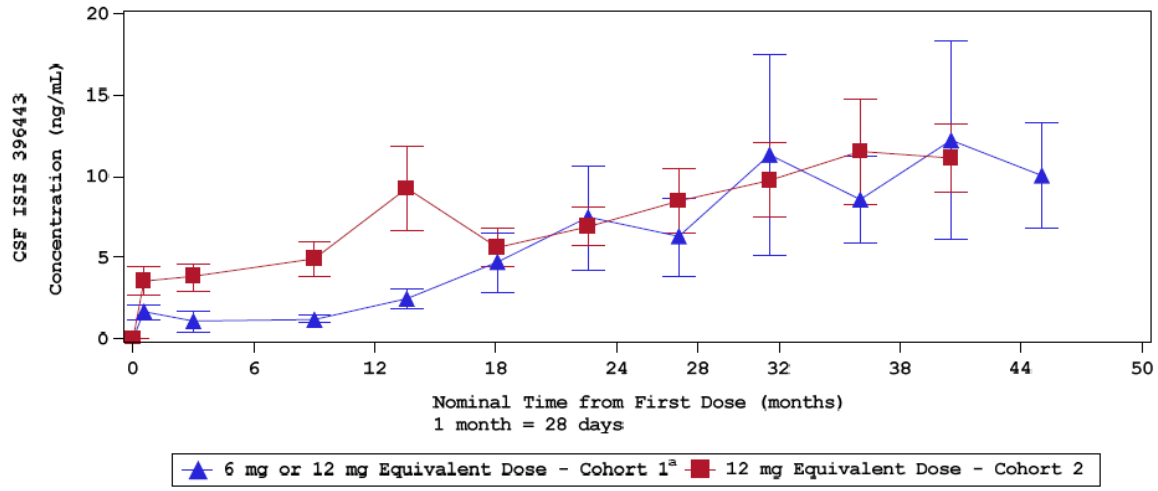
Efficacy results

Pharmacokinetics:

Concentrations of ISIS 396443 in Cerebrospinal Fluid

Overall, interpretation of the data for ISIS 396443 concentrations in CSF was limited by the small number of subjects, especially in Cohort 1 (N = 4) and the high degree of variability observed in the ISIS 396443 concentrations (coefficient of variation ranging from 34% to >100%). Nevertheless, the mean ISIS 396443 concentrations in CSF increased over time on all predose evaluations up to Day 1261 (45 months) in Cohort 1 and Day 1135 (40.5 months) in Cohort 2, and apparent steady-state CSF concentrations were achieved in both (Figure 10). The mean (SD) CSF concentrations achieved at Day 1135 in Cohorts 1 and 2 were 12.2 ng/mL (8.60) and 11.1 ng/mL (4.99), respectively. These profiles were anticipated given the long terminal half-life of the drug (4 to 6 months) and the time required for concentrations to reach steady state (5 half-lives, approximately 2 years). The dose level in Cohort 1 was lower than that in Cohort 2 for the loading dose period (6 versus 12 mg) and increased from 6 to 12 mg (the dose level of Cohort 2) for the maintenance dose period, which began 9 months after initiation of dosing. Nevertheless, after an additional 30 months of dosing in Cohort 1 (up to Day 1261), the mean concentration range achieved between Days 1135 and 1261 (12.2 ng/mL and 10.0 ng/mL, respectively) was similar to the mean steady-state trough concentration level observed in Cohort 2 on Day 1135 (11.1 ng/mL). Actual half-life for ISIS 396443 in CSF could not be calculated for Study CS3A because postdose samples were not collected during the elimination phase.

Figure 10: Mean (±SE) Cerebrospinal Fluid Concentrations of ISIS 396443 Versus Time by Administered Dose (Linear Scale) (PK Population)

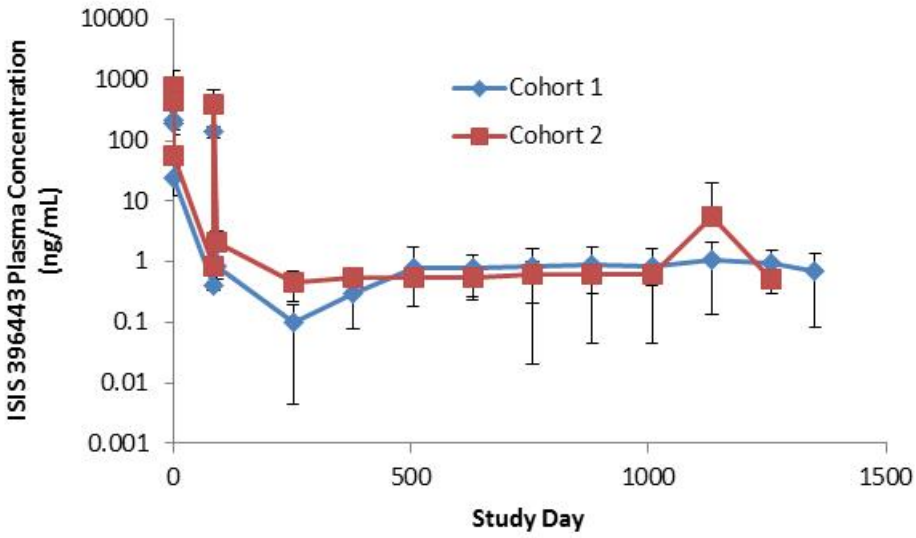


Concentrations of ISIS 396443 in Plasma and Pharmacokinetic Parameters

As discussed during the MAA evaluation, while being distributed within the CNS, IT administered ISIS 396443 also appears to be transferred from the site of administration (CSF) into the systemic circulation, with peak plasma levels observed at the first collected timepoint after single and multiple doses (1 hour on Day 1 and 4 hours on Day 85). After reaching the observed peak level following the 1st dose (Day 1) and the 3rd dose (Day 85), mean plasma concentrations of ISIS 396443 declined to less than 10% of peak concentration values at 24 hours after IT dosing on Day 1 and less than 1% of peak concentration values at 168 hours after IT dosing on Day 85. The rapid decline over the first 24

hours was followed by a much slower elimination through 168 days postdosing, indicating a biphasic disposition for ISIS 396443 in plasma following IT bolus administration. There was no accumulation in the mean plasma concentrations after multiple doses (Day 85 limited profile and predose values at subsequent timepoints) at the 6- or 12-mg dose level (Figure 11). The predose (trough) CSF to plasma ratio was 3- to 19-fold during the loading and maintenance dose periods. The mean (SD) plasma concentration achieved on Day 1009 in Cohorts 1 and 2 was 0.855 (0.809) ng/mL and 0.634 (0.226) ng/mL, respectively.

Figure 11: Mean (±SE) Plasma Concentrations of ISIS 396443 Versus Time (Linear Scale) (PK Population)

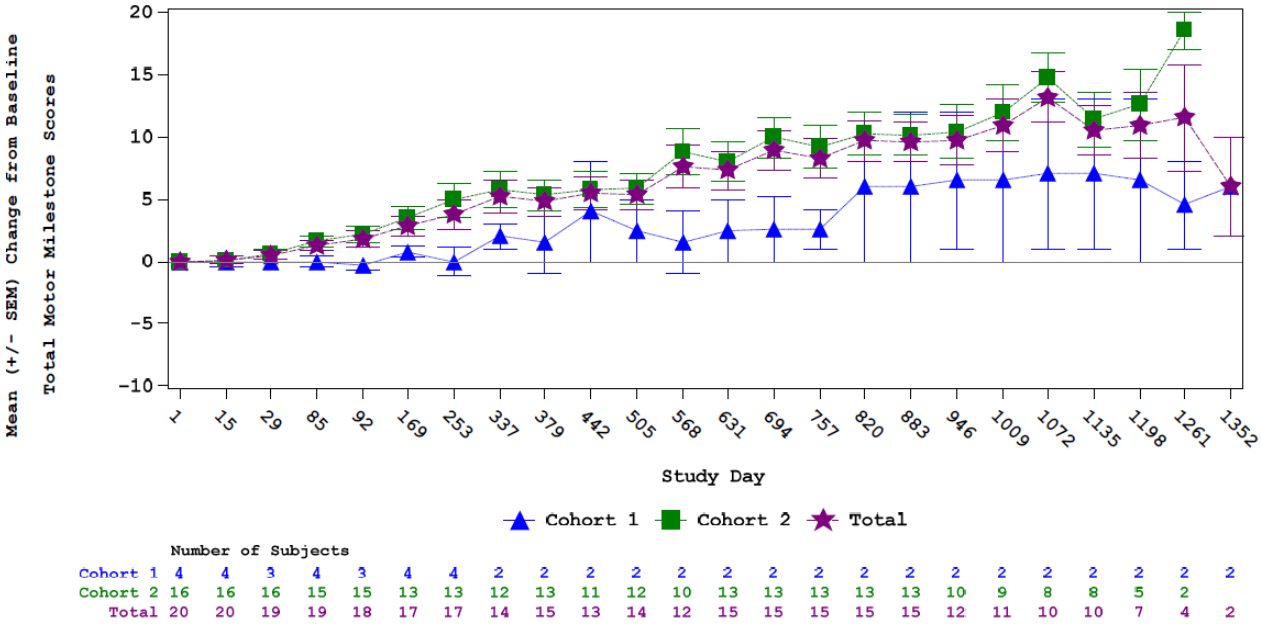


Clinical:

Motor Function

- Sustained and clinically significant improvements in HINE Section 2 mean motor milestone total scores were observed in both dose cohorts over time. ISIS 396443-treated subjects achieved a mean of 13.20 new motor milestones after approximately 3 years on study (Day 1072).
    - Overall, 12 of 20 subjects (60%) in the study met the primary endpoint of protocol-defined improvement in motor milestones, as assessed by Section 2 of the HINE, as of the last evaluable study visit.
    - For subjects with 2 copies of the SMN2 gene and subjects with symptom onset at ≤12 weeks of age, the majority met the primary endpoint of protocol-defined improvement in motor milestones.
    - As of the last study visit, 2 subjects (10%) achieved walking (holding on or unaided), 4 subjects (20%) achieved standing (with support or unaided), 8 subjects (40%) achieved independent sitting (either prop, stable sit, or pivot), and 8 subjects (40%) achieved full head control (all the time upright).

Figure: Total Motor Milestones Over Time: Mean Change From Baseline, Safety Population (N = 20)



- Sustained and clinically significant improvements in mean CHOP INTEND total scores were observed in both dose cohorts over time, with a mean improvement of 21.30 points after approximately 3 years on study (Day 1072), in contrast to the natural history of Type I SMA, which is consistent with an overall decline in CHOP INTEND scores over time.
    - Overall, 11 of 20 subjects (55%) met the secondary endpoint of an increase in total CHOP INTEND score ≥4 points as of the last study visit.
    - For subjects with 2 copies of the SMN2 gene, 10 of 17 (58.8%) had an increase of ≥4 points as of the last study visit.
    - For subjects with symptom onset at ≤12 weeks of age, 9 of 16 (56.3%) had an increase of ≥4 points as of the last study visit.
- Sustained and clinically significant improvements of mean CMAP amplitude of the ulnar and peroneal nerve were observed in both dose cohorts over time. ISIS 396443-treated subjects experienced a mean increase from baseline in ulnar amplitude (0.703 mV) and peroneal amplitude (2.62 mV) after approximately 3 years on study (Day 1072), in contrast to CMAP studies in untreated Type I SMA where subjects normally have values <1 mV after symptom onset and do not improve over time.
- Achievement of new motor milestones and increased CHOP INTEND scores and CMAP values generally began sooner and showed greater improvement over time in subjects who received the 12-mg loading dose (Cohort 2) compared to those who received the 6-mg loading dose (Cohort 1), suggesting that this may be an effect of the higher loading dose for subjects in Cohort 2.

Growth Parameters

- Overall, increases from baseline were observed in all growth parameters measured. When considering growth results, it is important to note that the majority of subjects were receiving supplemental nutrition by gastrostomy tube or some other means during the study.

Overall and Event-free survival

- Of the 20 subjects in the Safety Population, 11 (55%) were alive and free of permanent ventilation at the last visit. Of the 5 subjects who died (all of SMA-related causes), 1 died after approximately 2.5 years on study, 1 died after less than 1 year on study, and 3 died after less than 6 months on study. The subjects who died received 2 to 9 doses of study treatment.
- In addition to the 5 deaths, 4 subjects met the criteria for permanent ventilation (including 2 subjects who voluntarily withdrew from the study).

Safety results

MAH stated that ISIS 396443 was well tolerated when administered as multiple IT injections, and no maximum tolerated dose was identified. No specific safety concerns were identified in the overall safety profile of ISIS 396443.

Adverse events

Of the 802 AEs reported in these 20 subjects, 504 events (62.8%) were assessed as mild, 225 events (28.1%) were assessed as moderate, and 73 events (9.1%) were assessed as severe. The most frequently observed AEs were pyrexia (52 events [6.5%] in 17 subjects [85.0%]), upper respiratory tract infection (47 events [5.9%] in 12 subjects [60%]), joint contracture (38 events [4.7%] in 10 subjects [50%]), respiratory distress (16 events [2.0%] in 9 subjects [45%]), and constipation (10 events [1.2%] in 9 subjects [45%]).

- Three events (1 AE of transient neutropenia, 1 AE of vomiting, and 1 AE of diarrhea) were assessed as possibly related to study treatment. Vomiting and diarrhea were also considered possibly related to the LP dosing procedure. All events were assessed as mild in severity. No other events were assessed as related or possibly related to study treatment.
- When measured by 90-day intervals, the incidence of AEs and SAEs tended to decrease from Day 1 through 720, with notably fewer events over time in the gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders SOCs.
- AEs occurring within 24 or 72 hours of dose administration appeared to be not related to study treatment or treatment administration, and no safety concerns were identified in the periods immediately following dosing.
- The LP procedure for treatment administration was well tolerated. The frequency and nature of the events occurring after LP during the study were consistent with those typically observed following an LP procedure.

Serious Adverse Events

Overall, 101 SAEs were reported in 16 subjects (80%). SAEs reported with the highest frequency were respiratory in nature, which is consistent with the natural history of Type I SMA:

SAEs were most frequently reported in the respiratory, thoracic, and mediastinal disorders SOC (46 events [45.5%] in 15 subjects [75%]) and the infections and infestations SOC (44 events [43.6%] in 13 subjects [65%]), the majority of which were respiratory in nature. Less common were cardiac disorders (5 events [5.0%] in 3 subjects [15%]), metabolism and nutrition disorders and nervous system disorders (2 events [2.0%] in 2 subjects each [10%]), and gastrointestinal disorders and musculoskeletal and connective tissue disorders (1 event each [1.0%] in 1 subject each [5%]).

SAEs occurring in more than 1 subject were as follows:

- Acute respiratory failure: 13 events (12.9%) in 6 subjects (30%)
- Respiratory distress: 12 events (11.9%) in 8 subjects (40%)
- Pneumonia: 8 events (7.9%) in 5 subjects (25%)
- Respiratory failure: 6 events (5.9%) in 5 subjects (25%)
- Respiratory syncytial virus bronchiolitis and rhinovirus infection: 4 events (4.0%) in 4 subjects each (20%)
- Bronchiolitis and pneumonia viral: 4 events (4.0%) in 3 subjects each (15%)
- Pneumonia aspiration: 3 events (3.0%) in 3 subjects (15%)
- Atelectasis: 3 events (3.0%) in 2 subjects (10%)
- Apnea, corona virus infection, metapneumovirus infection, pneumonia bacterial, pneumonia pseudomonas aeruginosa, viral infection, and viral upper respiratory tract infection: 2 events each (2.0%) in 2 subjects each (10%)

For all other SAEs, there was 1 event each reported in 1 subject each.

None of the SAEs were considered related to study treatment or related to the LP procedure.

Deaths

Five of the 20 subjects died as a result of SAEs that were either accidental or consistent with the rapid natural progression of Type I SMA. None of the deaths or SAEs was considered related to study treatment by the Investigator.

Overall, there were no clinically relevant changes related to ISIS 396443 in serum chemistry, hematology, coagulation, urinalysis, vital signs, physical or neurological examinations, or ECGs. Elevations of CSF RBCs in 3 subjects appear to have resulted from the LP procedure and are not considered related to ISIS 396443.

There were no clinically significant differences in the type or incidence of AEs between the loading and maintenance dose periods, or between Cohort 1 (6-mg equivalent loading dose) and 2 (12-mg equivalent loading dose) during the loading dose period.

2.3.3. Discussion on clinical aspects

Pharmacokinetics

On Pharmacokinetic grounds, the updated data confirmed the overall conclusions obtained in the reduced number of subjects and shorter period of time data evaluated during the MAA application. As such, as described at the time, ISIS 396443 trough concentrations in the CSF accumulated approximately 3.0-fold and reached steady state after multiple 12 mg loading and maintenance doses at around 30 months in infants diagnosed with SMA. No further significant accumulation in CSF concentrations were observed with additional doses after steady state. From the plasma data, it is also confirmed that ISIS 396443 trough concentrations in plasma were relatively low compared to those in CSF. After reaching the peak level, plasma concentrations of ISIS 396443 declined rapidly followed by

a much slower decline, indicating a biphasic disposition in plasma. There was no accumulation in the mean plasma concentrations after multiple doses

Following the circulation of the preliminary AR, comments were received from several Member States.

MS-1 and MS-2 are both in agreement with the Rapporteur and MS-3 has commented the following:

The MAH should discuss whether the PK results with longer exposure warrant any changes in section 5.2 of the SmPC "Pharmacokinetic properties".

Rapporteur´s position: Currently, the SmPC section 5.2 contains the following information related to the data under evaluation, "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." The presented data was not subjected to any PK modelling procedure, and only limited descriptive statistics were performed on the CSF concentrations. From the presented data, no major differences were seen in terms of accumulation and time tendency to multiple dose steady state from the ones initially reported. Overall, these profiles were in accordance with a long terminal half-life (4 to 6 months) and the time required for concentrations to reach steady state (5 half-lives, approximately 2 years).

Clinical:

Efficacy results confirmed the effect of IT nusinersen in a population of subjects with infantile-onset SMA. There seems to exist a dose response effect, with patients receiving higher and earlier doses having a better response to treatment. The fact that the study was terminated early than expected did not allow to have data from the second cohort from day 1352, and data from the 3 earlier visits was also curtailed. Notwithstanding, there appears to exist a plateau phase, and only a couple of children (who reached day 1261) have evolved beyond a mean plateau.

Safety data is also aligned with the interim analysis report and MA. Most AEs have reduced in frequency as time went by, including procedure related events. Although the number of patients is limited, it is interesting to see that none of the events that have been recently related to nusinersen such as meningitis / encephalitis and intracranial hypertension have been identified. Still, some of the symptoms such as nausea / vomiting and headaches can be symptoms of the inflammation / increase in CSF pressure.

Following circulation of the preliminary AR, comments on the E&S clinical part were received from MS-1, MS-2 and MS-3. MS-1 and MS-2 were in agreement, and MS-3 further proposes that the information on long term safety and efficacy, including event free survival and "the plateau phase" of motor skill attainment described in the AR, is considered relevant to the prescriber. This position is endorsed by the Rapp and therefore it is added as a Request for Supplementary Information.

3. Rapporteur's CHMP overall conclusion and recommendation

The MAH has provided the final results of study CS3A of nusinersen in Infantile SMA. The interim analysis of this study has been used as main data for the assessment and MA of nusinersen. The final results have confirmed efficacy in the immediate and medium-long term which corroborate the interim analysis data that was considered when giving MA. Safety results in this small sample have not shown recently identified severe adverse events, namely encephalitis or intracranial hypertension, but the

adverse events observed are not different from the ones already known for the product, procedure and SMA.

In conclusion, the final results of the study CS3A are in line with the data provided by the interim analysis, and do not raise new concerns in terms of PK, efficacy and safety. The PAM is considered fulfilled.

☒ Fulfilled:

The MAH should submit a variation application within 60 days of finalisation of this procedure.

It is proposed that updated information on long term safety and efficacy, including event free survival and "the plateau phase" of motor skill attainment described in the AR, is considered relevant to the prescriber. Therefore an update to the interim result of study ISIS 396443-CS3A which is already in the SmPC should be performed.

The wording below is proposed for the second paragraph on study CS3A:

"~~At the time of the planned interim analysis patients in the study had a median time on study of 670 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). ~~At this time, 13 out of 20 patients (65%) had~~Twelve of 20 subjects (60%) in the study met the primary endpoint with a plateau improvement in mean motor milestone achievement over time. A sustained improvement in mean CHOP INTEND score was observed from baseline to day ~~694~~1072 (mean change ~~16.90~~21.30), but most patients have not evolved beyond the mean plateau. Overall, 11 out of 20 patients (55%) met the endpoint of an increase in total CHOP INTEND score of ≥4 points as of ~~their last study visit prior to data cut-off~~ 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 subjects met the criteria for permanent ventilation and 5 patients died during the study."