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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Safety Team Leader Review

Date	December 15, 2017
From	Sally Usdin Yasuda
Subject	Safety Team Leader Review
NDA/BLA # Supplement#	NDA 209531
Applicant	Biogen, Inc.
Date of Submission	September 23, 2016
PDUFA Goal Date	May 23, 2017
Proprietary Name / Non-Proprietary Name	Spinraza (nusinersen)
Dosage form(s) / Strength(s)	Solution for intrathecal injection, 2.4 mg/ml
Applicant Proposed Indication(s)/Population(s)	Treatment of spinal muscular atrophy (SMA)
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of nusinersen outweigh the risks, then I recommend approval
Recommended Indication(s)/Population(s) (if applicable)	

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Nusinersen is proposed to be used for treatment of spinal muscular atrophy (SMA). If efficacy is demonstrated and the benefits of nusinersen outweigh the risks, then I recommend approval with labeling language including WARNINGS and PRECAUTIONS to mitigate the risks.

This document reviews the risk profile of nusinersen. I summarize the findings of Dr. Evelyn Mentari and I agree with her recommendations regarding risk and strategies to reduce the risk. Please refer to Dr. Rainer Paine's review for discussion of Analysis of Condition and Current Treatment Options and Benefit.

Risk:

Nusinersen is associated with adverse effects that have potentially severe consequences.

- Six of 56 (11%) nusinersen patients had a platelet level below the lower limit of normal, compared to 0 of 28 sham procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in that study. Five of 173 (3%) nusinersen patients had a hemorrhagic complication of lumbar puncture. Coagulation abnormalities have been observed after administration of some antisense oligonucleotides. Low platelet levels or coagulation abnormalities may increase the risk of adverse outcomes after intrathecal administration of nusinersen. Monitoring platelets and coagulation parameters at baseline and prior to each maintenance dose may help mitigate this risk.
- Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile onset SMA compared to 5/25 (20%) sham control subjects. Proteinuria occurred in 36 of 52 (69%) of nusinersen subjects with later-onset SMA subjects with a longer duration of treatment. Treatment emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured; measurements from a comparator control were not performed. Low serum bicarbonate levels are characteristic of proximal renal tubular acidosis. Nusinersen accumulates in the kidney and renal toxicity is a class effect of oligonucleotides. Monitoring for proteinuria and monitoring serum electrolytes including bicarbonate may help mitigate a risk of an adverse clinical outcome.
- Severe hyponatremia occurred in a patient treated with nusinersen. Monitoring serum electrolytes at baseline and before each dose may help mitigate this risk.
- Decreased growth (height and weight) was observed in nusinersen subjects compared to sham control subjects in Study CS3B. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment.
- Rash and possible vasculitis were reported in 2 patients out of 173 treated with nusinersen. A third subject had new onset seizures and cerebral infarction after starting nusinersen, with no known risk factor or potential cause for cerebral infarction; the etiology in this case is unknown but vasculitis is a possible cause of cerebral infarction.
- Nusinersen, like other phosphorothioate oligonucleotides, accumulates in the liver. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control

subjects. Monitoring hepatic tests, including gamma-glutamyl transferase (GGT) may help mitigate the risk of hepatotoxicity.

Paragraph #5

If nusinersen is approved, I recommend WARNINGS and PRECAUTIONS in labeling regarding the risks of thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, decreased growth, possible vasculitis, and hepatotoxicity. If nusinersen is approved, the label should include recommendations for monitoring to mitigate these risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Paine's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Paine's review of clinical efficacy.	
Benefit	• Please refer to Dr. Paine's review of clinical efficacy.	
Risk	• The safety database for nusinersen includes all patients from the Phase 3 controlled study and the Phase 2 uncontrolled study in patients with symptomatic infantile onset SMA, the Phase 2 open-label study in infants with pre-symptomatic SMA, and open label trials in subjects with later onset SMA. Drug exposure is adequate for NDA	Safety issues that occur at the proposed dose of nusinersen include thrombocytopenia, proteinuria, hyponatremia, decreased growth, and rash and possible vasculitis. Increased liver enzymes have also been observed in some

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	submission, but longer durations of exposure may occur in the postmarketing setting. The safety database did not include patients with Type 4 SMA (age of symptom onset in the second or third decade), who are included in the proposed treatment indication. • The most common AEs in the Phase 3 controlled trial (Study CS3B) in symptomatic infantile onset (at least 20%, and at least 5% greater or at least 2 times as frequently as sham control) were: upper respiratory infection (44%); lower respiratory infections (43%); and constipation (30%). In later onset patients, common adverse events that were not commonly reported in Study CS3B included headache (50%), back pain (41%), and post lumbar puncture syndrome (41%) most of which occurred within 5 days of lumbar puncture. • Six of 56 (11%) nusinersen patients had a platelet level below the lower limit of normal, compared to 0 of 28 sham procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in that study. Five of 173 (3%) nusinersen patients had a hemorrhagic complication of lumbar puncture. Coagulation abnormalities have been observed after administration of some antisense oligonucleotides. • Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile onset SMA compared to 5/25 (20%) sham control subjects. Proteinuria occurred in 26 of 52 (69%) of later-onset SMA subjects with a longer duration of treatment. Nusinersen accumulates in the kidney in humans and accumulation in proximal tubule cells has been described in nonclinical studies. The urinary dipstick test used in nusinersen clinical studies is relatively insensitive to proteins that are major constituents of tubular proteinuria. Treatment emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured; measurements from a comparator control were not performed. Low serum bicarbonate levels are characteristic of proximal renal tubular acidosis. Renal toxicity is a class effect of oligonucleotides, and life-threatening sequelae of	patients. Bleeding abnormalities, renal accumulation, and hepatic accumulation are class effects of phosphorothioate antisense oligonucleotides. The safety issues potentially could have life-threatening outcomes; monitoring could mitigate the risk. The magnitude of the potential for serious harm after approval is unknown. Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	proteinuria have been reported with other antisense oligonucleotides. • Severe hyponatremia occurred in a patient treated with nusinersen. The sodium level normalized after salt supplementation treatment, which continued for 14 months. • Decreased growth (height and weight) was observed in nusinersen subjects compared to sham control subjects in Study CS3B. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment. • Rash and possible vasculitis were reported in 2 patients treated with nusinersen; one patient did not have a biopsy and the other patient had a post-operative diagnosis of vasculitis vs vascular occlusion, although the biopsy reported stated "there are no features of vasculitis". A third subject had new onset seizures and cerebral infarction after starting nusinersen, with no known risk factor or potential cause for cerebral infarction; the etiology in this case is unknown but vasculitis is a possible cause of cerebral infarction. • Nusinersen, like other phosphorothioate oligonucleotides, accumulates in the liver. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects. • • Safety in the postmarketing setting: Laboratory values as markers of renal, hepatic, and thrombocytopenia adverse events would be useful at baseline and prior to each maintenance dose in the postmarket setting if the drug is approved. • Other uncertainties: The risk of serious toxicity with longer term exposure and with exposure in more patients is unknown.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Strong product labeling with recommendations for monitoring of laboratory parameters may help to mitigate the risks of renal, hepatic, and thrombocytopenia adverse events. However, even with adequate monitoring, some patients may experience serious adverse events.	WARNINGS and PRECAUTIONS should be included in labeling to describe the risks of renal and hepatic adverse events, and thrombocytopenia and coagulation abnormalities, and to provide recommendations for monitoring. I also recommend informing prescribers about hyponatremia, decreased growth, and possible vasculitis in WARNINGS and PRECAUTIONS.

2. Background

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Evelyn Mentari, of the nusinersen NDA 209531 and provides my conclusions and recommendations regarding the safety findings and management of the risks.

- *The product information and the applicant's proposals*

Nusinersen (also known as ISIS 396443) is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (a phosphorothioate oligonucleotide). The proposed indication is treatment of SMA. The proposed dose in patients older than 2 years of age is 12 mg given as is a loading dose on Days (b) (4) followed by a maintenance dose given every 4 months. (b) (4) Nusinersen is not approved for any other indication in the United States.

- *Therapeutic context*

SMA is a neuromuscular disease characterized by degeneration of spinal cord neurons, resulting in progressive muscular atrophy and weakness. A deletion or mutation in the SMN1 gene that is responsible for the majority of SMN protein production causes SMA. A deficiency of SMN protein results in degeneration of the motor neurons in the anterior horn of the spinal cord. According to the Sponsor, SMN2 is normally responsible for a small amount of SMN protein products. According to the Sponsor, nusinersen binds to splicing specific sequence of the SMN2 pre-mRNA that the Sponsor states is present in all patients with spinal muscular atrophy (SMA), increasing the amount of full-length protein produced from the SMN2 gene. Infants with the worst form of SMA die within a few weeks of birth. Patients with all other forms are asymptomatic following birth, with more severe disease associated with earlier symptom onset and less protein production. SMA is classified as follows as shown in Dr. Mentari's review:

Table 1. Clinical Classification of Spinal Muscular Atrophy

SMA Type	Age of Onset	Highest Function	Natural Age of Death
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SMA = Spinal Muscular Atrophy
Source: Wang CH, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *J Child Neurol* 2007 22: 1027

The Sponsor characterizes patients in this NDA as symptomatic (infantile onset and later onset) and presymptomatic, genetically diagnosed SMA. Data are from 10 clinical studies that enrolled newborns up to aged 15 years at first dose with a genetic diagnosis of 5q SMA and multiple copies of the *SMN2* gene.

SMA occurs in 8.5 to 10.3 per 100,000 live births, with similar prevalence reported in the US. Therapy is supportive. There are no approved treatments for SMA in the US.

- *Regulatory background and marketing history*

Orphan drug designation and fast track designation were granted in 2011. With respect to nusinersen drug safety in humans, according to minutes from the September 15, 2015, Type C meeting, the Sponsor was told that a thorough QT/QTc study would not be required before NDA filing, but that the Sponsor must ensure that patients are adequately monitored during drug development, and the possible need for such a study post-approval would remain a review issue.

There is no foreign marketing experience with nusinersen. (b) (4)

3. Product Quality

Please refer to the CMC review.

4. Nonclinical Pharmacology/Toxicology

Please refer to reviews of Drs. Ed Fisher and Lois Freed.

5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information is primarily from the Clinical Overview and Summary of Clinical Pharmacology Studies in the nusinersen NDA submission and reflects the findings most relevant to safety.

- Pharmacokinetics and pharmacodynamics were evaluated in infants and children with SMA aged 8 days to 15 years at screening
- Dose was based on CSF volume which increases from birth to 2 years and, according to the Sponsor, then remains constant
- Elimination half-life in human CSF is approximately 135-177 days; steady state concentrations were reached within 24 months.
- Nusinersen appears in the peripheral circulation with Cmax in the peripheral circulation occurring approximately 2 to 6 hours after intrathecal administration; the sponsor states that the plasma half- life is up to 86.5 days.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Please refer to Dr. Rainer Paine's review of efficacy.

8. Safety

8.1 Safety Review Approach

Dr. Mentari's review used the following pools in the analysis of nusinersen clinical safety where the numbers shown represent the number of subjects in each group (as shown in Dr. Mentari's review):

Presymptomatic and Infantile-Onset SMA						
Presymptomatic (SM201): ISIS 396443 *Pool A*	Controlled Study (CS3B) *Pool B*		Symptomatic (Infantile-Onset; CS3B and CS3A): ISIS 396443 *Pool C*	Presymptomatic and symptomatic (SM201, CS3B, and CS3A): ISIS 396443 *Pool D*	Later-onset CS1, CS10, CS2, CS12: ISIS 396443 *Pool E*	All Treated Subjects (Pools D and E Combined): ISIS 396443 *Pool F*
	Control	ISIS 396443				
17	41	80	100	117	56	173

Source: Summary of Clinical Safety Table 3

The treatment periods were 394 days (13 months) for the Controlled Study CS3B (infantile onset, Pool B), 29 months for Pool A, 45 months for Study CS3A (open label), 29 months for SM201, and up to 36 months for the studies in Pool E (later onset).

Dosing was as follows:

Study	Nusinersen dose	Dosing Days
SM201	12 mg	1, 15, 29, 64, 183, 302, 421, 540, 659, and 778
CS3B	12 mg	1, 15, 29, 64, 183, and 302
CS3A	12 mg (except Cohort 1 that had 6 mg loading dose (LD) followed by 12 mg maintenance doses)	LD Days 1, 15, 85 Maintenance doses on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261
CS1	1, 3, 6, or 9 mg	Single dose
CS2	Cohorts 1,2, 4: 3, 6, or 12 mg Cohort 3: 9 mg	Cohorts 1, 2, 4: Days 1, 29, and 85 Cohort 3: Days 1 and 85
CS10	6 or 9 mg	Single dose
CS12	12 mg	1, 169, 351, 533

8.2 Review of the Safety Database

Adequacy of the drug exposure experience (i.e., the safety database)
A total of 173 patients were exposed to nusinersen in the development program. The table below, from Dr. Mentari's review, shows duration of exposure.

Nusinersen Safety Population. Duration of Exposure

	Number of patients exposed to nusinersen:				
	Total	>=6 months	>=12 months	>=18 months	>=24 months
Controlled study subjects[a]	80	41	19	0	0
All subjects	173	120	83	62	54

[a] Study CS3B subjects
Source: Submission to NDA 209531 on 10/25/2016

In the controlled trial and in Pool A, the nusinersen dose was 12mg. Pool E subjects received varying nusinersen doses ranging from 1-12 mg.

In the Controlled Study CS3B, subjects were males and females ≤ 7 months (210 days) of age at screening. Exclusion criteria included "clinically-significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Site Investigator, at screening that would render the subject unsuitable for inclusion".

The mean age at first dose was 22 days for pre-symptomatic infantile onset subjects in Pool A, 161 days in Pool C symptomatic infantile onset subjects in controlled and uncontrolled studies, and 7 years for the later onset subjects. Approximately half the patients were male (49% in infantile onset, 46% in later onset, and 50% in all treated subjects). Approximately 80% of subjects were white. Fifty-six percent of infantile onset subjects, 100% of later onset, and 73% overall were from North America. Dr. Mentari notes that in Study CS3B, characteristics of nusinersen and sham control subjects were similar.

I agree with Dr. Mentari that because SMA is a rare disease, the overall subject exposure and demographics are acceptable. Dr. Mentari notes that because all subjects in CS3B were less than 1 year old at first dose, adverse events which require self-reporting from the subject could not be assessed in the controlled data.

8.3 Adequacy of Applicant's Clinical Safety Assessments

Dr. Mentari finds that the submission was well organized and that coding of adverse events was appropriate. She notes the following deficiencies in laboratory assessments in the development program: no quantitative urine protein measurements, serum bicarbonate levels were routinely evaluated, coagulation laboratory parameters not measured in controlled trials and only measured post baseline in Study CS2, and GGT was not measured to assess hepatic toxicity.

8.4 Safety Results

Deaths

In the controlled Study CS3B, deaths occurred in 12 of 80 (15%) of nusinersen-treated subjects compared to 13 of 41 (32%) sham procedure control subjects. In all studies (Pool F), 16 of 173 (9%) nusinersen-treated subjects died. Dr. Mentari notes that all deaths occurred in subjects with symptomatic infantile-onset SMA and I agree that all appeared related to complications of SMA (mostly respiratory disorders or cardio-respiratory arrest) except for Study CS3B Subject 2037-5167. Study CS3B Subject 2037-5167 had an unclear cause of death, but had been hospitalized twice within 2 months of death for "weight stagnation", and 2 weeks prior to her death, weight was in the 2nd percentile for age and sex (and Dr. Mentari notes that growth failure is a universal problem in non-sitting SMA patients).

Serious adverse events

Please refer to Dr. Mentari's review for details regarding serious adverse events (SAEs). Overall, there were fewer SAEs for nusinersen than for sham control, although some specific SAEs (atelectasis, aspiration, and pneumonia and other lower respiratory infections) did occur more frequently on nusinersen than sham control as discussed below.

Dr. Mentari identified no adverse events of aplastic anemia, pancytopenia, acute pancreatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms (DRESS) in the clinical development program.

In controlled study CS3B, 33 of 41 (80%) sham control subjects and 56 of 80 (70%) nusinersen subjects had SAEs. In all nusinersen subjects (Pool F), 84 of 173 (49%) patients had a SAE. Dr. Mentari notes that most of the SAEs were manifestations of spinal muscular atrophy. I agree with her that the lower incidence of SAEs in Pool F is likely because Pool F includes subjects with pre-symptomatic or later onset SMA who generally have less severe manifestations of SMA than the subjects in Study CS3B.

The system organ class (SOC) with the most SAEs was *Respiratory, thoracic, and mediastinal disorders* (58% of 80 nusinersen subjects vs 63% of 41 control subjects). Dr. Mentari shows that incidences of individual Preferred Terms in this SOC for nusinersen were generally similar to or less than the control group in Study CS3B, except for SAEs coded to atelectasis which occurred in 11 of 80 (14%) of nusinersen subjects compared to 2 of 41 (5%) control subjects. Aspiration SAEs were also more common in nusinersen subjects (4%) compared to 0 control subjects but Dr. Mentari notes that aspiration adverse events were less common in nusinersen subjects vs sham controls. The basis for atelectasis could be due to inhalation anesthesia for the procedure, although few subjects in either treatment group (8% for nusinersen vs 5% for sham control) received inhalation anesthesia in Study CS3B. I agree with Dr. Mentari that the increase in atelectasis could also be due to an increase in pneumonia SAEs in the nusinersen-treated subjects compared to control in Study CS3B.

Forty of 80 (50%) nusinersen treated subjects compared to 15 of 41 (37%) sham control subjects in Study CS3B had SAEs in the *Infections and infestations* SOC. Dr. Mentari notes that pneumonia and other lower respiratory infection SAEs were more common nusinersen subjects (29 of 80, 36%) compared to sham control subjects (9 of 41, 22%).

The incidence of *Cardiac Disorders* SAEs was similar in nusinersen subjects (9 of 80, 11%) compared to sham control (5 of 41, 12%) in Study CS3B. These included cardio-respiratory arrest, cardiac arrest, cyanosis, and ventricular tachycardia, all of which occurred less frequently in nusinersen subjects than in control, and I agree with Dr. Mentari that these events likely were related to cardio-respiratory compromise in patients with advanced symptomatic SMA.

Seven of 80 (9%) nusinersen subjects compared to 4 of 41 (10%) sham control subjects had SAEs in the *Metabolism and nutrition disorders* SOC in Study CS3B. As Dr. Mentari notes, the most frequent SAEs in this SOC, Weight gain poor, Failure to thrive, Feeding disorder of infancy or early childhood , Feeding intolerance) are common issues in SMA patients. An SAE of hyponatremia was reported in Pool F, as discussed under Laboratory Findings on page 14, below.

Six of 80 nusinersen (8%) subjects compared to 3 of 41 (7%) sham control subjects had SAEs coded to the *Gastrointestinal Disorders SOC*. Dr. Mentari shows a slight imbalance in SAEs of vomiting (4% in nusinersen vs 2% for sham control) and dysphagia (2% in nusinersen vs 0 in sham control) but I agree that these are common SMA-related issues.

SAEs coded to the *Nervous system disorders* SOC are discussed under Evaluations of Submission-Specific Safety Issues, page 18, below.

One SAE was coded to the *Immune system disorders* SOC, but was drug hypersensitivity with lip swelling and hives considered likely related to fentanyl in a patient who had 5 subsequent doses of nusinersen with no event of drug hypersensitivity.

One SAE was coded to the *Musculoskeletal and connective tissue disorders* SOC and that was in the all nusinersen subjects pool F (<1%). Subject CS3A 1833-2303 was a 31 month old male who developed vomiting, diarrhea, and fever on Study Day 756. He received his 8th nusinersen dose on Study Day 757. He developed symptoms of synovitis on Day (b) (6) and was treated with an IV bolus of sodium chloride and ibuprofen with no further episodes of pain. On Day (b) (6) he was discharged to home. I agree with Dr. Mentari that the etiology is unclear but could be due either to a viral etiology or drug-related. Dr. Mentari notes that the subject did not test positive for anti-drug antibodies.

One SAE coded to the *Skin and subcutaneous tissue disorders* SOC CS3B Subject 1999-5251) in which the subject had intermittent skin inflammation near the right eye which was intermittent and had occurred prior to the first dose. I agree with Dr. Mentari that a role for nusinersen is unlikely.

Study CS3B Subject 1780-5032 had an SAE coded to the preferred term Shock in the *Vascular disorders SOC*. Dr. Mentari reports that the event was a result of advanced respiratory disease related to SMA, with hypoxic brain injury and death occurring after pneumonia and uncompensated shock.

Dr. Mentari notes that her review of the ongoing blinded aggregate data for ongoing studies shows SAEs similar to those reported in the NDA submission.

In summary, SAEs that occurred more frequently in nusinersen subjects than in sham control subjects included events of atelectasis, aspiration, and pneumonia and other lower respiratory infections. Other events occurred with similar frequency and appeared related to manifestations of SMA.

Discontinuations due to AEs

Dr. Mentari notes that in subjects with infantile-onset SMA in Study CS3B and CS3A, all events leading to discontinuation were a result of death that occurred before the next scheduled dose and that there were no events leading to treatment discontinuation in subjects with Pre-symptomatic or later onset SMA.

Significant Adverse Events

In addition to SAEs and significant AEs discussed under submission-specific safety issues, Dr. Mentari notes a severe AE of myalgia lasting 2 hours on study Day 2 in a 3 y.o. female (Study CS2 Subject 1775-2208) and a severe AE of hypertension starting on Study Day 330 and lasting for 54 days in a 15 month old male (Study CS3B Subject 2000-5203). She notes that limited information was provided and the causes are unclear.

Treatment Emergent Adverse Events and Adverse Reactions

Dr. Mentari shows the adverse events that occurred in at least 5% of nusinersen subjects with a risk difference of 5% or at least 2 times as frequently than in control subjects. Those adverse events are shown in the table below, extracted from Dr. Mentari's review:

Adverse Event Preferred Term	Nusinersen 12 mg N=80 n (%)	Sham Procedure Control N=41 n (%)
Upper respiratory infection	35 (44)	16 (39)
Lower respiratory infection	34 (43)	12 (29)
Constipation	24 (30)	9 (22)
Teething	11 (14)	3 (7)
Upper respiratory tract congestion	5 (6)	1 (2)
Aspiration	4 (5)	1 (2)
Ear infection	4 (5)	1 (2)
Scoliosis	4 (5)	1 (2)

Sources: 10/17/2016 submission to NDA 209531 and Summary of Clinical Safety dataset ADAE (submitted 9/23/2016)

Upper respiratory infection and lower respiratory infection include combined terms that were related. Please refer to Dr. Mentari's review for the Preferred Terms that were combined. I agree with this approach to avoid splitting terms.

Dr. Mentari notes that Study CS3B subjects were less than 1 year old at first dose and were unable to verbally report adverse events reported in later onset SMA subjects (Pool E, age range of 2-16 y.o. at study entry) that included headache (34%), back pain (52% including back pain and puncture site pain), and post-lumbar puncture syndrome (38%) that occurred within 5 days of lumbar puncture. Overall in Pool E, headache occurred in 50%, and back pain alone and post-lumbar puncture syndrome each occurred in 41%.

Laboratory Findings

Please refer to Dr. Mentari's review of laboratory findings. I discuss laboratory results associated with renal toxicity as adverse events of special interest, as does Dr. Mentari.

Clinical Chemistry

Dr. Mentari shows the incidences of abnormal (high and low) electrolyte measurements for sodium, potassium, chloride, and glucose (and mean changes in glucose from baseline) from Study CS3B, that appear to be generally similar for nusinersen compared to control, and she notes that high blood glucose levels, as seen in nusinersen subjects (31%) and in control subjects (39%), have been described in SMA patients. She notes that serum bicarbonate was not routinely measured in the controlled study CS3B, and that low serum bicarbonate levels were seen in 2 of the 3 (67%) nusinersen subjects compared to 0 of 1 sham control subjects in whom it was measured in Study CS3B. In all nusinersen subjects, treatment emergent low serum bicarbonate occurred in 32 of 48 (67%) nusinersen subjects. Dr. Mentari notes that low serum bicarbonate levels have been described in SMA patients, but she also notes, as discussed under renal toxicity, that low serum bicarbonate is characteristic of proximal tubular dysfunction. I discuss laboratory results associated with renal toxicity (urine dipstick and serum bicarbonate) as adverse events of special interest, as does Dr. Mentari.

Dr. Mentari does note that 1 of 59 (2%) nusinersen subjects and 0 of 28 sham subjects had treatment-emergent low serum sodium in Study CS3B and 6 of 151 (4%) of all treated nusinersen subjects had at least 1 treatment-emergent low serum sodium measurement. Three subjects had a treatment-emergent serum sodium less than 130 mmol/L; in two of the subjects the cause was likely not related to nusinersen[1]. **CS3A Subject 1776-2305** had a serious adverse event (SAE) of hyponatremia, with serum sodium levels of 94 mmol/L[2] to 103 mmol/L from Days 89-232. Lethargy was noted on Day 227. The subject required sodium supplementation for 14 months after the initial hyponatremia diagnosis while nusinersen continued to be given. I agree with Dr. Mentari that factors of oral suctioning, excess sweating, and maternal breast milk that was low in sodium were not likely sufficient to explain the degree of hyponatremia. Dr. Mentari notes that hyponatremia has been reported with some drugs given intrathecally but not when they have been given intravenously, and that could suggest a direct central effect. A mechanism for hyponatremia with intrathecally administered nusinersen has not been evaluated. I agree with Dr. Mentari's recommendation to add information related to hyponatremia to Warnings and Precautions, and to recommend checking blood sodium level prior to nusinersen administration.

Hepatic Laboratory Measurements

[1] These 2 subjects with hyponatremia had non-drug related causes corresponding to the dates of low sodium measurement: **CS3A Subject 1776-2306** corresponding to the dates of low sodium measurement had pulmonary infections and pyrexia and treatment with levetiracetam that has been associated with hyponatremia; **CS3B Subject 2010-5096** had pneumonia and weight loss.

[2] A laboratory error cannot be ruled out for the profoundly low level of 95 mmol/L. However, severe hyponatremia was observed again with a level of 103 mmol/L and the need for supplementation.

The liver is a target organ of nusinersen because, like most antisense oligonucleotides, nusinersen is deposited in the liver. Because it is deposited in the liver, nusinersen has the potential for hepatotoxicity.

Dr. Mentari shows that in Study CS3B, the frequency of elevated liver enzymes (ALT, AST, alkaline phosphatase, and bilirubin) was comparable to findings in sham procedure control subjects. She notes that in all clinical studies, no nusinersen subject had a post-treatment AST level ≥ 3 times the upper limit of normal.

She identifies 1 subject (Study CS3B Subject 2010-5096) with an isolated post-treatment ALT level ≥ 3 times the upper limit of normal at 3 hours after administration of the 5th nusinersen dose; AST was slightly elevated (< 2x) and alkaline phosphatase, total and direct BR were within normal limits; repeat ALT 1 week later was within normal limits. I agree with Dr. Mentari that elevated ALT is possibly related to nusinersen, but that it could also be due to tissue injury during lumbar puncture. Study CS3B Subject 1776-5097 had a post-treatment ALT level ≥ 5 times the upper limit of normal in the setting of Tylenol administration, 96 days after the 6th nusinersen dose, and that reportedly resolved within 15 days. The amount of acetaminophen, a potentially hepatotoxic drug, was not provided. No additional doses of nusinersen were scheduled after the high ALT measurement. It is not possible to assess the role of either acetaminophen in this case, and a role for nusinersen cannot be ruled out.

Dr. Mentari states that there were no cases of Hy's law drug-induced liver injury (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥2 x ULN) during treatment in nusinersen clinical studies.

Dr. Mentari notes that liver enzymes most frequently evaluated (AST, ALT, and LDH) can be elevated in patients with SMA, and that with muscle degeneration, these enzymes can be released from skeletal muscle. Because the liver is a target organ for nusinersen and other antisense oligonucleotides, and because there are 2 cases of elevated ALT for which a role for nusinersen cannot be ruled out, I agree with Dr. Mentari's recommendation to include information about the potential for hepatotoxicity in Warning and Precautions in labeling. I agree with her recommendation that gamma-glutamyl transferase (GGT) be used to evaluate for liver toxicity as it is produced primarily in liver rather than skeletal muscle, and that liver tests including GGT be evaluated at baseline and before each maintenance dose.

Hematology measurements

Thrombocytopenia

As noted by Dr. Mentari, thrombocytopenia occurred more frequently in nusinersen subjects compared to sham control subjects in the controlled trial CS3B: 6 of 56 (11%) nusinersen subjects had a platelet level below the lower limit of normal (LLN), compared to 0 of 28 sham control subjects. In all nusinersen subjects 3 of 145 (2%) had thrombocytopenia < 100 x 10^9/L. No subject had a platelet count < 50 X 10^9/L, and there were no adverse events related to thrombocytopenia.

Dr. Mentari notes that thrombocytopenia has been seen with other oligonucleotides. She notes that for drisapersen, in particular, mild thrombocytopenia occurred with early exposure but severe thrombocytopenia occurred with longer exposures. Thrombocytopenia and adverse consequences may be of particular concern with intrathecal administration that will be the route of administration for nusinersen. I agree with Dr. Mentari's recommendation that thrombocytopenia be described in Warnings and Precautions and I agree with her recommendation for checking complete blood count prior to each nusinersen administration.

Coagulation Laboratory Measurements

Dr. Mentari notes that prolonged activated partial thromboplastin time (aPTT) has been described with other phosphorothioate oligonucleotides. She notes that the data for coagulation laboratory tests for nusinersen are limited and that in the controlled clinical trial they were measured sporadically. She does, however, note that 10 of 53 (19%) of all nusinersen subjects in whom these parameters were measured had shift from baseline to a high aPTT. I agree with Dr. Mentari that given the risk of bleeding complications with lumbar puncture, patients should have coagulation laboratory testing prior to each nusinersen administration.

Other Hematology Laboratory Measurements

Dr. Mentari shows that shifts in other hematology laboratory measurements for WBC decreased, lymphocyte count decreased, neutrophil count decreased, or anemia were similar for nusinersen and control groups in Study CS3B.

Vital Signs

Please refer to Dr. Mentari's review of vital sign changes that were measured at screening, visits for doses 1-3 and 5 (pre-dose, post-dose, and 1 day after dosing), at visits scheduled for dosing day 302 (the last dose), and at Study Day 120 and Study Day 394 (follow up visit) in Study CS3B. Dr. Mentari that shows that vital signs meeting outlier criteria post-baseline were similar for nusinersen and sham control for systolic and diastolic blood pressure. She shows that post-treatment decreases in pulse rate > 15 bpm or > 30 bpm from baseline were more frequent in nusinersen subject compared to sham control. However, there was no imbalance in post-treatment low heart rates outside of the range of normal. Fewer nusinersen subjects compared sham subjects (6% vs 10%) had an adverse event coded to the preferred term bradycardia. She notes that short term variations in heart rate are part of normal homeostatic mechanisms.

Electrocardiograms (ECGs)

ECGs were obtained at the following times:
Study CS3B: Screening, Day 2 (dose was on Day 1), post-dose on Day 29, Day 70, and Day 394
Study CS1: Screening, 4-6 hours post-dose on Day 1, 1 week post-dose Days 29 and 85, follow-up Days 169 and 253
Study CS2: Screening; 1 week post Days 1, 29, and 85 doses; follow-up Days 169 and 253
Study CS10: Screening, 4-6 hours post-dose on Day 1, follow-up Days 8 and 85
Study CS12: Screening, 4-6 hours post-dose on Day 1, follow-up Days 442 and 715

ECGs were centrally read. Dr. Mentari notes that in Study CS3B, 5 subjects (8%) in the nusinersen group and non in the sham-controlled group shifted from ECGs that were qualitatively read as normal or unknown at baseline to abnormal, clinically significant post-baseline. She reviews the findings (one with 2 subsequent normal echocardiograms; 1 with findings consistent with pericarditis on 1 ECG that was normal 9 days later; one with "right atrial enlargement and likely benign ventricular hypertrophy" on the day of the 3rd dose with no treatment or additional work-up reported and no follow-up ECG provided; and one consistent with probably right ventricular hypertrophy with no treatment reported and no follow-up ECGs provided). One subject (CS3B 2037-5063) had a prolonged QT interval. I agree with Dr. Mentari that the first 4 cases do not represent clinically significant cardiac disease or are of unclear clinical significance. QT prolongation is discussed below.

For evaluation of QT interval, in Study CS3B, Dr. Mentari notes that 4 of 80 (5%) nusinersen subjects had a QTcf above 500 msec and an increase of > 60 msec from baseline compared to 0 sham control subjects. She notes that no subjects from other studies had these changes in QTcF. The Sponsor notes (p. 67, Summary of Clinical Safety) that of the 4 subjects in the nusinersen group with QTcF value > 500 and a change of >60 msec, 1 subject had an AE of cardiopulmonary arrest on Day 112; the subject's most recent study exposure prior to the event was on Day 70, and the abnormal ECG was obtained on Day 29. The subject recovered and continued in the study, with last exposure on Day 183. The Sponsor states that the 3 other subjects did not have an event of this nature or any other cardiovascular event reported.

The Sponsor states that the ECG and cardiovascular AE data are consistent with the observation of no biologically meaningful changes in hERG function noted among 7 antisense oligonucleotides tested . A thorough QT study was not performed. A consult from Dr. Christine Garnett from the QT IRT regarding the QT findings noted the difficulty in interpreting the data and noted that prolonged QTc interval in individual patients could have also occurred for reasons related to concomitant medications, the underlying disease or associated adverse events related to the disease. Dr. Garnett recommended that the potential for nusinersen to delay cardiac repolarization be evaluated in a dedicated QT study and that if nusinersen cannot be given to heathy volunteers, high quality 12-lead ECGs (replicate, digital ECGs) can be incorporated in on-going controlled clinical trials in patients to characterize the QTc interval. Based on DNP's assessment of benefit-risk of nusinersen in this patient population, she wrote that it may be reasonable to design the QT study to rule out large effects (>20 ms) on QTc interval in patients.Dr. Garnett recommended language describing the QTc data for Section 12.2. As a result of this recommendation, as noted by Dr. Mentari, DNP recommended to the Sponsor on December 8, 2016, that ongoing and future studies of nusinersen should incorporate high quality 12-lead ECGS (replicate, digital ECGs) to characterize the QT interval, and that any QTc greater than 500 ms should be repeated.

Immunogenicity

Plasma samples from all 7 clinical studies were analyzed for anti-drug antibody (ADA) presence. Using an analysis with a 1% false positive rate, Dr. Mentari notes that 5 nusinersen-exposed subjects were identified as having an ADA-positive results, with a rate ranging from 1-5% of patients in a given study being ADA positive. In only 1 of those cases was the response

considered to be persistent. Dr. Mentari reviewed the adverse events for the 5 subjects and finds that they included manifestations of SMA and complications of lumbar puncture and she does not find an apparent effect of ADA development on the adverse events in these subjects.

Evaluations of submission-specific safety issues

Renal toxicity

Dr. Mentari notes that the kidney is a target organ for nusinersen, as observed for other antisense oligonucleotides, with concentrations in human kidney similar to those in the lumbar spinal cord.

Dr. Mentari notes no renal toxicity adverse events in the clinical studies (she notes that 1 event of urine output decreased was related to hypoxic cardiac arrest and rhinovirus infection and not to nusinersen). In terms of serum markers of renal function, Dr. Mentari notes no subjects with treatment-emergent high levels of serum creatinine (that may have limited value because of reduced muscle mass in SMA patients) and no subjects with treatment-emergent high levels of the biomarker cystatin C.

Dr. Mentari does find treatment-emergent elevated urine protein (to trace level or higher) in 17 of 51 (33%) nusinersen subjects compared to 5/25 (20%) sham control subjects in Study CS3B, and in later onset SMA subjects (Pool E) in 36 of 52 (69%) nusinersen subjects. She notes that urine protein was measured semi-quantitatively with urine dipstick testing, and that the results are predictive of significant proteinuria. She also notes that, based on animal studies and findings with other phosphorothioate oligonucleotides, the proteinuria is likely tubular in origin, and that the standard urine dipstick primarily detects albumin but is relatively insensitive to constituents of tubular proteinuria such that urine dipstick findings may be falsely negative. Dr. Mentari also notes that treatment-emergent low serum bicarbonate, although not available from the control group in Study CS3B, occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured. She notes that although metabolic acidosis has been described in SMA patients, low serum bicarbonate levels are characteristic of proximal renal tubular acidosis, and that proteinuria and low serum bicarbonate are seen with generalized proximal tubular dysfunction (Fanconi syndrome), although other features of Fanconi syndrome (hypophosphatemia, glycosuria) not reported in Study CS3B and were infrequent in the clinical studies.

Dr. Mentari notes that proteinuria is a cause of progressive kidney damage. I agree with her recommendation to describe the risk of proteinuria in Warnings and Precautions and I agree with her recommendation for quantitative spot urine protein testing at baseline and prior to each nusinersen maintenance dose in the proposed prescribing information and in ongoing and future studies, as well as testing for serum electrolytes, including bicarbonate, prior to each dose[3].

Neurologic toxicity

[3] The Division of Neurology Products conveyed this recommendation regarding ongoing and future studies to the Sponsor on 12/2/16.

Dr. Mentari notes that neurologic toxicity can occur with intrathecal drug delivery as a result of active drug, excipients, buffers, solubility enhancers or preservatives. She notes that the nonclinical review of Dr. Edward Fisher describes findings of neurotoxicity including hippocampal vacuolization and necrotic cells, as well as possible treatment-related changes in learning test performance in juvenile cynomolgus monkeys.

Dr. Mentari presents adverse events in the Nervous System Disorders SOC from controlled Study CS3B and in all nusinersen subjects. In the controlled study, adverse events occurred in 10% of nusinersen subjects vs 5% of control subjects; individual adverse events in the controlled study were too few to determine a relationship to study drug. Dr. Mentari notes that 3% of nusinersen-treated subjects in CS3B had serious adverse events (SAEs) in this SOC, compared to none of the sham procedure controlled subjects; I agree with her that these SAEs (brain injury in **CS3B subject 1780-5032** with chronic respiratory failure in the setting of advanced SMA, hypoxic-ischaemic encephalopathy in **CS3B subject 2000-5145** after aspiration) were likely related to complications of SMA. She also notes one SAE of seizure in Pool F (all nusinersen treated subjects); that is **CS3A subject 1776-2306** with possible vasculitis, discussed below under the section on Rash and Possible Vasculitis.

Dr. Mentari notes that headache was the most common adverse event preferred term in the Nervous System Disorders SOC, reported in 50% of later onset SMA nusinersen-treated subjects, of which 68% reported headache within 5 days of lumbar puncture and is likely related to lumbar puncture[4]. She notes that the controlled study data do not capture such events that rely on reporting from the subjects themselves as that study only included infantile-onset SMA subjects. She notes one patient (**subject CS3A 1776-2305**) with lethargy in the setting of hyponatremia (discussed under hyponatremia). She notes one patient with dyslexia associated with attention deficit/hyperactivity disorder and I agree with her it is unclear whether nusinersen could have played a role. She identifies neurologic AEs that are likely to be complications of lumbar puncture or related treatment (hyperreflexia, hypotonia, CSF leakage, and aphonia), and neurologic AEs that are common manifestations of SMA (AEs coded to preferred terms Muscle contractions involuntary and Drooling, AEs of syncope and tremor) and an AE of syncope thought due to heat.

I agree with Dr. Mentari that because of the potential neurotoxic effect of nusinersen, it is reasonable to include the nonclinical neurotoxicity information in Warnings and Precautions, particularly given the potential for long-term use in some children. I also agree with her recommendation to pursue enhanced pharmacovigilance regarding neurotoxicity if the NDA is approved.

Safety Issues Related to Lumbar Puncture

Nusinersen is given intrathecally. Dr. Mentari shows that ultrasound guidance was used for administration in 99% of patients in CS3B and that some patients had inhalation anesthesia and sedation. The proposed label includes language regarding intrathecal administration, imaging techniques, and sedation.

[4] The International Classification of headache Disorders Post-dural puncture headache is considered to be headache occurring within 5 days of lumbar puncture.

Dr. Mentari shows that among the most frequent adverse events in the 120 hours following nusinersen injection were back pain, post lumbar puncture syndrome, headache, vomiting, and nausea, and as discussed under neurotoxicity, the data do not come primarily from the controlled trial but from the open-label studies in later onset SMA subjects because infantile SMA subjects are generally unable to report these adverse events. She also notes that complications of anesthesia that were more common in nusinersen subjects in Study CS3B were atelectasis that occurred in 11 of 80 (14%) nusinersen patients compared to 2 of 41 (5%) sham procedure control subjects.

As discussed above under Laboratory Findings/Hematology measurements, on p. 15, thrombocytopenia occurred after administration of nusinersen and has been observed with other antisense oligonucleotides. Dr. Mentari notes that 5 of 173 (3%) subjects had 6 events that were hemorrhagic complications of attempted or successful lumbar puncture (all but one were in Study SM201 and were 2 months of age or less at the time of study entry). I agree with Dr. Mentari that because of the risk of thrombocytopenia from nusinersen and potential coagulation abnormalities (p. 15), patients may be at increased risk for adverse reactions after lumbar puncture for intrathecal administration of nusinersen. I agree with her recommendation to advise prescribers to perform a complete blood count and coagulation laboratory testing prior to lumbar puncture.

Rash and Possible Vasculitis

Dr. Mentari notes that pro-inflammatory effects of antisense nucleotides have been described in the published literature. She has identified 3 cases of possible vasculitis with nusinersen: **CS3B Subject 2010-5026**, a 14 month old male who developed suspected vasculitis on right hand and on left hand 10 months (on the day of the 6th dose) and 11 months, respectively, after first dose (no biopsy) that resolved after 3 months with no further nusinersen administered because it was the end of the study; **CS3B Subject 2002-5370**, a 13 month old male developed red macular lesions on forearm, leg, and foot over a period of 8 weeks (8 months after first dose and 2 months after fifth dose) that ulcerated and scabbed over; left leg skin biopsy with post-op diagnosis of vasculitis vs vascular occlusion, but biopsy report included a comment that "there are no features of vasculitis". He received one additional dose after the rash started. Lesions resolved without treatment over several months. **CS3A subject 1776-2306** was an 8 month old male who had new onset seizures and cerebral infarction with MRI showing two punctate acute or subacute infarcts, 5 months after starting nusinersen (2 months after his 3rd dose). MRI showed two punctate acute or subacute infarcts, with no known risk factors; Dr. Mentari notes that vasculitis is a possible cause for cerebral infarction.

Dr. Mentari notes that distal necrosis has been reported in SMA patients not taking nusinersen. She shows that the lesions described in the publications appear to be different from those observed in the NDA. I note that the cases in the literature (a total of 4 as identified by Dr. Mentari) and the 2 cases observed in the NDA are few and do not allow for definitive comparisons. However, she notes that the published cases of distal necrosis are rare (2), while 2 cases of possible vasculitis occurred in 173 nusinersen exposed subjects. I agree with her recommendation to add information regarding these cases of possible vasculitis to Warnings and Precautions if nusinersen is approved.

Safety Analyses by Demographic Subgroups

Dr. Mentari notes that with respect to age, infants with SMA who experienced at least 1 AE were fewer in the < 90 days of age subgroup (81%) than in the ≥ 90 days of age subgroup (92%). The overall incidence of AEs by SOC was similarly lower in the < 90 days of age subgroup. Dr. Mentari proposes that the difference is likely influenced by the presymptomatic infants who generally do not have AEs related to manifestations of SMA.

In later onset SMA, at least 1 AE was experienced by all subjects in each age group (< 6 y.o. and ≥6 y.o.), although Dr. Mentari notes that lumbar puncture related were more commonly reported in the older age group than in the younger age group for (example post lumbar puncture syndrome that occurred in 61% of the older age group and 21% in the younger age group).

Dr. Mentari notes that AE incidences were similar between subgroups characterized by sex in the infants and in the later-onset SMA subjects.

Dr. Mentari notes that incidences in AEs were similar between racial subgroups of White (n=93) and non-White (n=20) infants with SMA. I agree with her that the few non-White subjects (n=7) compared to the White subgroup (n=49) in the later onset SMA subjects limit meaningful comparisons.

Specific Safety Studies/Clinical Trials

Dr. Mentari notes that no specific clinical safety studies were performed in the nusinersen development program.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Dr. Mentari notes that there were 4 subjects with AEs of benign neoplasms (benign submucosal vascular proliferation, skin papilloma, acrochordon , seborrheic keratosis), but otherwise no neoplasms were reported in the nusinersen submission.

Human Reproduction and Pregnancy

No pregnancies were reported. Dr. Mentari notes that there were 10 female subjects over age 12 at the time of study entry.

Pediatrics and Assessment of Effects on Growth

Dr. Mentari shows that in Study CS3B, nusinersen subjects had reduced growth compared to sham control subjects. At Day 394 the results were as follows:

	Mean change from baseline in Study CS3B	
	Nusinersen	**Sham Control**
Height/length	13 cm	21 cm
Height/length percentile for age	-26	26
Weight	3.1 kg	3.9 kg
Weight for age percentile	0	27

Given the difficulty in obtaining height/length measurements, it is conceivable that these measurements might be easier to obtain in infants that have less mobility. However, the weight change provides support for an effect on growth. Although I note that at Day 394 these measurements were only recorded in 16 nusinersen subjects and 7 control subjects, these findings were present, particularly for the height/length assessments, at earlier time points with more subjects being assessed.

I agree with Dr. Mentari's proposal to describe this issue in labeling.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The FDA Controlled Substance Staff did not recommend scheduling under the Controlled Substances Act in a review dated 11/30/16, given that nonclinical studies do not suggest abuse potential, the intrathecal rout is unlikely to have potential for abuse, nusinersen does not cross the blood brain barrier when administered IV or SQ, and no abuse-related AEs were found in the clinical trials involving children and adolescents.

Dr. Mentari did not identify withdrawal or rebound adverse events in nusinersen clinical studies.

Concerns identified through U.S. or foreign postmarket experience
Nusinersen is not yet marketed in the US or in the rest of the world.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting
Because of relatively limited experience to date, the clinical study findings may not fully represent the clinical safety of nusinersen. I agree with Dr. Mentari that known issues will likely be further characterized and new issues likely identified as more patients are exposed for longer durations of treatment.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The studies were conducted in pediatric patients.

11. Other Relevant Regulatory Issues

Please refer to the clinical efficacy review.

12. Labeling

Prescribing Information

If nusinersen is approved, I have the following labeling recommendations:

- DOSAGE AND ADMINISTRATION:
  I suggest that recommendations for laboratory monitoring be included in labeling to mitigate the risk of thrombocytopenia, renal toxicity, and hepatic toxicity.
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  1. I do not have recommendations for a BOXED WARNING or CONTRAINDICATIONS.

  2. If nusinersen is approved, I agree with Dr. Mentari's suggestions to describe several issues in Warnings and Precautions, including thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, effect on growth, rash and possible vasculitis, neurologic toxicity, and hepatic effects.

     These adverse reactions are serious, causally related to the use of nusinersen (or in the case of hyponatremia a role for nusinersen could not be ruled out), are class effects in some cases (thrombocytopenia and coagulation abnormalities, renal toxicity, and hepatic effects), and have implications for patient management.

Other Labeling

I agree with Dr. Mentari's recommendation to use the label Section 17 (Patient Counseling) to provide information for clinicians to communicate to patients and caregivers about information in the WARNINGS and PRECAUTIONS, the need for laboratory monitoring, and symptoms for which patients should monitor between visits.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

REMS are required risk management plans that use risk minimization strategies beyond the product labeling to ensure that the product's benefits outweigh its risks in the postmarket setting.

If sufficient evidence of benefit supports approval, at this time I believe that WARNINGS and PRECAUTIONS including information regarding thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, effect on growth, rash and possible vasculitis, neurologic toxicity, and hepatic effects, as well as guidance for monitoring and administration, along with Patient Counseling through information conveyed in Section 17 of the label will be most appropriate to ensure that any benefit is not outweighed by the risk.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

I do not have recommendations of PMRs related to safety at this time. I suggest enhanced pharmacovigilance for thrombocytopenia and coagulation abnormalities, renal toxicity, serious hyponatremia, effect on growth, suspected vasculitis, neurologic toxicity, and hepatic effects.

PMRs related to other disciplines will include the following:

1) A study to test available ADA-positive patient samples for cross-reactivity to dsDNA, and to test any future ADA-positive patient samples for anti-dsDNA antibodies.
2) Nonclinical carcinogenicity study
3) Nonclinical pre- and postnatal study in rodent.

14. Recommended Comments to the Applicant

In ongoing or future clinical studies and through postmarketing surveillance, the sponsor should continue to monitor for adverse events of special interest. These should include thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, vasculitis, neurologic toxicity, and hepatic effects.

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/s/

SALLY U YASUDA
12/15/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209531
Priority or Standard	Priority
Submit Date(s)	September 23, 2016
Received Date(s)	September 23, 2016
PDUFA Goal Date	May 23, 2017
Division/Office	Division of Neurology Products / Office of New Drugs
Reviewer Name(s)	Evelyn Mentari, M.D., M.S.
Review Completion Date	December 14, 2016
Established Name	Nusinersen
(Proposed) Trade Name	Spinraza
Applicant	Biogen
Formulation(s)	Intrathecal
Dosing Regimen	Initiate treatment as 4 loading doses on approximately days (b) (4) followed by a maintenance dose once every 4 months. The recommended dosage is 12 mg (5 mL).
Applicant Proposed Indication(s)/Population(s)	Treatment of spinal muscular atrophy (SMA)
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of nusinersen outweigh the risks, we recommend approval with labeling language including WARNINGS and PRECAUTIONS to mitigate the risks.
Recommended Indication(s)/Population(s) (if applicable)	Patients with spinal muscular atrophy (children and adults)

APPEARS THIS WAY ON ORIGINAL

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Glossary

2'-MOE ASO	2-methoxyethyl antisense oligonucleotide
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASO	antisense oligonucleotide
BiPAP	bilevel Positive Airway Pressure
bpm	beats per minute
CMAP	compound Muscle Action Potential (CMAP) Test
CSR	clinical study report
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
GGT	gamma-glutamyl transferase
hERG	human ether-a-go-go-related gene
HINE	Hammersmith Infant Neurological Examination
HLT	High Level Term (MedDRA)
IND	investigational new drug application
INR	international normalized ratio
IR	information request
ISIS 396443	nusinersen
IT	intrathecal
IU	international units
L	liter
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
msec	milliseconds
NDA	new drug application
PT	Preferred Term (MedDRA)
QTcF	QT interval value corrected according to Fridericia's formula
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SCS	summary of clinical safety
SMA	spinal muscular atrophy
SMN2 gene	survival of motor neuron 2 gene
SOC	System Organ Class (MedDRA)
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Nusinersen is a uniformly modified, 2'-O-(2-methoxyethyl) antisense oligonucleotide (2'-MOE ASO) designed to bind to a specific sequence in intron 7 of the SMN2 pre-mRNA. The proposed proprietary name is Spinraza. The proposed indication is the treatment of spinal muscular atrophy (SMA). Nusinersen is a new molecular entity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Rainer Paine.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Nusinersen is proposed to be used for treatment of spinal muscular atrophy (SMA). If efficacy is demonstrated and the benefits of nusinersen outweigh the risks, then I recommend approval with labeling language including WARNINGS and PRECAUTIONS to mitigate the risks.

This document reviews the risk profile of nusinersen. Please refer to Dr. Rainer Paine's review for discussion of Analysis of Condition and Current Treatment Options and Benefit.

Nusinersen is associated with adverse effects that have potentially severe consequences.

- Six of 56 (11%) nusinersen patients had a platelet level below the lower limit of normal, compared to 0 of 28 sham procedure control patients in the controlled study in infantile onset SMA (Study CS3B). No patient had a platelet count less than 50,000 cells per microliter in that study. Five of 173 (3%) nusinersen patients had a hemorrhagic complication of lumbar puncture. Coagulation abnormalities have been observed after administration of some antisense oligonucleotides. Low platelet levels or coagulation abnormalities may increase the risk of adverse outcomes after intrathecal administration of nusinersen. Monitoring hematologic and coagulation parameters at baseline and prior to each maintenance dose may help mitigate this risk.
- Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile onset SMA, compared to 5/25 (20%) sham control subjects. Proteinuria occurred in 26 of 52 (69%) of later-onset SMA subjects with a longer duration of treatment. Treatment-emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured; measurements from a control group were not performed. Low serum bicarbonate levels are characteristic of proximal renal tubular acidosis. Nusinersen accumulates in the kidney and renal toxicity is a class effect of oligonucleotides. Monitoring for proteinuria and monitoring serum electrolytes including bicarbonate at baseline and prior to each maintenance dose may help mitigate a risk of an adverse clinical outcome.
- Severe hyponatremia occurred in a patient treated with nusinersen. Monitoring serum electrolytes at baseline and before each maintenance dose may help to mitigate this risk.
- Decreased growth (height and weight) was observed in nusinersen subjects compared to sham control subjects in Study CS3B. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment.
- Rash and possible vasculitis were reported in 2 patients treated with nusinersen. A third subject had new onset seizures and cerebral infarction after starting nusinersen, with no known risk factor or potential cause for cerebral infarction; the etiology in this case is unknown, but vasculitis is a possible cause of cerebral infarction.

- Nusinersen, like other phosphorothioate oligonucleotides, accumulates in the liver. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects. Monitoring hepatic tests, including gamma-glutamyl transferase (GGT) and bilirubin at baseline and before each maintenance dose may help to mitigate the risk of hepatotoxicity.

If nusinersen is approved, I recommend WARNINGS and PRECAUTIONS in labeling regarding the risks of thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, decreased growth, rash and possible vasculitis, and hepatotoxicity. If nusinersen is approved, the label should include recommendations for monitoring to mitigate these risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Paine's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Paine's review of clinical efficacy.	
Benefit	• Please refer to Dr. Paine's review of clinical efficacy.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for nusinersen includes all patients from the Phase 3 controlled study and the Phase 2 open-label study in patients with symptomatic infantile-onset SMA, the Phase 2 open-label study in infants with presymptomatic SMA, and open-label studies in subjects with later-onset SMA. Drug exposure is adequate for NDA submission, but longer durations of exposure may occur in the postmarketing setting. The safety database did not include patients with Type 4 SMA (age of symptom onset in the second or third decade), who are included in the proposed treatment indication. • In Study CS3B, the Phase 3 controlled study in symptomatic infantile onset SMA patients, common AEs (occurring in at least 20% of nusinersen patients, and occurring in nusinersen patients at least 5% more frequently or at least 2 times as frequently than in control patients) were: upper respiratory infection (44%); lower respiratory infections (43%); and constipation (30%). In later onset patients, common adverse events that were not commonly reported in Study CS3B included headache (50%), back pain (41%), and post lumbar puncture syndrome (41%). • Six of 56 (11%) nusinersen patients had a platelet level below the lower limit of normal, compared to 0 of 28 sham procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in that study. Five of 173 (3%) nusinersen patients had a hemorrhagic complication of lumbar puncture. Coagulation abnormalities have been observed after administration of some antisense oligonucleotides. • Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile	Safety issues that occur at the proposed dose of nusinersen include thrombocytopenia, proteinuria, hyponatremia, decreased growth, and rash and possible vasculitis. Increased liver enzymes have also been observed in some patients. Coagulation laboratory abnormalities, renal accumulation, and hepatic accumulation are class effects of phosphorothioate antisense oligonucleotides. The safety issues potentially could have life-threatening outcomes; monitoring could mitigate the risk. The magnitude of the potential for serious harm after approval is unknown. Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	onset SMA compared to 5/25 (20%) sham control subjects. Proteinuria occurred in 26 of 52 (69%) of later-onset SMA subjects with a longer duration of treatment. Nusinersen accumulates in the kidney in humans and accumulation in proximal tubule cells has been described in nonclinical studies. The urinary dipstick test used in nusinersen clinical studies is relatively insensitive to proteins that are major constituents of tubular proteinuria. Treatment-emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured; measurements from a control group were not performed. Low serum bicarbonate levels are characteristic of proximal renal tubular acidosis. Monitoring for proteinuria and monitoring serum electrolytes including bicarbonate at baseline and prior to each maintenance dose may help mitigate a risk of an adverse clinical outcome. • Severe hyponatremia occurred in a patient treated with nusinersen. The sodium level normalized after salt supplementation treatment, which continued for 14 months. • Decreased growth (height and weight) was observed in nusinersen subjects compared to sham control subjects in Study CS3B. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment. • Rash and possible vasculitis were reported in 2 patients treated with nusinersen; one patient did not have a biopsy and the other patient had a post-operative diagnosis of vasculitis vs vascular occlusion, although the biopsy reported stated “there are no features of vasculitis”. A third subject had new onset seizures and cerebral infarction after starting nusinersen, with no known risk factor or potential cause for cerebral	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infarction; the etiology in this case is unknown but vasculitis is a possible cause of cerebral infarction. • Nusinersen, like other phosphorothioate oligonucleotides, accumulates in the liver. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects. • Safety in the postmarketing setting: Laboratory values as markers of renal, hepatic, and thrombocytopenia adverse events would be useful at baseline and prior to each maintenance dose in the postmarket setting if the drug is approved. • Other uncertainties: The risk of serious toxicity with longer term exposure and with exposure in more patients is unknown.	
Risk Management	• Strong product labeling with recommendations for monitoring of laboratory parameters may help to mitigate the risks of renal, hepatic, and thrombocytopenia adverse events. However, even with adequate monitoring, some patients may experience serious adverse events.	WARNINGS and PRECAUTIONS should be included in labeling to describe the risks of renal and hepatic adverse events and thrombocytopenia and to provide recommendations for monitoring. I also recommend informing prescribers about hyponatremia, decreased growth, and rash and possible vasculitis in WARNINGS and PRECAUTIONS.

2 Therapeutic Context

2.1. Analysis of Condition

Spinal muscular atrophy is an autosomal recessive neuromuscular disease characterized by degeneration of the spinal cord neurons, which results in progressive muscular atrophy and weakness. The clinical spectrum of spinal muscular atrophy ranges from early infant death to adult life with weakness that can be classified as mild (see table below).

Table 1. Clinical Classification of Spinal Muscular Atrophy

SMA Type	Age of Onset	Highest Function	Natural Age of Death
COPYRIGHT MATERIAL WITHHELD			

SMA = Spinal Muscular Atrophy
Source: Wang CH, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *J Child Neurol* 2007 22: 1027

2.2. Analysis of Current Treatment Options

There are no FDA approved treatments for SMA.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nusinersen is a new molecular entity. It is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Summary of designations:

- 4/18/2011: Orphan drug designation
- 11/29/2011: Fast track designation

Ownership changed from Ionis to Biogen on 8/1/2016.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience. (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Office of Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Evidence of neurotoxicity was reported in nonclinical studies of nusinersen in juvenile cynomolgus monkeys (see Section 8.5.2 Neurologic Toxicity). For additional detail, the reader is referred to pharmacology/toxicology review.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review for additional details. The following information is primarily from the Clinical Overview and Summary of Clinical Pharmacology Studies in the NDA submission and reflects the findings most relevant to safety.

- Pharmacokinetics and pharmacodynamics were evaluated in infants and children with SMA aged 8 days to 15 years at screening.
- Dose was based on CSF volume.
- Elimination half-life in human CSF is approximately 135-177 days; steady state concentrations were reached within 24 months.

- Nusinersen appears in the peripheral circulation with maximum concentration in the peripheral circulation occurring approximately 2 to 6 hours after intrathecal administration; the Sponsor states that the plasma half-life is up to 86.5 days.

4.5.1. Mechanism of Action

SPINRAZA (nusinersen) is a modified antisense oligonucleotide, where the 2'-hydroxy groups of the ribofuranosyl rings are replaced with 2'-O-2-methoxyethyl groups and the sugar-phosphate backbone is replaced with a sugar-phosphorothioate backbone. Nusinersen binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript.

4.5.2. Pharmacodynamics

Please refer to the summary in Section 4.5 and to the Clinical Pharmacology review

4.5.3. Pharmacokinetics

Please refer to the summary in Section 4.5 and to the Clinical Pharmacology review

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below summarizes clinical studies supporting safety in NDA 209531. The figure below summarizes the relationship between Studies CS1, CS10, CS2, and CS12.

Table 2. Clinical Studies Supporting Safety in NDA 209531

Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled and Completed	Patient Population Enrolled	Duration of Treatment	Study Status; Type of Report	Countries
Studies in Patients with Symptomatic SMA							
Infantile-Onset							
ISIS 396443 - CS3B (Study CS3B)	Phase 3, randomized, double-blind, multiple-dose, sham-procedure controlled	ISIS 396443; 12-mg equivalent dose or sham procedure Days 1, 15, 29, 64, 183, and 302 IT	~111 planned; 121 randomized and received double-blinded medication and 22 completed as of data cutoff date of 15 June 2016; Randomization: 2 active to 1 control	Subjects ≤7 months of age with infantile-onset SMA and 2 copies of *SMN2* who had onset of clinical signs and symptoms consistent with SMA at ≤6 months of age	~10 months	Ongoing; Interim CSR	United States, Spain, Germany, Italy, France, Turkey, Australia, Canada, Great Britain, Japan, Sweden, Republic of Korea, Hong Kong, Belgium, Thailand
ISIS 396443 -CS3A (Study CS3A)	Phase 2, open-label, multiple dose; Uncontrolled	ISIS 396443; • Cohort 1: 6-mg equivalent loading dose + 12-mg maintenance dose • Cohort 2: 12-mg equivalent loading dose + 12-mg maintenance dose Loading doses on Days 1, 15, and 85 Maintenance doses on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261 IT	Enrollment complete at 21: • Cohort 1: 4 • Cohort 2: 16 (1 subject withdrew prior to receiving treatment.) 0 completed as of data cutoff date of 26 January 2016	Subjects ≥21 days and ≤7 months of age with infantile-onset SMA who had onset of clinical signs and symptoms consistent with SMA at ≥21 days and ≤6 months of age	~3.5 years	Ongoing; Interim CSR	United States, Canada

Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled and Completed	Patient Population Enrolled	Duration of Treatment	Study Status; Type of Report	Countries
Later-Onset							
ISIS 396443 -CS4 (Study CS4)	Phase 3, randomized, double-blind, multiple-dose, sham-procedure controlled	ISIS 396443; 12 mg Days 1, 29, 85, and 274 IT	Enrollment complete at 126; Randomization: 2 active to 1 control; 0 completed as of data cutoff date of 02 May 2016	2- to 12-year-old subjects with later-onset SMA	~9 months	Ongoing; Progress report and SAE listing	*
ISIS 396443 -CS1 (Study CS1)	Phase 1, open-label, single ascending dose; Uncontrolled	ISIS 396443; • Cohort 1: 1 mg • Cohort 2: 3 mg • Cohort 3: 6 mg • Cohort 4: 9 mg; IT	28 enrolled and completed • Cohort 1: 6 • Cohort 2: 6 • Cohort 3: 6 • Cohort 4: 10	2- to 14-year-old subjects with later-onset SMA	Single dose	Completed; Full CSR	United States
ISIS 396443 -CS2 (Study CS2)	Phase 1/2a, open-label, multiple ascending-dose; Uncontrolled	ISIS 396443; • Cohort 1: 3 mg • Cohort 2: 6 mg • Cohort 3: 9 mg • Cohort 4: 12 mg Days 1, 29, and 85: Cohorts 1, 2 and 4 Days 1 and 85: Cohort 3 only; IT	34 enrolled • Cohort 1: 8 • Cohort 2: 8 • Cohort 3: 9 • Cohort 4: 9 33 completed	2- to 15-year-old subjects with later-onset SMA	~12 weeks	Completed; Full CSR	United States
ISIS 396443 -CS10 (Study CS10)	Phase 1, open-label, single dose; extension study; Uncontrolled	ISIS 396443; 6 or 9 mg; IT	18 enrolled and completed 6 mg: 4 9 mg: 14	2- to 14-year-old subjects with later-onset SMA who completed Study CS1	Single dose	Completed; Full CSR	United States
ISIS 396443 -CS12 (Study CS12)	Phase 1, open-label, multiple dose; extension study; Uncontrolled	ISIS 396443; 12 mg Days 1, 169, 351, and 533; IT	Approximately 52 eligible; 47 enrolled and 23 completed as of 07 April 2016	3- to 17-year-old subjects with later-onset SMA who completed Study CS2 or Study CS10	~18 months	Ongoing; Interim CSR	United States

Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled and Completed	Patient Population Enrolled	Duration of Treatment	Study Status; Type of Report	Countries
Infantile-Onset or Later-Onset							
232SM202 (Study SM202)	Phase 2, randomized, double-blind, multiple-dose, sham-procedure controlled	ISIS 396443; 12-mg Days 1, 15, 29, 64, 183, and 302 IT	Enrollment complete at 21; Randomization: 2 active to 1 control; 0 completed as of data cutoff date of 04 May 2016	Subjects with clinical signs and symptoms of SMA and 2 or 3 copies of *SMN2* who are not eligible for Study CS3B or Study CS4.	~10 months	Ongoing; Progress report and SAE listing	*

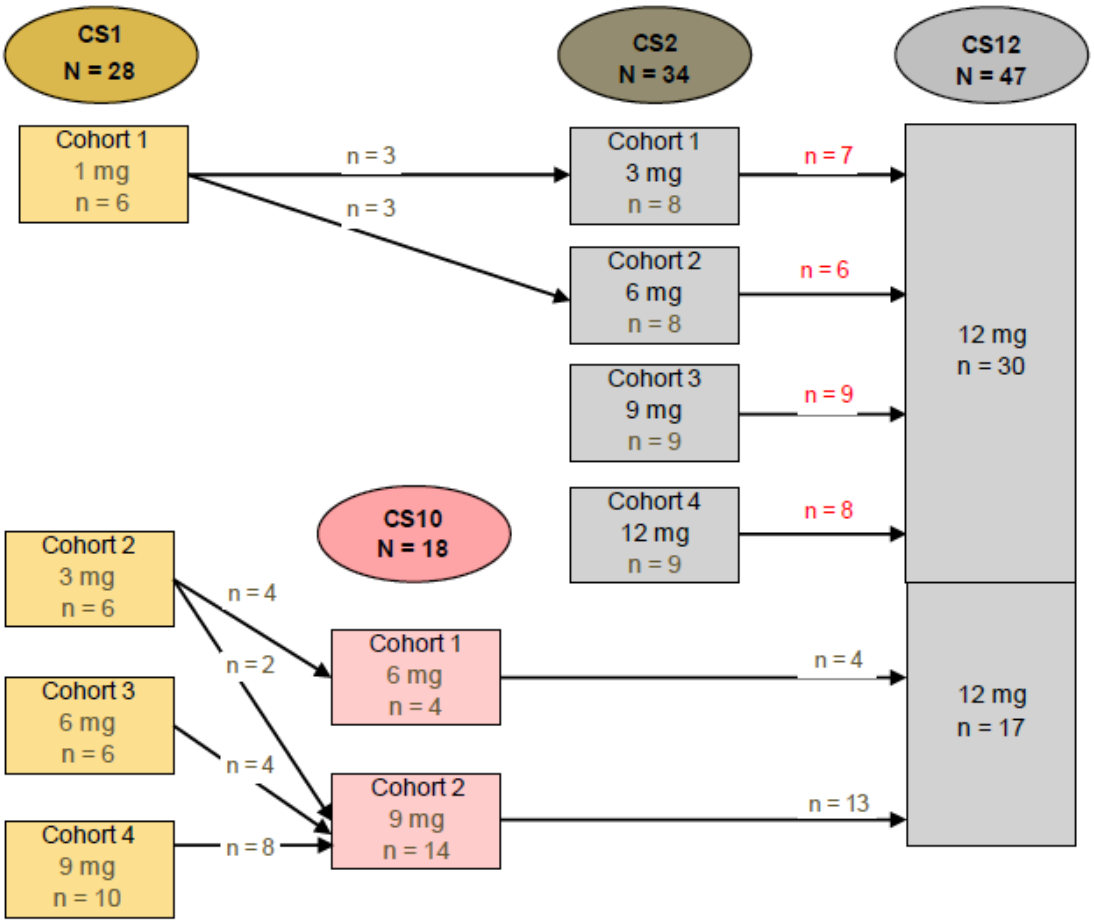
Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled and Completed	Patient Population Enrolled	Duration of Treatment	Study Status; Type of Report	Countries
ISIS 396443 -CS11 (Study CS11)	Phase 3, open-label, multiple dose; extension study (blinding during loading phase only); Uncontrolled	ISIS 396443;12-mg Blinded loading period and open-label maintenance period. Group 1A: Subjects who received sham procedures in CS3B receive 4 loading doses on Days 1, 15, 29, and 64 and 6 maintenance doses on Days 184, 304, 424, 544, 664, and 784. Group 1B: Subjects who received ISIS 396443 in CS3B receive 3 sham procedures on Days 1, 15, and 64 and 7 ISIS 396443 doses on Days 29, 184, 304, 424, 544, 664, and 784. Group 2A: Subjects who received sham procedures in CS4 receive 3 loading doses on Days 1, 29, and 85 and 4 maintenance doses on Days 265, 445, 625, and 805. Group 2B: Subjects who received ISIS 396443 in CS4 receive 1 sham procedure on Day 29 and 6 ISIS 396443 doses on Days 1, 85, 265, 445, 625, and 805. Group 3: Subjects who received ISIS 396443 in CS12 receive 5 ISIS 396443 doses on Days 1, 181, 361, 541, and 721. IT	Up to 274 planned; 4 enrolled and 0 completed as of data cutoff date of 02 May 2016	Subjects with SMA who completed Study CS3B, Study CS4, or Study CS12.	~2.0 to 2.2 years	Ongoing; Progress report and SAE listing	*

Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled and Completed	Patient Population Enrolled	Duration of Treatment	Study Status; Type of Report	
Studies in Patients with Presymptomatic SMA							
232SM201 (Study SM201)	Phase 2, open-label, multiple dose	ISIS 396443; 12-mg equivalent dose Days 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778 IT	~25 planned; 17 enrolled and 0 completed as of data cutoff date of 08 June 2016	Presymptomatic infants ≤6 weeks of age who were genetically diagnosed with SMA and have 2 or 3 copies of *SMN2*.	~26 months	Ongoing; Interim CSR	United States, Germany, Italy, Australia, Turkey, Taiwan

CSF = cerebrospinal fluid; CSR = clinical study report; IT = intrathecal/intrathecally; PK = pharmacokinetics; SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2 gene

* Note: Information on countries of subject origin was not provided for some ongoing studies.

Figure 1. Relationship between Studies CS1, CS10, CS2, and CS12



Note: The number of subjects enrolling in a subsequent study is noted (lines with arrows). The number of doses of ISIS 396443 administered in each study: 1 dose in CS1; 1 dose in CS10; 3 doses of 3 mg, 6 mg, or 12 mg in CS2; and 2 doses of 9 mg in CS2.
N = number of subjects; n = number of subjects in subgroup.
Source: ISIS 396443-CS12 Interim Clinical Study Report, Figure 3

5.2. Review Strategy

The clinical review of NDA 209531 is divided into a review of clinical efficacy (by Dr. Rainer Paine) and this review of clinical safety.

Information submitted as part of NDA 209531, published information related to oligonucleotides as a pharmacologic class, and other relevant published literature are discussed in this review.

6 Review of Relevant Individual Trials Used to Support Efficacy

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Rainer Paine.

7 Integrated Review of Effectiveness

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Rainer Paine.

8 Review of Safety

8.1. Safety Review Approach

The safety subject pools used in analyses of nusinersen clinical safety are summarized in the tables below.

Table 3. Nusinersen Clinical Studies. Safety Subject Pools.

Description	Study (Duration)	Treatment Groups in Individual Study	Sample Size
Pool A: Open-label, uncontrolled study in infants with presymptomatic SMA	SM201 (868 days/29 months)	Nusinersen 12 mg	Nusinersen: 17
Pool B: Blinded, controlled study in infantile-onset SMA	CS3B (394 days/13 months)	Nusinersen 12 mg Sham-procedure control	Nusinersen: 80 Sham procedure control: 41
Pool C: Blinded, controlled and open-label, uncontrolled studies in all ISIS 396443-treated infantile-onset SMA	CS3B (394 days/13 months)	Nusinersen 12 mg	Nusinersen:100
	CS3A (1352 days/45 months)	Nusinersen 6 mg × 3 then 12 mg × 9 Nusinersen 12 mg × 12	
Pool D: Blinded, controlled and open-label, uncontrolled studies in all nusinersen-treated infants diagnosed with SMA (presymptomatic SMA and infantile-onset SMA) in Pools A and C	SM201 (868 days/29 months)	Nusinersen 12 mg	Nusinersen:117
	CS3B (394 days/13 months)	Nusinersen 12 mg	
	CS3A (1352 days/45 months)	Nusinersen 6 mg × 3 then 12 mg × 9 Nusinersen 12 mg x 12	
Pool E: Open-label, uncontrolled studies in later-onset SMA	CS1, CS10, CS2, CS12* (up to 36 months)	Combinations of doses from different studies as highlighted in Figure 1	Nusinersen:56
Pool F: Blinded, controlled and open-label, uncontrolled studies in all nusinersen-treated subjects with SMA in Pools A, B, C, D, and E	SM201 (868 days/29 months)	Nusinersen 12 mg	Nusinersen:173
	CS3B (394 days/13 months)	Nusinersen 12 mg	
	CS3A (1352 days/45 months)	Nusinersen 6 mg × 3 then 12 mg × 9 Nusinersen 12 mg × 12	
	CS1, CS10, CS2, CS12	Combinations of doses from different studies	

Source: Summary of Clinical Safety Table 2

Table 4. Sample Size for Each Safety Subject Pool

Presymptomatic and Infantile-Onset SMA						
Presymptomatic (SM201): ISIS 396443 *Pool A*	Controlled Study (CS3B) *Pool B*		Symptomatic (Infantile-Onset; CS3B and CS3A): ISIS 396443 *Pool C*	Presymptomatic and symptomatic (SM201, CS3B, and CS3A): ISIS 396443 *Pool D*	Later-onset CS1, CS10, CS2, CS12: ISIS 396443 *Pool E*	All Treated Subjects (Pools D and E Combined): ISIS 396443 *Pool F*
	Control	ISIS 396443				
17	41	80	100	117	56	173

Source: Summary of Clinical Safety Table 3

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The tables below describe the size and subject duration of exposure for the nusinersen safety population.

Table 5. Nusinersen Safety Population. Size and Denominators.

Nusinersen Safety Database for Treatment of Spinal Muscular Atrophy (SMA)			
Clinical Trial Groups	Nusinersen (n=173)	Active Control (n=0)	Sham Procedure Control (n= 41)
Normal Volunteers	0	0	0
Controlled trials conducted for this indication[2]	80	0	41
All other than controlled trials conducted for this indication[3]	93	0	0
Controlled trials conducted for other indications[4]	0	0	0

Source: Sponsor Table 3. Summary of Clinical Safety.

Table 6. Nusinersen Safety Population. Duration of Exposure.

	Number of patients exposed to nusinersen:				
	Total	>=6 months	>=12 months	>=18 months	>=24 months
Controlled study subjects[a]	80	41	19	0	0
All subjects	173	120	83	62	54

[a] Study CS3B subjects
Source: Submission to NDA 209531 on 10/25/2016

Subject exposure to treatment by subject pool is summarized in the table below. Most of the experience with nusinersen exposure longer than 2 years occurred in the Later-onset SMA subject pool (Pool E). However, Pool E subjects did not receive the full dose of nusinersen under consideration for marketing (12 mg) for the entire treatment duration. Pool E subjects received varying nusinersen doses ranging from 1-12 mg (see Figure 1).

Table 7. Subjects Diagnosed with SMA: Exposure to Treatment

	Infants diagnosed with SMA				
	Presymptomatic	Symptomatic (infantile-onset): controlled and uncontrolled studies	Presymptomatic and symptomatic	Later-onset SMA	All subjects treated
>= 90 days	13 (76)	78 (78)	91 (78)	55 (98)	146 (84)
>= 180 days	10 (59)	58 (58)	68 (58)	52 (93)	120 (69)
>= 270 days	5 (29)	42 (42)	47 (40)	48 (86)	95 (55)
>= 360 days	1 (6)	34 (34)	35 (30)	48 (86)	83 (48)
>= 540 days	0	15 (15)	15 (13)	48 (86)	63 (36)
>= 720 days	0	8 (8)	8 (7)	46 (82)	54 (31)
>= 900 days	0	2 (2)	2 (2)	39 (70)	41 (24)
>= 1080 days	0	0	0	31 (55)	31 (18)
>= 1260 days	0	0	0	22 (39)	22 (13)
>= 1440 days	0	0	0	9 (16)	9 (5)
Time on study (days)					
n	17	100	117	56	173
Mean	198.4	285.1	272.5	1035.7	519.5
SD	114.71	234.22	222.66	437.49	472.10
Median	241.0	224.5	225.0	1112.5	324.0
25th, 75th percentiles	120.0, 302.0	103.5, 395.0	108.0, 388.0	786.5, 1388.5	132.0, 806.0
Min, Max	6, 386	6, 994	6, 994	31, 1536	6, 1536
Total number of subject-years	9.23	78.06	87.29	158.79	246.08

Summary of Clinical Safety Source Table 1

8.2.2. Relevant Characteristics of the Safety Population

Demographics and Subject Characteristics

The table below displays demographics for nusinersen clinical safety subject pools.

Table 8. Demographic Characteristics for Nusinersen Clinical Study Subject Pools

	Infants diagnosed with SMA				
	Presymptomatic	Symptomatic (infantile-onset): controlled and uncontrolled studies	Presymptomatic and symptomatic	Later-onset SMA	All subjects treated
Number of subjects dosed	17	100	117	56	173
Age at first dose/sham procedure					
<30 days (less than 1 month)	14 (82)	0	14 (12)	0	14 (8)
>=30 days to <90 days (1 to 3 months)	3 (18)	10 (10)	13 (11)	0	13 (8)
>=90 days to <180 days (3 to 6 months)	0	51 (51)	51 (44)	0	51 (29)
>=180 days to <365 days (6 months to 1 year)	0	39 (39)	39 (33)	0	39 (23)
>=1 year to <2 years	0	0	0	0	0
>=2 years to <6 years	0	0	0	28 (50)	28 (16)
>=6 years	0	0	0	28 (50)	28 (16)
n	17	100	117	56	173
Mean	21.9	160.9	140.7	7.19	951.8
SD	11.19	52.23	69.04	4.078	1447.19
Median	19.0	164.5	148.0	6.15	199.0
25th, 75th percentiles	13.0, 27.0	118.0, 210.0	96.0, 200.0	4.10, 9.35	118.0, 1501.0
Min, Max	8, 42	37, 242	8, 242	2.0, 15.9	8, 5833
Sex					
n	17	100	117	56	173
Male	11 (65)	49 (49)	60 (51)	26 (46)	86 (50)
Female	6 (35)	51 (51)	57 (49)	30 (54)	87 (50)
Ethnicity					
n	17	100	117	56	173
Hispanic or Latino	2 (12)	13 (13)	15 (13)	8 (14)	23 (13)
Not Hispanic or Latino	11 (65)	87 (87)	98 (84)	48 (86)	146 (84)
Not Reported	4 (24)	0	4 (3)	0	4 (2)
Race					
n	17	100	117	56	173
Asian	2 (12)	6 (6)	8 (7)	2 (4)	10 (6)
Black	0	4 (4)	4 (3)	3 (5)	7 (4)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
White	9 (53)	84 (84)	93 (79)	49 (88)	142 (82)
Other	2 (12)	4 (4)	6 (5)	1 (2)	7 (4)
Multiple	0	2 (2)	2 (2)	1 (2)	3 (2)
Not Reported	4 (24)	0	4 (3)	0	4 (2)
Geographic region					
North America	12 (71)	58 (58)	70 (60)	56 (100)	126 (73)
Europe	3 (18)	30 (30)	33 (28)	0	33 (19)
Asia-Pacific	2 (12)	12 (12)	14 (12)	0	14 (8)
Height (cm)					
n	17	100	117	33	150
Mean	52.6	64.2	62.5	120.9	75.4
SD	2.99	4.68	6.06	24.97	27.40
Median	52.3	64.8	63.0	120.2	65.1
25th, 75th percentiles	50.3, 55.0	60.7, 66.5	59.0, 66.2	98.9, 144.5	60.4, 73.0
Min, Max	49, 59	54, 75	49, 75	82, 171	49, 171
Weight (kg)					
n	17	100	117	56	173
Mean	3.9	6.6	6.2	26.2	12.7
SD	0.74	1.05	1.38	17.76	13.77
Median	3.9	6.6	6.3	19.1	7.0
25th, 75th percentiles	3.3, 4.5	5.8, 7.1	5.4, 7.0	13.4, 32.8	5.8, 13.3
Min, Max	3, 5	5, 9	3, 9	10, 83	3, 83

Age at first dose was calculated in 'years' for Later Onset study and 'days' were used for all other columns.
Summary of Clinical Safety Source Table 7.

Mean ages at first dose were 22 days, 161 days (5 months), and 7 years for Presymptomatic Infantile-onset SMA Subjects (Pool A), Presymptomatic Infantile-Onset SMA Subjects (Pool C), and Later-onset Subjects (Pool E), respectively.

In Study CS3B (Pool B), characteristics of nusinersen and sham procedure control subjects were similar, including age at first treatment, gestational age, sex, ethnicity, race, geographic region, height, weight, and SMN2 copy number.[1]

The table below summarizes SMN2 copy number for nusinersen clinical safety subject pools.

Table 9. SMN2 Copy Number. Nusinersen Clinical Safety Subject Pools.

	Infants diagnosed with SMA				
	Presymptomatic	Symptomatic (infantile-onset): controlled and uncontrolled studies	Presymptomatic and symptomatic	Later-onset SMA	All subjects treated
Number of subjects dosed	17	100	117	56	173
SMN2 copy number					
1 copy	0	0	0	0	0
2 copies	12 (71)	95 (95)	107 (91)	1 (2)	108 (62)
3 copies	5 (29)	2 (2)	7 (6)	46 (82)	53 (31)
4 copies	0	0	0	8 (14)	8 (5)
5 copies	0	0	0	1 (2)	1 (<1)
Unknown	0	3 (3)	3 (3)	0	3 (2)

Source: Summary of Clinical Safety Source Table 8

8.2.3. Adequacy of the Safety Database

Because spinal muscular atrophy is a rare disease, the overall subject exposure and demographics are acceptable for NDA submission.

All subjects with infantile-onset SMA (117 of all 173 nusinersen-treated subjects) were less than 1 year old at first dose, including all of the controlled study CS3B subjects. Thus, adverse events which require self-reporting from the subject could not be assessed in the controlled data.

The Later-onset SMA Subject Pool (age range 2-16) had the longest mean duration of exposure (34 months).[2] Most of the subjects with greater than 2 years of nusinersen exposure were in this subject pool. However, Pool E subjects did not receive the full dose of nusinersen under

[1] Summary of Clinical Safety Source Tables 5 and 6.
[2] Summary of Clinical Safety Source Table 1.

consideration for marketing (12 mg) for the entire treatment duration. Pool E subjects received varying nusinersen doses ranging from 1-12 mg (see Figure 1).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The NDA submission was well-organized. Requests for additional information were addressed promptly by the Sponsor.

8.3.2. Categorization of Adverse Events

The Sponsor's process for recording adverse events (AEs) was appropriate. The Sponsor's coding resulted in appropriate translation of verbatim terms to Preferred Terms.

The Sponsor categorized AEs as mild, moderate, or severe. Adverse events were coded to MedDRA 18.1 in the summary of clinical safety.[3]

An AE was regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen or first sham procedure and subsequently worsened in severity, or it was not present prior to receiving the first dose of nusinersen or first sham procedure but subsequently appeared.

8.3.3. Routine Clinical Tests

The laboratory assessment schedule in the nusinersen clinical development program is summarized in Appendix 1; deficiencies in these laboratory assessments include:

- No quantitative urine protein measurements were performed. (See Section 8.5.1 Renal Toxicity)
- Serum bicarbonate is listed as a routine laboratory assessment in Study CS3B,[4] but serum bicarbonate was not routinely evaluated in this study.[5] (See Section 8.5.1 Renal Toxicity)
- Coagulation laboratory parameters were measured post-baseline only in Study CS2. (See Section 8.4.6. Laboratory Findings)
- Gamma-glutamyl transferase (GGT) was not measured to assess hepatic toxicity. (See Section 8.4.6. Laboratory Findings)

[3] P. 20 IR response submitted to NDA 209531 on 11/8/2016.
[4] P. 5 Multiple module information amendment submitted to NDA 209531 on 9/23/2016.
[5] P. 3 IR response submitted to NDA 209531 on 11/29/2016.

8.4. Safety Results

8.4.1. Deaths

Deaths in nusinersen clinical studies are listed in the table below. In Controlled Study CS3B, deaths occurred in 12 of 80 (15%) nusinersen-treated subjects, compared to 13 of 41 (32%) sham procedure control subjects. In all studies (Pool F), 16 of 173 (9%) nusinersen-treated subjects died.

Table 10. Deaths in nusinersen clinical studies

System Organ Class Preferred Term	Study CS3B: Nusinersen (N=80)	Study CS3B: Control (N=41)	All Nusinersen subjects (N=173)
Total	12 (15)	13 (32)	16 (9)
Respiratory, thoracic and mediastinal disorders	7 (9)	10 (24)	10 (6)
Respiratory failure	4 (5)	7 (17)	6 (3)
Acute respiratory failure	1 (1)	1 (2)	1 (<1)
Asphyxia	0	0	1 (<1)
Respiratory arrest	1 (1)	0	1 (<1)
Respiratory distress	1 (1)	2 (5)	1 (<1)
Cardiac disorders	2 (3)	2 (5)	2 (1)
Cardio-respiratory arrest	2 (3)	2 (5)	2 (1)
Nervous system disorders	2 (3)	0	2 (1)
Brain injury	1 (1)	0	1 (<1)
Hypoxic-ischaemic encephalopathy	1 (1)	0	1 (<1)
General disorders and administration site conditions	1 (1)	1 (2)	1 (<1)
Death	1 (1)	1 (2)	1 (<1)
Infections and infestations	0	0	1 (<1)
Lower respiratory tract infection viral	0	0	1 (<1)

Source: Sponsor Tables 42 and 44 in Section 5.3.5.3. Source Tables for Summary of Clinical Safety. Submitted to NDA 20951 on 9/23/2016.

All of the deaths occurred in subjects with symptomatic infantile-onset SMA, and the deaths were related to complications of SMA [except for Study CS3B Subject 2037-5167 (SAE PT Death) who has an unclear cause of death]. Most deaths were attributed to respiratory disorders or cardio-respiratory arrest. In controlled study CS3B, 2 deaths in nusinersen-treated subjects coded to the Nervous system disorders SOC were related to complications of SMA:

- **SAE PT Brain injury:** Subject 1780-5032 had advanced respiratory disease related to SMA. Hypoxic brain injury and death occurred after this subject developed pneumonia and uncompensated shock.
- **SAE PT Hypoxic-ischaemic encephalopathy:** Subject 2000-5145 had a cardiac arrest after aspirating post-nasogastric tube feeding. Aspiration is a common complication of SMA.[6]

In controlled study CS3B, 2 deaths were coded to the PT "Death":

- **SAE PT Death:** Subject 2037-5167 (nusinersen group) was found dead at home at age 7.5 months (81 and 52 days after the subject's first and latest nusinersen dose, respectively). While her immediate cause of death was unclear, complications of SMA likely contributed to her death. She had been hospitalized twice within 2 months of death for "weight stagnation" and 2 weeks prior to her death weighed 6 kg (2nd percentile in weight for her age and sex).[7] Growth failure is a universal problem in nonsitting SMA patients.[8]
- **SAE PT Death:** Subject 1835-5103 (sham control procedure group) died after initiating palliative comfort care that included morphine.

There were no deaths in infants with presymptomatic SMA or subjects with later onset SMA.

8.4.2. Serious Adverse Events

Reviewer comment: In the review of individual serious adverse events, this reviewer evaluated information from the Sponsor's narrative summaries. In specific cases, this reviewer also evaluated information from case report forms or related medical records.

In the controlled study CS3B, 56 of 80 (70%) of nusinersen-treated subjects had a serious adverse event (SAE), compared to 33 of 41 (80%) of sham procedure control subjects. Most of the serious adverse events were manifestations of spinal muscular atrophy.

Similar to controlled study CS3B, most of the SAEs in Pool F (all nusinersen-treated subjects) were manifestations of spinal muscular atrophy. In all treated subjects, the incidence of SAEs is lower [84 of 173 (49%)] compared to controlled study subjects, likely because this pool includes subjects with presymptomatic or later onset SMA, who generally have less severe

[6] Birnkrant, David J., et al. "Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding." *Pediatric neurology* 18.5 (1998): 407-410.
[7] World Health Organization (WHO) Growth Standards. Accessed on 10/22/2016 at: http://www.cdc.gov/growthcharts/who_charts.htm
[8] Wang, Ching H., et al. "Consensus statement for standard of care in spinal muscular atrophy." *Journal of Child Neurology* 22.8 (2007): 1027-1049.

manifestations of SMA compared to Study CS3B subjects with symptomatic infantile onset SMA. Serious Adverse Events by System Organ Class (SOC) are summarized in the table below.

Table 11. Summary of Serious Adverse Events by System Organ Class. Controlled Study CS3B and in all Nusinersen-Treated Subjects

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Number of subjects with an event	56 (70)	33 (80)	84 (49)
Respiratory, thoracic and mediastinal disorders	46 (58)	26 (63)	64 (37)
Infections and infestations	40 (50)	15 (37)	60 (35)
Cardiac disorders	9 (11)	5 (12)	12 (7)
Metabolism and nutrition disorders	7 (9)	4 (10)	10 (6)
Gastrointestinal disorders	6 (8)	3 (7)	8 (5)
Injury, poisoning and procedural complications	3 (4)	2 (5)	5 (3)
General disorders and administration site conditions	4 (5)	1 (2)	4 (2)
Nervous system disorders	2 (3)	0	3 (2)
Investigations	2 (3)	2 (5)	2 (1)
Immune system disorders	0	0	1 (<1)
Musculoskeletal and connective tissue disorders	0	0	1 (<1)
Skin and subcutaneous tissue disorders	1 (1)	0	1 (<1)
Vascular disorders	1 (1)	0	1 (<1)
Psychiatric disorders	0	1 (2)	0

Source: 11/01/2016 Submission to NDA 209531

Reviewer comment: There were no adverse events of aplastic anemia, pancytopenia, acute pancreatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome reported in the nusinersen clinical development program.

Respiratory, thoracic and mediastinal disorders SOC

In controlled study CS3B, 46 of 80 (58%) nusinersen-treated subjects had an SAE in the Respiratory, thoracic and mediastinal disorders SOC, compared to 26 of 41 (63%) of sham procedure control subjects. For individual Preferred Terms in this SOC, incidences were generally similar between treatment groups or higher in the sham procedure control group (see table below).

One exception was SAEs coded to the Preferred Term Atelectasis, which occurred in 11 of 80 (14%) of nusinersen-treated subjects, compared to 2 of 41 (5%) sham procedure control subjects.

Reviewer comment: Nusinersen subjects had increased frequencies of upper and lower respiratory infections (see Section 8.4.5. Treatment Emergent Adverse Events and Adverse

Reactions). Obstructive atelectasis related to infection and mucus plugging may have contributed to the increased frequency of serious atelectasis in nusinersen subjects. One nusinersen subject[9] received nitrous oxide prior to developing serious atelectasis. The use of sedation with nitrous oxide during lumbar puncture procedures may have contributed to serious atelectasis in this patient. Development of atelectasis with use of nitrous oxide has been described in the published literature.[10-11]

In Study CS3B, SAEs coded to the PT Aspiration were more common in nusinersen subjects [3 of 80 (4%) compared to 0 of 41 control subjects], but aspiration adverse events were less common in nusinersen subjects compared to sham procedure control subjects.[12]

Table 12. Serious Adverse Events. Respiratory, Thoracic and Mediastinal Disorders SOC. Controlled Study CS3B and All Nusinersen-treated Subjects. [13]

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Respiratory, thoracic and mediastinal disorders	46 (58)	26 (63)	64 (37)
Respiratory distress	19 (24)	10 (24)	26 (15)
Respiratory failure	17 (21)	14 (34)	23 (13)
Acute respiratory failure	11 (14)	7 (17)	16 (9)
Atelectasis	11 (14)	2 (5)	13 (8)
Pneumonia aspiration	6 (8)	4 (10)	8 (5)
Dyspnoea	4 (5)	2 (5)	5 (3)
Apnoea	2 (3)	2 (5)	4 (2)
Aspiration	3 (4)	0	4 (2)
Hypoxia	3 (4)	1 (2)	4 (2)
Respiratory arrest	3 (4)	4 (10)	3 (2)
Hypoventilation	1 (1)	0	2 (1)
Respiratory disorder	2 (3)	0	2 (1)
Acute respiratory distress syndrome	1 (1)	0	1 (<1)
Asphyxia	0	0	1 (<1)
Bronchial secretion retention	1 (1)	2 (5)	1 (<1)
Chronic respiratory failure	1 (1)	0	1 (<1)
Hypercapnia	1 (1)	0	1 (<1)
Increased bronchial secretion	1 (1)	0	1 (<1)
Lung disorder	1 (1)	0	1 (<1)
Obstructive airways disorder	1 (1)	0	1 (<1)
Pneumomediastinum	0	0	1 (<1)
Apparent life threatening event	0	2 (5)	0
Respiratory tract congestion	0	1 (2)	0

[9] CS3B Subject 2037-5139. P. 10 Response to FDA IR submitted to NDA 209531 on 11/23/2016.
[10] Gunnarsson L, et al. Atelectasis and gas exchange impairment during enflurane/nitrous oxide anaesthesia. *Acta Anaesthesiol Scand.* 1989 Nov;33(8):629-37.
[11] Hedenstierna G, Edmark L. Mechanisms of atelectasis in the perioperative period. Best Pract Res Clin Anaesthesiol. 2010 Jun;24(2):157-69.
[12] In Study CS3B, adverse events coded to the Preferred Terms "Aspiration" or "Pneumonia aspiration" occurred in 9 of 80 (11%) nusinersen subjects, compared to 7 of 41 (17%) sham procedure control subjects.
[13] Source for each table in this review of serious adverse events was submitted to NDA 209531 on 11/1/2016.

Infections and Infestations SOC

In controlled study CS3B, 40 of 80 (50%) nusinersen-treated subjects had an SAE in the Infections and Infestations SOC, compared to 15 of 41 (37%) of sham procedure control subjects (see table below). Pneumonia and other lower respiratory infection SAEs[14] were more common in nusinersen subjects [29 of 80 (36%)], compared to sham procedure control subjects [9 of 41 (22%)].

Table 13. Serious Adverse Events. Infections and Infestations SOC. Controlled Study CS3B and All Nusinersen-treated Subjects.

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Infections and infestations	40 (50)	15 (37)	60 (35)
Pneumonia	14 (18)	4 (10)	20 (12)
Rhinovirus infection	6 (8)	2 (5)	10 (6)
Pneumonia viral	5 (6)	1 (2)	9 (5)
Bronchiolitis	4 (5)	1 (2)	7 (4)
Viral infection	4 (5)	1 (2)	6 (3)
Respiratory syncytial virus bronchiolitis	3 (4)	3 (7)	5 (3)
Respiratory tract infection	4 (5)	0	5 (3)
Upper respiratory tract infection	4 (5)	0	5 (3)
Bronchitis	3 (4)	0	4 (2)
Lower respiratory tract infection	3 (4)	0	4 (2)
Pneumonia bacterial	3 (4)	1 (2)	4 (2)
Viral upper respiratory tract infection	3 (4)	6 (15)	4 (2)
Bronchitis viral	2 (3)	0	2 (1)
Lower respiratory tract infection viral	1 (1)	0	2 (1)
Metapneumovirus infection	0	0	2 (1)
Pneumonia respiratory syncytial viral	1 (1)	0	2 (1)
Respiratory tract infection viral	1 (1)	1 (2)	2 (1)
Corona virus infection	0	1 (2)	1 (<1)
Ear infection	1 (1)	0	1 (<1)
Enterovirus infection	0	0	1 (<1)
Gastroenteritis	0	0	1 (<1)
Gastroenteritis rotavirus	1 (1)	0	1 (<1)
Lung infection	1 (1)	0	1 (<1)
Nasopharyngitis	1 (1)	0	1 (<1)
Nosocomial infection	1 (1)	0	1 (<1)
Parainfluenzae virus infection	0	0	1 (<1)
Pneumonia influenzal	1 (1)	0	1 (<1)
Pneumonia moraxella	1 (1)	0	1 (<1)
Pneumonia parainfluenzae viral	1 (1)	1 (2)	1 (<1)
Pneumonia pseudomonal	0	1 (2)	1 (<1)
Staphylococcal sepsis	1 (1)	0	1 (<1)
Stoma site abscess	1 (1)	0	1 (<1)
Urinary tract infection	0	0	1 (<1)

[14] Pneumonia and other lower respiratory infection SAEs in Study CS3B included adverse events coded to the following Preferred Terms: Pneumonia, Pneumonia viral, Respiratory syncytial virus bronchiolitis, Bronchiolitis, Lower respiratory tract infection, Pneumonia bacterial, Bronchitis, Bronchitis viral, Pneumonia moraxella, Pneumonia parainfluenzae viral, Lower respiratory tract infection viral, Lung infection, Pneumonia influenzal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral.

Cardiac Disorders SOC

In controlled study CS3B, the incidence of SAEs in the Cardiac disorders SOC was similar between nusinersen subjects [9 of 80 (11%)], compared to sham procedure control subjects [5 of 41 (12%)] (see table below).

Reviewer comment: All of the cardiac disorder SAEs occurred in patients with symptomatic infantile-onset SMA. I have reviewed these events and assess them to be likely related to cardio-respiratory compromise in patients with advanced symptomatic SMA.

Table 14. Serious Adverse Events. Cardiac Disorders SOC. Controlled Study CS3B and All Nusinersen-treated Subjects.

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Cardiac disorders	9 (11)	5 (12)	12 (7)
Cardio-respiratory arrest	5 (6)	3 (7)	6 (3)
Cardiac arrest	2 (3)	2 (5)	3 (2)
Cyanosis	1 (1)	1 (2)	2 (1)
Bradycardia	0	0	1 (<1)
Pneumopericardium	0	0	1 (<1)
Ventricular tachycardia	1 (1)	0	1 (<1)

Metabolism and Nutrition Disorders SOC

In controlled study CS3B, the incidence of SAEs in the Metabolism and Nutrition Disorders SOC was similar between nusinersen subjects [7 of 80 (9%)], compared to sham procedure control subjects [4 of 41 (10%)] (see table below). The most frequent SAEs in this SOC (i.e., PTs Weight gain poor, Failure to thrive, Feeding disorder of infancy or early childhood, and Feeding intolerance) are common issues in SMA patients.[15] Nusinersen-treated Study CS3B Subject 1997-5277 had an SAE of dehydration as part of her feeding disorder.

[15] Tilton AH, et al. Nutrition and swallowing in pediatric neuromuscular patients. *Semin Pediatr Neurol*. 1998 Jun;5(2):106-15.

Table 15. Serious Adverse Events. Metabolism and Nutrition Disorders SOC. Controlled Study CS3B and All Nusinersen-treated Subjects.

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Metabolism and nutrition disorders	7 (9)	4 (10)	10 (6)
Weight gain poor	3 (4)	2 (5)	3 (2)
Failure to thrive	0	0	2 (1)
Feeding disorder of infancy or early childhood	2 (3)	2 (5)	2 (1)
Feeding intolerance	2 (3)	0	2 (1)
Dehydration	1 (1)	0	1 (<1)
Hyponatraemia	0	0	1 (<1)

The SAE of Hyponatraemia is discussed in Section 8.4.6.1.1.

Gastrointestinal Disorders SOC

In controlled study CS3B, 6 of 80 nusinersen (8%) subjects compared to 3 of 41 (7%) sham control subjects had SAEs coded to the Gastrointestinal Disorders SOC (see table below). PTs in this SOC are common SMA-related issues, and they occur in similar frequencies between treatment groups.

Table 16. Serious Adverse Events. Gastrointestinal Disorders SOC. Controlled Study CS3B and All Nusinersen-treated Subjects.

	Study CS3B Nusinersen Subjects N=80	Study CS3B Control Subjects N=41	All Nusinersen Subjects (Pool F) N=173
Gastrointestinal disorders	6 (8)	3 (7)	8 (5)
Vomiting	3 (4)	1 (2)	4 (2)
Dysphagia	2 (3)	0	2 (1)
Abdominal distension	0	0	1 (<1)
Gastric haemorrhage	1 (1)	0	1 (<1)
Gastrointestinal haemorrhage	0	1 (2)	0
Salivary hypersecretion	0	1 (2)	0

Nervous System disorders SOC

SAEs coded to the Nervous system disorders SOC are discussed in Section 8.5.2. Neurologic Toxicity.

Immune system disorders SOC

One SAE coded to this SOC (SAE PT Drug hypersensitivity; Study CS2 Subject 1780-1202 treated with nusinersen 3 mg) occurred in a 9 year old subject. He received IV fentanyl as part of a procedure to remove a plantar wart and then received his third dose of nusinersen.[16] In the post-anesthesia care unit, he had upper lip swelling, hives, and redness. Subsequent to this event, the subject responded to treatment with supplemental oxygen, epinephrine 1:1000, Decadron (dexamethasone), Versed (midazolam), Benadryl (diphenhydramine), and ranitidine, and the event resolved on the same day. An immunology consultation assessed the event as possibly a side effect of fentanyl rather than a true IgE-mediated reaction due to the lack of elevated histamine, tryptase, or absolute eosinophil count approximately 1 hour after the start of the reaction. Subsequent to this event, the subject received 1 additional 3 mg dose of nusinersen in Study CS2 and 4 additional 12 mg doses of nusinersen in Study CS12. No adverse event indicative of hypersensitivity was reported after this SAE.

Reviewer comment: This case of drug hypersensitivity occurred after administration of fentanyl and nusinersen. Because this subject had 5 subsequent doses of nusinersen with no event of drug hypersensitivity, a relationship to nusinersen is unlikely.

Musculoskeletal and connective tissue disorders SOC

One SAE coded to this SOC (SAE PT Synovitis; CS3A Subject 1833-2303 treated with nusinersen 12 mg) occurred in a 31 month old male, who developed vomiting, diarrhea, and fever on Study Day 756. He received his 8th nusinersen dose on Study Day 757. On Day (b) (6) he developed fever, right knee pain, and back pain. X-rays of the right knee and both hips were reported as negative. There was no joint swelling or erythema, but the subject was not able to stand or bear weight. There was no tenderness or stiffness in the neck and back on physical exam, and no bruising at the lumbar puncture site and no tenderness along the spine. No pain or discomfort was elicited with range of motion at the hips and knees although the left hip.

The subject was treated with an IV bolus of sodium chloride and ibuprofen. Later that day he had no further episodes of pain, and was able to change from a supine to sitting position and sitting to supine without assistance; he was also able to stand and bear weight without difficulty. The next day, on Study Day (b) (6), the subject was discharged home.

Reviewer comment: The etiology of this SAE is unclear. He had symptoms of infection (vomiting, diarrhea, and fever) 2 days prior to the onset of his synovitis symptoms. However, the SAE occurred 1 day after nusinersen administration. Both a viral etiology and a drug-related etiology

[16] P. 755 CS2 Study Report submitted to NDA 209531 on 9/23/2016.

are possible causes for this case of synovitis. This subject did not test positive for anti-dug antibodies.

Skin and subcutaneous tissue disorders SOC

One SAE coded to this SOC (SAE PT Dermatitis; CS3B Subject 1999-5251 treated with nusinersen 12 mg) was reported. This subject had skin inflammation near the right eye, which was intermittent and had occurred prior to the first nusinersen dose.

Reviewer comment: Because this subject had similar symptoms prior to starting nusinersen, a causal role of nusinersen is unlikely.

Vascular disorders SOC

Study CS3B Subject 1780-5032 had an SAE coded to the PT Shock as a result of advanced respiratory disease related to SMA. Hypoxic brain injury and death occurred after this subject developed pneumonia and uncompensated shock.

Reviewer comment: The SAE of Shock was a complication of advanced symptomatic SMA.

Reviewer comment: For ongoing studies CS4, 232SM202, and CS11, I reviewed the submitted progress reports with blinded aggregate data. According to the available information, the SAEs reported in these studies were similar to those reported in the NDA submission.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In subjects with infantile-onset SMA in Study CS3B and Study CS3A, all events leading to treatment discontinuation were a result of death that occurred before the next scheduled dose.[17] There were no events that lead to treatment discontinuation in subjects with Presymptomatic SMA or later-onset SMA.

8.4.4. Significant Adverse Events

The Sponsor categorized clinical study adverse events by severity (mild, moderate, or severe) in the summary of clinical safety datasets. Most adverse events categorized as severe were also categorized as Serious Adverse Events and are discussed in Section 8.4.2. Most of the remaining

[17] P. 51 Summary of Clinical Safety

severe adverse events were manifestations of SMA, including adverse events of respiratory infection, respiratory compromise/failure, gastritis, dysphagia, and joint contracture.
Other severe adverse events in nusinersen-treated subjects that were not SAEs or manifestations of SMA and are not discussed elsewhere in this review include:

- Study CS2 Subject 1775-2208 (3 year old female from the United States) had an AE of Myalgia lasting 2 hours on Study Day 2.
- Study CS3B Subject 2000-5203 (15 month old male from the United States) had an AE of Hypertension starting on Study Day 330 and lasting for 54 days.

Reviewer comment: The causes for these adverse events are unclear. Limited information was provided.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events that occurred in at least 5% of nusinersen subjects and occurred more frequently than sham procedure control subjects in Study CS3B are summarized in the table below.

Table 17. Study CS3B. Summary of Adverse Events that Occurred in at Least 5% of Nusinersen Subjects and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Subjects

Adverse Event Preferred Term	Nusinersen 12 mg N=80 n (%)	Sham Procedure Control N=41 n (%)
Upper respiratory infection	35 (44)	16 (39)
Lower respiratory infection	34 (43)	12 (29)
Constipation	24 (30)	9 (22)
Teething	11 (14)	3 (7)
Upper respiratory tract congestion	5 (6)	1 (2)
Aspiration	4 (5)	1 (2)
Ear infection	4 (5)	1 (2)
Scoliosis	4 (5)	1 (2)

Sources: 10/17/2016 submission to NDA 209531 and Summary of Clinical Safety dataset ADAE (submitted 9/23/2016)

Reviewer comments: Analyses were performed to combine the frequencies of split terms related to upper respiratory infection. Preferred terms[18] included in the Upper respiratory infection High Level Term were combined in the table above. Analyses were performed to combine the

[18] Subjects had at least one of these Preferred Terms categorized under the Upper respiratory infection High Level Term: Upper respiratory tract infection, Nasopharyngitis, Rhinitis, Pharyngitis, or Tracheitis.

frequencies of split terms related to lower respiratory infection;[19] the results of these analyses are also included in the table above.

Study CS3B subjects were less than 1 year old at first dose and were unable to verbally report adverse events. Later onset SMA subjects (Pool E; age range at study entry 2-16) were able to verbally report adverse events. In later-onset SMA patients, common adverse events that were not SMA complications and were not commonly reported in Study CS3B subjects included Headache (50%), Back pain (41%), and Post lumbar puncture syndrome (41%).

8.4.6. Laboratory Findings

Reviewer note: The denominators in the laboratory findings section of this review correspond to the number of subjects with at least one post-treatment measurement of the parameter being discussed.

8.4.6.1. Clinical Chemistry Laboratory Measurements

8.4.6.1.1. Hyponatremia

In Study CS3B, 1 of 59 (2%) nusinersen subjects had treatment-emergent low serum sodium, compared to 0 of 28 sham procedure control subjects. Of all treated nusinersen subjects, 6 of 151 (4%) had at least 1 treatment-emergent low serum sodium measurement. Three subjects had a treatment-emergent serum sodium less than 130 mmol/L:

CS3A Subject 1776-2305 SAE PT Hyponatraemia:[20] Female subject from the United States (4 months old at study entry) with Type 2 SMA[21] and adverse events consistent with advanced SMA, including AEs coded to PTs: Use of accessory respiratory muscles, Hypoxia, Apnoea, and Cyanosis. She had treatment-emergent hyponatremia first measured on Study Day 89 (124 mmol/L). Lethargy was noted on Study Day 227, and she had a nadir serum sodium measurement of 94 mmol/L on Study Day 231.

[19] Pneumonia and other lower respiratory infection AEs in Study CS3B included adverse events coded to the following Preferred Terms: Pneumonia, Bronchiolitis, Pneumonia viral, Respiratory syncytial virus bronchiolitis, Lower respiratory tract infection, Pneumonia bacterial, Bronchitis, Bronchitis viral, Pneumonia moraxella, Pneumonia parainfluenzae viral, Lower respiratory tract infection viral, Lung infection, Pneumonia influenzal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral.
[20] Narrative on p. 17 of the information request response submitted to NDA 209531 on 10/14/2016.
[21] Dataset ADSL Section 5.3.5.3. of the NDA 9/23/2016 submission to NDA 209531.

Table 18. CS3A Subject 1776-2305. Serum Electrolyte Values and Dates of Nusinersen Administration.

Date (Study Day)	Bicarbonate (Ref. range 22-30 mmol/L)	Calcium (Ref. range 8.7-10.2 mg/dL)	Chloride (Ref. range 102-109 mmol/L)	Glucose (Ref. range 60-100 mg/dL)	Phosphorus (Ref. range 2.5 to 4.3 mg/dL)	Potassium (Ref. range 3.6-5.0 mmol/L)	Sodium (Ref. range 136-146 mmol/L)
November 11, 2013 (Screening)	22	**10.6 H**	104	82	**6.4 H**	4.7	139
Nusinersen Dose 1: November 25, 2013 (Study Day 8)							
Nusinersen Dose 2: December 9, 2013 (Study Day 22)							
December 16, 2013 (Study Day 29)	**21 L**	**10.6 H**	106	94	**5.4 H**	4.9	139
February 14, 2014 (Study Day 89)	22	**12.6 H**	**85 L**	73	**6.5 H**	4.0	**124 L**
Nusinersen Dose 3: 10.3 mg on February 24, 2014 (Study Day 99)							
May 20, 2014 (Study Day 184)	**17 L**	**11.2 H**	**92 L**	67	**5.4 H**	4.6	**128 L**
(b) (6)	-	-	-	-	-	-	**94 L**
(b) (6)							**103 L**
August 8, 2014 (Study Day 264)	**19 L**	**10.7 H**	102	91	**5.1 H**	4.8	**135 L**
Nusinersen Dose 4: August 11, 2014 (Study Day 267)							
Nusinersen Dose 5: December 11, 2014 (Study Day 389)							
March 4, 2015 (Study Day 472)	**20 L**	9.8	109	67	**5.7 H**	4.4	**141**
Nusinersen Dose 6: August 19, 2015 (Study Day 640)							
September 23 2015 (Study Day 675)	**20 L**	9.8	107	69	**5.1 H**	4.2	**140**
October 21, 2015 (Study Day 703)	**20 L**	10	111	86	**5.6 H**	4.2	**143**

On Study Day (b) (6) she was treated with intravenous sodium chloride. (Information on the concentration of sodium chloride solution administered was not provided). She was treated with oral sodium chloride 3 mL 3 times a day and oral sodium citrate/citric acid (Bicitra) 1 mL twice a day (BID) from Study Day (b) (6) to Study Day 320. On Study Day (b) (6) her sodium level improved to 103 mmol/L.

Reviewer comment: The subject's nadir sodium level of 94 mmol/L is profoundly low; it is unclear whether a laboratory error has affected this measurement. The repeat sodium

measurement of 103 mmol/L, measured a day after treatment for hyponatremia, also reflects a severe degree of hyponatremia.

The subject was discharged from the hospital on Study Day (b) (6) with a sodium level of 127 mmol/L. The subject continued to receive oral sodium citrate/citric acid 1 mL BID through Study Day 422. The subject also received oral glucose/sodium citrate/potassium chloride/sodium chloride (Osmosal) 6 mL every 4 hours for rehydration from Study Day 298 to Study Day 320. The subject received oral glucose/electrolyte solution (Rehydron) 60 mL once daily (QD) from Study Day 399 to Study Day 677; the dose was subsequently increased to 120 mL QD on Study Day 678. On Study Day 472, the subject received 500 mL intravenous dextrose/sodium chloride for fluid replenishment prophylaxis.

Reviewer comment: The Investigator considered increased losses from frequent oral suctioning, excess sweating, and a complete reliance on maternal breast milk, which was low in sodium, to be the causes of this subject's hyponatremia. In the opinion of this reviewer these factors are not sufficient to explain this subject's hyponatremia. This subject had severe treatment-emergent hyponatremia and required sodium supplementation for 14 months after the diagnosis of hyponatremia, during the time of all nusinersen doses subsequent to the initial hyponatremia diagnosis. The subject's sodium was normal at baseline and during the first study month, and the electrolyte composition of human breast milk is reported to be stable after 4 months postpartum[22] (the time of this subject's study entry). I consider this case of hyponatremia to possibly be drug related.

CS3A Subject 1776-2306 AE PT Hyponatraemia:[23] Male subject from the United States (2 months old at study entry) had an adverse event of hyponatremia on Study Day 183 (result: 125 mmol/L; reference range: 133 to 145 mmol/L) while hospitalized during Study Days (b) (6) for serious adverse events (SAEs) of coronavirus infection, bronchiolitis, respiratory failure, and seizure. He was treated with oral sodium chloride 5 mEq as needed beginning on an unspecified date during hospitalization ((b) (6) 2014), and sodium returned to 134 mmol/L on Study Day 187. Treatment with sodium chloride 5 mEq as needed was continued through an unspecified date in (b) (6) 2014. On Study Day 442 he had a serum sodium level of 129 mmol/L at the time of an AE of pyrexia from Study Day 441 to 545).

[22] Wack RP, et al. Electrolyte composition of human breast milk beyond the early postpartum period. *Nutrition*. 1997 Sep;13(9):774-7.
[23] Information request response submitted to NDA 209531 on 11/10/2016.

Table 19. CS3A Subject 1776-2306. Serum Electrolyte Values and Dates of Nusinersen Administration.

Date (Study Day)	Potassium (Ref. range: 3.6-5.0 mmol/L)	Sodium (Ref. range: 136-146 mmol/L)	Blood urea nitrogen (Ref. range: 7-20 mg/dL)
November 8, 2013 (Screening)	4.7	136	9
Nusinersen Dose 1: November 25, 2013 (Study Day 1)			
Nusinersen Dose 2: December 9, 2013 (Study Day 15)			
January 23, 2014 (Study Day 60)	4.1	**134 L**	8
Nusinersen Dose 3: February 24, 2014 (Study Day 92)			
March 3, 2014 (Study Day 99)	4.8	**135 L**	11
May 26, 2014 (Study Day 183)	NA	**125 L**	NA
May 30,2014 (Study Day 187)	NA	134[a]	NA
July 7, 2014 (Study Day 225)	4.3	141	9
August 8, 2014 (Study Day 257)	4.6	137	11
Nusinersen Dose 4: August 11, 2014			
November 10, 2014 (Study Day 351)	3.7	**134 L**	8
Nusinersen Dose 5: December 11, 2014			
February 9, 2015 (Study Day 442)	**3 L**	**129 L**	11
Nusinersen Dose 6: August 19, 2015			
October 28, 2015 (Study Day 703)	4.0	137	12

[a] Reference range: 133-145 mmol/L

Reviewer comment: This subject had non-drug-related causes for hyponatremia that corresponded with the dates of low sodium measurement, including pulmonary infections and pyrexia. He also was treated with levetiracetam since Study Day (b) (6) after experiencing seizures. Hyponatremia has been reported with levetiracetam treatment.[24]

CS3B Subject 2010-5096 (AE PT Decreased sodium):[25]

Male subject from Germany (7 months old at study entry) had an AE of pneumonia on Study Day (b) (6), which was treated with ciprofloxacin. The event of pneumonia was considered resolved on Study Day 190.

On Study Day 190, the same day as the latest injection of nusinersen and 189 days after the initial injection of nusinersen, the subject experienced AEs of decreased sodium (124 mmol/L), decreased chloride (75 mmol/L), decreased potassium (2.4 mmol/L), and increased alanine aminotransferase (ALT) [122 U/L] and increased aspartate aminotransferase (AST) [83 U/L]). The subject was also noted to have an AE of weight loss (weight not provided) on the same day. The subject started to receive oral rehydration salt formulations on the same day. On Study Day 197, 7 days after onset, the AEs of decreased sodium, decreased chloride,

[24] Nasrallah K. Hyponatremia Associated with Repeated Use of Levetiracetam. *Epilepsia,* 46(6):972–973, 2005.

[25] Narrative on p. 7 of the 11/8/2016 submission to NDA 209531.

and decreased potassium were considered resolved, with these parameters within the normal ranges upon retest. On Study Day 241, the AE of weight loss was considered resolved, and oral rehydration salt formulations were continued.

Table 2. CS3B Subject 2010-5096. Serum Electrolyte Values and Dates of Nusinersen Administration.

Date (Study Day)	Sodium (mmol/L)	Blood Urea Nitrogen (mmol/L)	Creatinine (µmol/L)	Potassium (mmol/L)
January 14, 2015 (Screening)	134	NA	NA	5
Nusinersen Dose 1: January 27, 2015				
Nusinersen Dose 2: February 10, 2015				
Nusinersen Dose 3: February 24, 2015				
April 13, 2015 (Study Day 77)	136	8.568	17.68	4.6
Nusinersen Dose 4: April 14, 2015				
August 4, 2015 (Study Day 190)	**124 L**	2.856	8.84	2.4
Nusinersen Dose 5: August 4, 2015				
August 11, 2015 (Study Day 197)	143	NA	NA	5
Nusinersen Dose 6: December 1, 2015				
April 11, 2016 (Study Day 441)	138	3.927	8.84	3.8

Reviewer comment: This subject had non-drug-related causes for hyponatremia that corresponded with the dates of low sodium measurement, including pneumonia and weight loss.

Hyponatremia: Conclusion and Labeling Recommendation

Severe treatment-emergent hyponatremia was reported in a nusinersen-treated subject. In the opinion of this reviewer, this event is possibly related to nusinersen. In certain drugs (e.g., methotrexate,[26] cytarabine[27]) hyponatremia has been reported with intrathecal administration but, according to a review of the literature performed by this reviewer, has not been reported with other routes of administration.

I recommend including information related to hyponatremia in Warnings and Precautions. I recommend checking the serum electrolytes (including sodium) at baseline and prior to each maintenance dose of nusinersen.

[26] Diskin C. Recurrent hyponatremia after intrathecal methotrexate not related to antidiuretic hormone: is a natriuretic peptide activated? *Am J Med Sci.* 2006 Jan;331(1):37-9.
[27] Section 6.2 DepoCyt (cytarabine liposome injection for intrathecal use) Prescribing Information. Accessed on 11/13/2016 at: http://www.depocyt.com/pdf/DepoCyt%20PI-%20I-070-21-US-F_Final_20150205151725_737679.pdf

8.4.6.1.2. Other Electrolyte Measurements

The incidences of abnormal electrolyte measurements in Study CS3B are displayed in the table below.

Table 20. Electrolyte measurement in Study CS3B.

		Controlled study (CS3B)	
		Control	ISIS 39644
Electrolytes			
Sodium (mmol/L)	Low	0/ 28	1/ 59 (2)
	High	0/ 28	0/ 59
Potassium (mmol/L)	Low	4/ 28 (14)	3/ 57 (5)
	High	1/ 28 (4)	4/ 56 (7)
Chloride (mmol/L)	Low	1/ 28 (4)	3/ 59 (5)
	High	0/ 28	1/ 58 (2)
Bicarbonate (mmol/L)	Low	0/ 1	2/ 3 (67)
	High	0/ 1	0/ 3
Glucose (mmol/L)	Low	2/ 27 (7)	2/ 58 (3)
	High	9/ 23 (39)	13/ 42 (31)

Source Table 79 Summary of Clinical Safety

Bicarbonate was not routinely measured in the controlled study CS3B. Low bicarbonate levels have been described in SMA patients as part of the underlying disease.[28] However, low bicarbonate levels also may indicate a drug-related toxicity to the proximal renal tubules. Low bicarbonate levels in nusinersen subjects are discussed in Section 8.5.1, which discusses renal toxicity.

The frequency of treatment-emergent high glucose, as well as mean changes in glucose from baseline,[29] were similar in nusinersen and control subjects in Study CS3B. High blood glucose levels seen in nusinersen subjects have been described in SMA patients.[30]

8.4.6.1.3. Renal Laboratory Measurements

Renal laboratory measurements are discussed in the Renal Toxicity Section 8.5.1.

[28] Crawford TO, et al. Abnormal fatty acid metabolism in childhood spinal muscular atrophy. *Ann Neurol.* 1999 Mar;45(3):337-43.

[29] P. 646-647 CS3B Study Report

[30] Bowerman M, et al. Glucose metabolism and pancreatic defects in spinal muscular atrophy. *Ann Neurol*. 2012 Aug;72(2):256-68.

8.4.6.1.4. Hepatic Laboratory Measurements

The liver is considered a target organ of nusinersen, because most antisense oligonucleotides accumulate in the liver. Because it is deposited in the liver (see Table 27 with liver tissue concentrations from autopsy study CS03APK), nusinersen has the potential for hepatotoxicity.

Liver function tests that are most frequently evaluated [e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT)] can be elevated in patients with SMA.[31] With muscle degeneration, these enzymes can be released from skeletal muscle.

In Study CS3B, the overall frequency of elevated hepatic laboratory measurements was comparable to findings in sham procedure control subjects (see table below).

Table 21. Summary of Shifts from Baseline to High for Hepatic Laboratory Measurements in Study CS3B

	Controlled study (CS3B)	
	Control	ISIS 396443
Liver function		
Aspartate Aminotransferase (U/L)	1/ 25 (4)	3/ 56 (5)
Alanine Aminotransferase (U/L)	4/ 25 (16)	6/ 55 (11)
Alkaline Phosphatase (U/L)	0/ 26	1/ 58 (2)
Direct Bilirubin (umol/L)	0/ 24	0/ 50
Indirect Bilirubin (umol/L)	0/ 23	0/ 50

Shift to high includes normal to high, low to high, and unknown to high.
Source Table 79 Summary of Clinical Safety

In all clinical studies, no nusinersen subject had a post-treatment AST level ≥ 3 times the upper limit of normal. There was 1 nusinersen subject with a post-treatment ALT level ≥ 3 times the upper limit of normal, and 1 additional nusinersen subject with a post-treatment ALT level ≥ 5 times the upper limit of normal:

- Study CS3B Subject 2010-5096: On Study Day 183 this subject had an ALT of 122 U/L (normal range 6-34 U/L) 3 hours after administration of his 5th nusinersen dose. Aspartate aminotransferase was also elevated at 83 U/L (normal range 10-69 U/L). Alkaline phosphatase, total bilirubin, and direct bilirubin were within normal limits. A repeat ALT measurement 1 week later was normal at 40 U/L. There was no information submitted about whether treatment was provided.

[31] Finkel RS, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014 Aug 26; 83(9): 810–817.

Reviewer comment: The increased ALT occurred 3 hours after nusinersen administration; it is possible that this measurement is related to nusinersen. AST and ALT can also be released from muscle tissue, so local tissue injury during the lumbar puncture procedure may have contributed to an elevation in these laboratory tests.

- Study CS3B Subject 1776-5097: AST and ALT levels were normal at screening and 183 days after the first dose of nusinersen. On Study Day 386 (96 days after his 6th nusinersen dose), he had an ALT level of 214 U/L (normal range 6-34 U/L), accompanied by an increased AST of 155 U/L. Total bilirubin was 1.7 µmol/L (reference range 3.4 – 20.5 µmol/L), and direct bilirubin was 0.9 µmol/L (reference range 0-6.8 µmol/L). The AE was reported as recovered 15 days after the start date. The patient received three doses of Tylenol the day prior to the abnormal report and another dose the day of the lab draw. [32] No follow-up ALT results after Study Day 386 were reported. No additional doses of nusinersen were scheduled after the high ALT measurement.
  Reviewer comment: The amount of acetaminophen consumed was not provided. While a role of acetaminophen in this subject's ALT and AST elevation is possible, the role of acetaminophen in this case cannot be assessed because the amount consumed is not known.

There were no cases of Hy's law drug-induced liver injury (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥2 x ULN) during treatment in nusinersen clinical studies.

Reviewer comment: Nusinersen accumulates in the liver in humans. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects.

Gamma-glutamyl transferase (GGT) is a membrane bound enzyme produced primarily in the liver, with little or none produced from human skeletal muscle. Because AST and ALT can be elevated in patients with SMA, I recommend that GGT be used evaluate for liver toxicity in patients taking nusinersen.

I recommend describing hepatic accumulation of nusinersen in the prescribing information. I recommend advising prescribers to check hepatic tests including gamma-glutamyl transferase (GGT) and bilirubin at baseline and before each maintenance dose of nusinersen.

8.4.6.2. Hematology Laboratory Measurements

[32] P. 11 Sponsor information request response submitted to NDA 209531 on 9/23/2016.

8.4.6.2.1. Thrombocytopenia

In Study CS3B, 6 of 56 (11%) nusinersen subjects had a platelet level below the lower limit of normal (LLN), compared to 0 of 28 control subjects. In all nusinersen subjects, 3 of 145 (2%) had thrombocytopenia <100 x 10^9/L. No subject had a platelet count <50 x 10^9/L, and there were no adverse events related to thrombocytopenia.

Thrombocytopenia Conclusion and Labeling Recommendation

Reviewer comment: In clinical studies, thrombocytopenia occurred more frequently in nusinersen subjects compared to sham procedure control subjects. Thrombocytopenia has been seen in other drugs in the oligonucleotide class. In studies of the oligonucleotide drisapersen,[33] an increased risk of thrombocytopenia that was mild in severity occurred in the controlled studies. However, after longer exposures of 10-29 months, severe thrombocytopenia <20 x 10^9/L occurred in 2% of subjects. The nusinersen clinical development program has fewer patients exposed to treatment for at least 1 year (83 patients compared to 223 patients in drisapersen studies). It is unclear whether severe thrombocytopenia may occur in nusinersen-treated patients with additional person-years exposure with a longer duration of treatment.

I recommend that thrombocytopenia be described in Warnings and Precautions. As part of nusinersen administration, patients undergo lumbar puncture, a procedure which has a risk of bleeding complications. Patients should obtain a complete blood count prior to each nusinersen administration. Patients and providers should be instructed to be vigilant for signs or symptoms of thrombocytopenia.

8.4.6.2.2. Other Hematology Laboratory Measurements

Shifts in Common Terminology Criteria for Adverse Events (CTCAE)[34] toxicity grade from baseline for hematology laboratory measurements in Study CS3B are summarized in the table below; results are similar between the nusinersen and control groups.

[33] Pages 229-236 of the FDA Briefing Document for the November 24, 2015 Peripheral and Central Nervous System Drugs Advisory Committee Meeting to discuss NDA 206031, drisapersen solution for injection. Accessed on 11/2/2016 at:
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm473737.pdf
[34] Accessed on 11/17/2016 at:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Table 22. Shifts in Toxicity Grades from Baseline for Hematology Laboratory Measurements in Study CS3B

		Worst post-baseline	
Adverse event	Shift	Control	ISIS 396443
Anemia	Increase to any grade	4/28 (14)	9/57 (16)
	Increase to Grade 3	0/28	0/57
White blood cell decreased	Increase to any grade	2/28 (7)	3/57 (5)
	Increase to Grade 3	0/28	0/57
	Increase to Grade 4	0/28	0/57
Lymphocyte count decreased	Increase to any grade	0/27	1/57 (2)
	Increase to Grade 3	0/27	0/57
	Increase to Grade 4	0/27	0/57
Neutrophil count decreased	Increase to any grade	2/27 (7)	5/56 (9)
	Increase to Grade 3	0/26	0/56
	Increase to Grade 4	0/27	0/56

Source: Appendix 1 Information Amendments submitted to NDA 209531 on 9/23/2016
-Hemoglobin CTC Grade Ranges in G/L Units: 0: ≥LLN; 1: ≥100 - <LLN; 2: ≥ 80 - <100; 3: ≥65 - <80; 4: <65.
- White blood cell decreased Ranges in 10^9/L Units: 0: ≥LLN; 1: 3.0-LLN; 2: ≥ 2.0 – 3.0; 3: ≥ 1.0-2.0; 4: <1.0.
-Platelet CTC Grade Ranges in 10^9/L Units: 0: ≥LLN; 1: ≥ 75 - <LLN; 2: ≥50 - <75; 3: ≥25 - <50; 4: <25.
-Lymphocytes decreased CTC Grade Ranges in 10^9/L Units: 0: ≥LLN, 1: < LLN - 0.8, 2: <0.8 - 0.5, 3: <0.5 - 0.2, 4: <0.2.
- Neutrophils CTC Grade Ranges in 10^9/L Units: 0: ≥LLN; 1: ≥1.5 - <LLN; 2: ≥ 1.0 - <1.5: 3: ≥0.5 - <1.0; 4: <0.5.

8.4.6.3. Coagulation Laboratory Measurements

Prolonged activated partial thromboplastin time (aPTT) has been described with other phosphorothioate oligonucleotides.[35-36]

In nusinersen clinical studies, the available data for coagulation laboratory tests are limited. Scheduled post-baseline coagulation laboratory testing was performed only in Study CS2,[37] which includes 9 subjects treated with nusinersen 12 mg and 25 other subjects with nusinersen doses ranging from 3-9 mg. Coagulation laboratory tests were sporadically measured in other clinical studies. The table below summarizes shifts from baseline (high or low) for aPTT and international normalized ratio (INR) for all measurements (scheduled measurements in Study CS2 and sporadic measurements from other studies). Ten of 53 (19%) nusinersen subjects had a shift to high aPTT.

[35] Sheehan JP, Lan HC. Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex. Blood. 1998 Sep 1;92(5):1617-25. Phase I trial of ISIS 104838, a 2'-methoxyethyl modified antisense oligonucleotide targeting tumor necrosis factor-alpha.
[36] Sewell KL, et al. Phase I trial of ISIS 104838, a 2'-methoxyethyl modified antisense oligonucleotide targeting tumor necrosis factor-alpha. *J Pharmacol Exp Ther.* 2002 Dec;303(3):1334-43.
[37] Table 1 Multiple Module Information Amendment. Submitted to NDA 209531 on 11/18/2016.

Table 23. Summary of Shifts from Baseline for Activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR)

	Control	ISIS 396443 12 mg	Other ISIS 396443 Treated	Total ISIS 396443 Treated
Activated Partial Thromboplastin Time (sec)				
Low	0/ 1	0/ 9	3/ 46 (7)	3/ 55 (5)
High	0/ 1	0/ 9	10/ 44 (23)	10/ 53 (19)
Prothrombin Intl. Normalized Ratio				
Low	0/ 1	0/ 8	2/ 37 (5)	2/ 45 (4)
High	0/ 1	1/ 8 (13)	4/ 37 (11)	5/ 45 (11)

Source: Table 4 Sponsor submission to NDA 209531 on 11/17/2016

Coagulation Laboratory Measurements: Conclusion and Labeling Recommendation

As part of nusinersen administration, patients undergo lumbar puncture, a procedure which has a risk of bleeding complications. Patients should have coagulation laboratory testing at baseline and prior to each nusinersen maintenance dose.

8.4.7. Vital Signs

In controlled study CS3B, vital signs were measured at: a) screening; b) at study visits for doses 1-3 and 5 (pre-dose, post-dose, and 1 day after dosing);[38] and c) at study visits scheduled for Study Days 120, 302, and 394.[39] Analyses of the number and percentage of Study CS3B subjects meeting vital sign outlier criteria post-baseline are displayed in the table below.

[38] Study visits were scheduled for Study Days 1, 2, 15, 16, 29, 30, 211, and 212.
[39] Appendix A Study CS3B Study Report

Table 24. Study CS3B Vital Sign Outlier Analyses. Changes from Baseline.

	Criterion	Control	ISIS 396443
Systolic blood pressure(a)	Increment >20 mmHg	25/41 (61)	41/80 (51)
	Increment >40 mmHg	1/41 (2)	9/80 (11)
	Decrement >20 mmHg	18/41 (44)	42/80 (53)
	Decrement >40 mmHg	1/41 (2)	7/80 (9)
Diastolic blood pressure (a)	Increment >10 mmHg	29/41 (71)	59/80 (74)
	Increment >20 mmHg	20/41 (49)	39/80 (49)
	Decrement >10 mmHg	30/41 (73)	60/80 (75)
	Decrement >20 mmHg	15/41 (37)	33/80 (41)
Pulse rate (a)	Increment >15 bpm	33/41 (80)	62/80 (78)
	Increment >30 bpm	16/41 (39)	26/80 (33)
	Decrement >15 bpm	32/41 (78)	70/80 (88)
	Decrement >30 bpm	14/41 (34)	43/80 (54)
Treatment emergent body temperature (b)	>38.0 C	7/41 (17)	5/80 (6)

Source: Appendix 8. Sponsor information request response submitted to NDA 209531 on 9/23/2016.
bpm = beats per minute

Decreases in pulse rate >15 bpm or >30 bpm from baseline were more frequent in nusinersen subjects compared to sham procedure control subjects. The reference range of normal heart rate in children (stratified by age and by whether the child is sleeping or awake) is displayed in the table below.

Table 25. Reference Range of Normal Heart Rate in Children

Heart Rate (rate/min)		
Age	**Awake Rate**	**Sleeping Rate**
Newborn to 3 months	85 to 205	80 to 160
3 months to 2 years	100 to 190	75 to 160
2 to 10 years	60 to 140	60 to 90
>10 years	60 to 100	50 to 90

Source: Pediatric Advanced Life Support (PALS) 2010

Five of 80 (6%) nusinersen subjects had an adverse event coded to the PT Bradycardia, compared to 4 of 41 (10%) sham procedure control subjects. One of 80 (1%) nusinersen subjects had a post-treatment low heart rate recorded in the Study CS3B vital signs dataset[40] (Subject 2008-5118 heart rate 70 bpm), compared to 1 of 41 (2%) sham procedure control subjects (Subject 2003-5201 heart rate 71).

[40] Analysis of Summary of Clinical Safety vital sign dataset ADVS. Sleeping versus awake status during a vital sign measurement was not recorded in clinical studies. Reference range criteria for sleeping children were used. Subject CS3B subjects ranged from 1-9 months of age at study entry.

Reviewer comment: In most cases, decreases in heart rate described in Table 24 were not associated with a bradycardia adverse event. Short term variations in heart rate are part of normal homeostatic mechanisms of the cardiovascular system.[41]

Reviewer comment: A heart rate of 32 for Study CS3B subject 2007-5136 was reported on Study Day 183 (1 hour post-nusinersen dosing). This was a transcription error; the actual heart rate was 132 bpm.[42]

8.4.8. Electrocardiograms (ECGs)

ECG qualitative results include an overall interpretation of 'normal', 'abnormal but not clinically significant' or 'abnormal and clinically significant'. This type of evaluation is available for infantile-onset SMA subjects only (Pools B and C only) and later-onset SMA subjects (Pool E).

In Study CS3B, ECGs were centrally read and scheduled at screening, on Study Day 2 (1 day after the first dose), on Study Day 29 post-dose after the third dose, and on Study Day 394 (approximately 92 days after the sixth dose). Five subjects (8%) in the nusinersen group and none in the sham-controlled group shifted from normal or unknown at baseline to abnormal, clinically significant post-baseline:[43]

- Subject 2037-5063 (4 month old male) had a shift from a normal ECG to an abnormal ECG with "marked sinus tachycardia." He had a normal ECG on Study Day 2 with a Fridericia-corrected QT interval (QTcF) of 363. On Study Day 29, he had normal vital signs predose but had a heart rate in the 180's measured 1-4 hours postdose. Mean ventricular rate on the ECG taken on Study Day 29, 3.5 hours post-nusinersen dosing, was 180 beats per minute, and QTcF was 566 msec. Concomitant medications at the time of the event included lidocaine/prilocaine as local anesthesia, nitrous oxide as sedation for the Day 29 injection of nusinersen. The subject had an AE of cardiopulmonary arrest on Study Day (b) (6) during an episode of respiratory infection with acute respiratory distress; the subject's most recent study exposure prior to that adverse event was on Study Day 70. The subject recovered and continued in the study with last exposure to study drug on Study Day 183 (no subsequent ECG results have been reported).
  Reviewer comment: Cases of QT prolongation in nusinersen subjects are discussed in Section 8.4.9.
- Subject 1833-5261 (6 month old female) had a shift from a normal ECG to an ECG read as an "increase in right ventricular forces" on Study Day 2, approximately 24 hours after

[41] Finley JP, et al. Heart rate variability in infants, children and young adults. *Journal of the Autonomic Nervous System* 51.2 (1995): 103-108.
[42] Information request response submitted to NDA 209531 on 11/23/2016.
[43] Response to FDA IR submitted to NDA 209531 on 11/30/2016.

the first nusinersen dose, as well as on Study Day 57, 3 hours after the second nusinersen dose. Blood pressure and heart rate measurements were within normal ranges. Lead misplacement was cited as a possible cause. On Study Days 84 and 274, echocardiograms were reported as normal. ECGs on Study Days 273 and 397 were reported as normal.
Reviewer comment: The subject had 2 echocardiograms, which were read as normal and did not indicate a right ventricular abnormality. Findings of right axis deviation and prominent anterior forces on ECG can occur for reasons other than right ventricular hypertrophy, including a not-infrequent normal variant[44].

- Subject 2037-5139 (3 month old female) had a shift from a normal ECG at baseline and on Study Day 2 (1 day after the first nusinersen dose) to a predose ECG on Study Day 14 (13 days after the first nusinersen dose) with "marked and unusual ST elevations in almost every lead that were consistent with pericarditis or some kind of artifact." On an Unscheduled Visit on Study Day 23 (9 days following the latest injection of nusinersen and 22 days after the initial injection of nusinersen), a follow-up ECG showed normal results.
  Reviewer comment: These ECG abnormalities are likely related to an artifact. No AEs related to pericarditis were reported, and the subject had a normal ECG 9 days later.
- Subject 1780-5032 (7 month old female) had a shift from a normal ECG at baseline to "right atrial enlargement and likely benign ventricular hypertrophy" on an ECG performed 2 hours after administration of the third dose on Study Day 29. (A repeat ECG performed minutes later on the same day showed the same results.) Two-hour postdose blood pressure and heart rate were 98/53 mmHg and 135 bpm, respectively. No treatment for the event or additional work-up was reported, and no follow-up ECG results were provided.
- Subject 2037-5009 (5 month old female) had a shift from a normal ECG at baseline and on Study Day 2 (1 day after the first nusinersen dose) to an abnormal ECG on Study Day 46 (3 hours after the 3rd nusinersen dose) with axis deviation and prominent right ventricular forces consistent with probable right ventricular hypertrophy. No treatment for the event was reported, and no follow-up ECG results were provided.
  Reviewer comment: The abnormal ECG findings for Subjects 1780-5032 and 2037-5009 are of unclear significance. In both cases no follow-up ECG was available.

Reviewer comment: Other than the findings (sinus tachycardia and prolonged QTcF) in Subject 2037-5063, these cases do not represent clinically significant cardiac disease (Subjects 1833-5261 and 2037-5139) or are of unclear clinical significance (Subjects 1780-5032 and 2037-5009).

Study CS3B Subject 2112-5101 (treated with nusinersen 12 mg) had ventricular tachycardia; the last dose prior to the event was on Day 29, and the event occurred on Day 59. At the time, the

[44] Hancock EW, et al. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part V. *J Am Coll Cardiol*. 2009;53(11):992-1002.

subject also had a respiratory infection and difficulty breathing and was treated with an antibiotic. The event resolved, and the subject continued to participate in the study. This subject had a QTc of 527 msec at screening, prior to exposure to nusinersen, which decreased to 400 msec on Day 2 and 490 msec on Day 29.

Study CS3B Subject 2037-5167 (treated with nusinersen 12 mg) died during sleep on Day 82. This subject had neither ECG values above 500 msec nor any increase of >30 msec (baseline: 408 msec, Day 2: 404 msec, Day: 29 415 msec).

In Study CS3A, 3 subjects had postdose ECG abnormalities that had initial ECG findings suggestive of ventricular hypertrophy. In each of these 3 cases, echocardiograms were performed as a result of the abnormal ECG findings. In each case the subject had an echocardiogram that was read as normal.[45]

In Study SM201, no clinically significant abnormal ECG results were reported. AEs associated with ECG abnormalities (tachycardia) were reported in 2 subjects.

In the later-onset studies, no clinically significant changes were reported as an AE for ECG findings.

Reviewer comment: Other than the case of prolonged QTcF, the ECG data discussed in this section does not indicate a cardiac safety issue with nusinersen.

8.4.9. QT

No thorough QT study has been performed with nusinersen. There were no AEs of torsade de pointes in any clinical study.

The table below summarizes the incidence of outliers in ECGs based on Fridericia-corrected QT interval.

[45] CS3A Study Report Section 12.4.4.

Table 26. Study CS3B. Incidence of Outliers in ECGs Based on Fridericia-corrected QT Interval

	Controlled study (CS3B)	
	Control	ISIS 396443
Number of subjects dosed	41	80
Number of subjects with:		
(i) any post-baseline ECG	41 (100)	80 (100)
Post-baseline corrected QTcF (msec)		
>450	13 (32)	20 (25)
>480	2 (5)	8 (10)
>500	0	5 (6)
(ii) a baseline and any post-baseline ECG	41 (100)	80 (100)
Increase from baseline in QTcF (msec)		
>30	10 (24)	14 (18)
>60	3 (7)	5 (6)
>500 msec post-baseline and >60 msec increase from baseline	0	4 (5)

Source: Summary of Clinical Safety Source Table 91
ISIS 396443 = nusinersen
QTcF = Fridericia-corrected QT interval

In Study CS3B, 4 of 80 (5%) of nusinersen subjects had had a QTc value above 500 milliseconds (msec) and an increase of >60 msec compared to baseline, compared to 0 sham procedure control subjects.[46] All ECGs meeting these criteria were performed 3.5-24 hours after nusinersen administration. However, most ECGS were scheduled in this time period.[47] Only Subject 2037-5063 received sedation or anesthesia during the lumbar puncture procedure prior to the prolonged QTcF measurement. Electrolytes were not measured on the days of the prolonged QTcF measurements, which occurred on Study Days 2 or 29. These subjects did not have electrolyte abnormalities at screening or at the next measurement (Study Day 64).

No subjects from other studies had these changes in QTcF compared to baseline.

[46] CS3B subjects with a QTc value above 500 milliseconds (msec) and an increase of >60 msec compared from baseline included Subjects 2037-5063 (discussed in detail in Section 8.4.8), 2007-5360, 2010-5096, and 2112-5018. Data provided in the response to FDA IR submitted to NDA 209531 on 11/30/2016.
[47] Only scheduled ECGs on Study Day 394 were not obtained within 24 hours post-dose. Sixteen nusinersen subjects and 7 control subject received ECGs on Study Day 394.

Reviewer comment: The Division of Neurology Products (DNP) consulted The Division of Cardiovascular and Renal Products (DCRP) regarding changes in QTcF in subjects treated with nusinersen (ISIS 396446) in Study CS3B. DCRP provided the following comments:[48]

ISIS 396443 is an antisense antisense oligonucleotide. We are not aware of other small therapeutic proteins that directly inhibit the hERG channel and cause QTc interval prolongation. However, the sponsor has not conducted *in vitro* safety pharmacology studies to rule out such a mechanism.

It's difficult to determine from the clinical data whether ISIS 396443 affects cardiac repolarization as measured by QTc prolongation. The primary evidence for QTc prolongation is based on outlier QTcF values observed in four subjects in the ISIS 396443 group in Study CS3B. There are important limitations in QTc data that cause uncertainty in its interpretation.

- The methods for ECG acquisition and QTc measurement were not described in either the protocol or clinical study report (CSR). It is not known if the ECGs showing QTcF values exceeding 500 msec were verified by a Cardiologist (CSR states that ECGs were read centrally at (b) (4)). Furthermore, there were no repeat ECGs to confirm the finding or follow-up ECGs to determine when the QTc interval returned to normal value.
- The QTc interval data are highly variable and difficult to interpret. In the ISIS 396446 group, mean and median changes from baseline QTcF were ±5 msec, but the standard deviation was large (~40 msec) and values ranged from -167 msec to +123 msec on Day 2 and -141 msec to +144 msec on Day 29. A similar large variability was observed in the sham-controlled group and the percentage of subjects with a change from baseline QTcF >60 msec was also similar (7% for control vs. 6% for ISIS 396443).
- The timing of the ECGs relative to dosing of ISIS 396443 was variable and did not coincide with peak ISIS 396443 concentrations that occur between 2-6 h after intrathecal (IT) dosing.

Prolonged QTc interval in individual patients could have also occurred for reasons related to concomitant medications, the underlying disease or associated adverse events related to the disease.

The potential for ISIS 396443 to delay cardiac repolarization should be evaluated in a dedicated QT study. If ISIS 396443 cannot be given to healthy volunteers, high quality 12-lead ECGs (replicate, digital ECGs) can be incorporated in on-going controlled clinical trials in patients to characterize the QTc interval. Based on DNP's assessment of benefit-risk of ISIS 396443 in this patient population, it may be reasonable to design the QT study to rule out large effects (>20 msec) on QTc interval in patients.

[48] QT-IRT consultation dated 12/8/2016.

For the USPI, we recommend that the QTc data are described in Section 12.2 (Pharmacodynamics). We do not recommend including statements in Section (b) (4) (b) (4) because there is uncertainty in these clinical QTc data. We defer the final labeling decisions to the Division.

Section 12.2 Pharmacodynamics

QTc Interval Prolongation

In 120 patients with spinal muscular atrophy randomized to receive either SPINRAZA or sham-control, QTcF values >500 msec and change from baseline values >60 msec were observed in 5% of patients receiving SPINRAZA. There were not any differences from the sham-control in the incidence of cardiac adverse reactions associated with delayed ventricular repolarization.

Reviewer comment: This reviewer agrees with the recommendation from DCRP to describe the frequency of subjects in Study CS3B with QTcF values >500 msec and change from baseline values >60 in Section 12 of the U.S. Prescribing Information (USPI). (b) (4) *DNP has also requested that the nusinersen Sponsor perform a repeat ECG for any QTc measurement greater than 500 msec.*

8.4.10. Immunogenicity

Plasma samples from all 7 clinical studies were analyzed for anti-drug antibody (ADA) presence. In the initial analyses (using a 0.1% false-positive rate), no clinical immunogenicity samples were positive for anti-drug antibodies in Studies CS1, CS2, CS10, and SM201. In study CS12, 2 out of 47 (4%) subjects (1433 and 1447) were classified as ADA positive. In Study CS3A, 1 out of 20 (5%) (Subject 1834-1301) was classified as ADA positive. In Study CS3B, 1 out of 113 (1%) (Subject 2006-5071) was classified as ADA positive.[49]

Three of the 4 ADA-positive subjects were considered to have a transient response (1 positive sample, with all samples before and after being negative), 1 subject in Study CS12 was considered to have a persistent response, based on 4 samples evaluated from predose to Day 351 of treatment. The reported titer values for the 4 ADA positive subjects ranged from 1 to 16.

Reviewer comment: A sensitivity analysis was performed using a new confirmatory cut point with a 1% false positive rate.[50] Based on the sensitivity analysis criteria, 1 additional subject was identified as having an ADA-positive result. Subject 2000-5203, a nusinersen-treated subject in Study CS3B, had a positive ADA response at a single time point on Day 183, with negative confirmation and negative ADA screening results for days 302 and 394, respectively.

[49] 10/16/2016 submission to NDA 209531
[50] 11/29/2016 submission to NDA 209531

Three subjects from Study CS3B (5185, 5201, and 5332)[51] had ADA positive samples but had not been exposed to nusinersen at the time of sampling. These results were not considered related to nusinersen and were not counted in the paragraphs above.

I have reviewed the adverse events for each of the 5 subjects with positive ADA samples after nusinersen treatment. Adverse events in these subjects included manifestations of SMA and complications of lumbar puncture. There was no apparent effect of ADA development on the adverse events in these subjects.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Renal Toxicity

Introduction

Accumulation of nusinersen[52] and other phosphorothioate oligonucleotides[53] in proximal tubule cells of the kidney has been described in studies of mice. In an autopsy study (Study CS03APK) of 3 patients who received nusinersen in Study CS3A, tissue concentrations in the kidney were similar to concentrations in the lumbar spinal cord (see tables below).[54]

[51] Subject 1778-5332 was in the nusinersen treatment group tested positive for ADA pre-dose on Study Day 1. Subjects 2003-5201 and 2007-5185 were in sham control group of Study CS3B.
[52] P. 32 Nonclinical Overview. Submitted to NDA 209531 on 8/9/2016.
[53] Rappaport J, et al. Transport of phosphorothioate oligonucleotides in kidney: implications for molecular therapy. *Kidney Int.* 1995 May;47(5):1462-9.
[54] P. 54 of the CS03APK Study Report. Submitted to NDA 209531 on 9/23/2016.

Table 27. Nusinersen (ISIS 396443) Tissue Concentrations in Human Spinal Cord after Treatment

Tissue	Observed ISIS 396443 Concentration (µg/g)			
	Patient 2302	Patient 1303	Patient 2311	Mean ± SD
Lumbar Spinal Cord	19.46	26.6	31.8	26.0 ± 6.21
Thoracic Spinal Cord	15.92	23.7	14.2	18.0 ± 5.07
Cervical Spinal Cord	11.93	15.5	23.3	16.9 ± 5.81

SD = Standard Deviation
Source: Table 1 CS03APK Study Report

Table 28. Nusinersen (ISIS 396443) Tissue Concentrations in Additional Human Tissues after Treatment

Tissue	Observed ISIS 396443 Concentration (µg/g)			
	Patient 2302	Patient 1303	Patient 2311	Mean ± SD
Cerebellum	4.36	4.16	2.77	3.76 ± 0.87
Hippocampus	2.10	2.80	7.30	4.07 ± 2.82
Thalamus	0.23[a]	1.31	3.95	1.83 ± 1.91
Brain Stem	3.68	13.82	8.13	8.54 ± 5.08
Liver	1.33	12.88	2.39	5.53 ± 6.38
Kidney	18.44	36.51	25.07	26.67 ± 9.14

Source: Table 3 CS03APK Study Report

Adverse Events

There were no renal toxicity adverse events in clinical studies. In an analysis of clinical study adverse events, 1 AE was found in a search using the MedDRA Acute renal failure SMQ. Study CS3B Subject 2019-5108 (4 month old male with symptomatic infantile onset SMA treated with nusinersen 12 mg) had an AE coded to PT Urine output decreased. This event is related to a hypoxic cardiac arrest and rhinovirus infection and is not related to nusinersen.

Serum Markers of Renal Function

Creatinine as a marker of renal function may have limited value in SMA patients, because of reduced muscle mass. Cystatin C has been evaluated as a biomarker for monitoring renal function.[55] In clinical studies, no nusinersen subject had a treatment-emergent high level of serum creatinine or cystatin C.[56]

[55] Violett L. Utility of Cystatin C to monitor renal function in Duchenne muscular dystrophy. Muscle Nerve. 2009 September ; 40(3): 438–442. This study demonstrates the potential value of cystatin C as a biomarker for

Urine Protein

In controlled study CS3B, 17 of 51 (33%) nusinersen subjects had treatment-emergent proteinuria (to trace level or higher), compared to 5/25 (20%) sham control subjects.[57] In later-onset SMA subjects (Pool E), 36 of 52 (69%) nusinersen subjects had treatment-emergent proteinuria.[58]

Reviewer comment: In clinical studies, urine protein was measured semi-quantitatively with urine dipstick testing. (Results were categorized as negative, trace, 1+, or 2+. No subject had a 3+ or 4+ urine protein measurement.) Quantitative urine protein measurements were not routinely performed in nusinersen clinical studies.

The levels of proteinuria seen in nusinersen clinical studies are consistent with significant proteinuria. In a published study of more than 2000 patients,[59] a urine dipstick for proteinuria of trace or 1+ was predictive of significant proteinuria (urine protein-to-creatinine ratio ≥500 mg/g) if the specific gravity was ≤ 1.025. In nusinersen clinical studies, 90% of urine specific gravity measurements were ≤ 1.025.

With tubular proteinuria, urine dipstick findings are often falsely negative.[60] Proteinuria with nusinersen treatment is likely tubular in origin. Accumulation of nusinersen[61] and other phosphorothioate oligonucleotides[62] in proximal tubule cells of the kidney has been described in studies of mice. The standard urine dipstick primarily detects albumin but is relatively insensitive to lower molecular weight proteins (e.g., beta2-microglobulin) that are major constituents of tubular proteinuria.

Other Urinalysis Results

In Study CS3B, other urine dipstick testing results in nusinersen subjects were similar to results in sham procedure control subjects, including urine pH, glucose, ketones, and bilirubin.[63]

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monitoring renal function in Duchenne muscular dystrophy. Its applicability extends to other neuromuscular diseases.

[56] Source Tables 79-80 for the Summary of Clinical Safety. Submitted to NDA 209531 on 9/23/2016.

[57] Source Table 81 for the Summary of Clinical Safety. Submitted to NDA 209531 on 9/23/2016.

[58] Source Table 82 for the Summary of Clinical Safety. Submitted to NDA 209531 on 9/23/2016.

[59] Constantiner M, Sehgal AR, Humbert L, et al. A dipstick protein and specific gravity algorithm accurately predicts pathological proteinuria. *Am J Kidney Dis* 2005; 45:833.

[60] Table 61 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Accessed 11/18/2016 at: http://www2.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g5.htm

[61] P. 32 Nonclinical Overview. Submitted to NDA 209531 on 8/9/2016.

[62] Rappaport J, et al. Transport of phosphorothioate oligonucleotides in kidney: implications for molecular therapy. *Kidney Int.* 1995 May;47(5):1462-9.

[63] Source Table 81 Summary of Clinical Safety. Submitted to NDA 209531 on 9/23/2016.

Serum Bicarbonate

Serum electrolyte data were reviewed to evaluate for signs of renal tubular dysfunction. (An overall discussion serum electrolyte laboratory results is located in Section 8.4.6.) Treatment-emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects.[64] Serum bicarbonate testing was not routinely performed in Study CS3B,[65] so serum bicarbonate data from the control group are not available for comparison.

Reviewer comment: Metabolic acidosis has been described in SMA patients.[66] However, a drug-related effect may also be a factor. Accumulation of nusinersen[67] and other phosphorothioate oligonucleotides[68] in proximal tubule cells of the kidney has been described in studies of mice. Low serum bicarbonate levels (from reduced bicarbonate reabsorption) are characteristic of proximal (Type 2) renal tubular acidosis (RTA).

Proteinuria and low serum bicarbonate are seen with generalized proximal tubular dysfunction (Fanconi syndrome). Other features of Fanconi Syndrome (hypophosphatemia, glycosuria) were not reported in Study CS3B and were infrequent in other clinical studies.[69]

Renal Toxicity: Conclusion and Labeling Recommendation

An increased frequency of proteinuria was seen with nusinersen in clinical studies. Proteinuria is a cause of progressive kidney damage. [70] Renal toxicity is a class effect of oligonucleotides, and nephrotic range proteinuria complicated by life-threatening thromboses and bilateral pulmonary emboli was reported in drisapersen,[71] another phosphorothioate oligonucleotide.

[64] Source Table 80 Summary of Clinical Safety. Submitted to NDA 209531 on 9/23/2016.
[65] One subject in the Study CS3B control group had a post-treatment serum bicarbonate measurement, which was within the range of normal.
[66] Finkel RS, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014 Aug 26; 83(9): 810–817.
[67] P. 32 Nonclinical Overview. Submitted to NDA 209531 on 8/9/2016.
[68] Rappaport J, et al. Transport of phosphorothioate oligonucleotides in kidney: implications for molecular therapy. *Kidney Int.* 1995 May;47(5):1462-9.
[69] Two of 149 (1%) nusinersen subjects had treatment-emergent low phosphate, and 2 of 145 (1%) had treatment-emergent glycosuria. (Source Table 80 Summary of Clinical Safety).
[70] Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol.* 2006 Nov;17(11):2974-84.
[71] P. 236 FDA Briefing Document. Peripheral and Central Nervous System Drugs Advisory Committee Meeting November 24, 2015. NDA 206031 Drisapersen. Accessed 11/13/2016 at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm473737.pdf

Treatment-emergent low serum bicarbonate measurements occurred in 67% of nusinersen subjects.

I recommend describing the risk of proteinuria in Warnings and Precautions. I recommend quantitative spot urine protein testing (preferably using a first morning specimen) at baseline and prior to each nusinersen maintenance dose. Quantitative testing for urine protein should also be performed in any ongoing and future clinical studies of nusinersen. I also recommend testing for serum electrolytes (including bicarbonate) at baseline and prior to each maintenance dose.

8.5.2. Neurologic Toxicity

Introduction

Neurologic toxicity can occur with intrathecal (spinal) drug delivery. Toxicity after intrathecal drug delivery can be a result of the active drug itself, excipients, buffers, solubility enhancers, or preservatives.[72]

Nonclinical Studies

Reviewer comment: For additional detail regarding the preclinical study findings, the reader is referred to the Pharmacology/Toxicology review by Dr. Edward Fisher. The following information was obtained from Dr. Fisher's review.

Evidence of neurotoxicity was reported in nonclinical studies of nusinersen in juvenile cynomolgus monkeys. Some animals showed dose-dependent hippocampal vacuolization (in both the 14-week study 396443-AS03 and the 53-week study 396443-AS06) with possible treatment-related changes in learning test performance. In the hippocampus, necrotic cells were identified in some monkeys who received high dose or middle dose nusinersen; findings correlated with duration of treatment. In the 14-week study, single necrotic neurons or glial cells were observed in monkeys treated with high dose nusinersen. In the 53 week study, necrotic cells in the hippocampus were seen in some monkeys treated with middle dose or high dose nusinersen, but the cell type(s) could not be identified. In low dose or control monkeys, no hippocampal cell necrosis or vacuolization was observed. In addition, there were decreases in reflexes measured within 48 hours of administering high dose nusinersen.

[72] The Sponsor has confirmed that the solution is free of preservatives in Section 3 of the proposed prescribing information submitted to NDA 209531 on September 23, 2016.

Clinical Studies

Adverse events in the Nervous System Disorders SOC from Study CS3B and in all nusinersen subjects are summarized in the table below.

Table 29. Adverse events in the Nervous System Disorders SOC. Summary of Clinical Safety Analysis.

	Study CS3B: Nusinersen (N=80)	Study CS3B: Control (N=41)	All Nusinersen subjects (N=173)
Nervous system disorders SOC	8 (10)	2 (5)	49 (28)
Headache	0	0	29 (17)
Muscle contractions involuntary	1 (1)	0	4 (2)
Nystagmus	2 (3)	1 (2)	3 (2)
Drooling	1 (1)	0	2 (1)
Hypoaesthesia	0	0	2 (1)
Seizure	1 (1)	0	2 (1)
Syncope	0	0	2 (1)
Aphonia	0	0	1 (<1)
Brain injury	1 (1)	0	1 (<1)
Cerebral infarction	0	0	1 (<1)
Cerebrospinal fluid leakage	0	0	1 (<1)
Clonus	1 (1)	0	1 (<1)
Dysgeusia	0	0	1 (<1)
Dyslexia	0	0	1 (<1)
Hyperreflexia	0	0	1 (<1)
Hypotonia	0	0	1 (<1)
Hypoxic-ischemic encephalopathy	1 (1)	0	1 (<1)
Lethargy	0	0	1 (<1)
Migraine	0	0	1 (<1)
Paraesthesia	0	0	1 (<1)
Somnolence	1 (1)	0	1 (<1)
Tremor	0	0	1 (<1)
Presyncope	0	1 (2)	0

Source: Summary of Clinical Safety Source Tables

In controlled study CS3B, 2 of 80 (3%) nusinersen-treated subjects had serious adverse events (SAEs) in the Nervous system disorders SOC, compared to 0 of 41 sham procedure-controlled subjects. However, these SAEs were related to complications of SMA:

- **SAE PT Brain injury:** Subject 1780-5032 (9 month old female; age of symptomatic onset 2 months; age at first nusinersen dose 8 months), required ventilatory support including daily Bilevel Positive Airway Pressure (BiPAP), cough assist, and suctioning. On Study Day (b) (6) days after last nusinersen dose), the subject developed a community acquired pneumonia, uncompensated shock, apnea, and hypothermia. She was treated and discharge from the hospital. On Study

Day (b) (6), she had a respiratory arrest at home with hypoxic brain injury (SAE PT Brain Injury) after which she was unresponsive. On Study Day (b) (6) she had an AE of Seizure. On Day (b) (6), mechanical support was discontinued, and the subject died.
Reviewer comment: This SAE of Brain injury occurred in a subject with chronic respiratory failure in the setting of advanced SMA and is unlikely related to nusinersen.

- **SAE PT Hypoxic-ischaemic encephalopathy:** Subject 2000-5145 (4 month old male; age of symptomatic onset 2 months; age at first nusinersen dose 4 months) had a cardiac arrest after aspirating post-nasogastric tube feeding on Study Day (b) (6) latest injection of nusinersen, respectively). He had an SAE of Hypoxic-ischaemic encephalopathy, and his family requested to withdraw respiratory support. He died the same day.
Reviewer comment: Aspiration is a common complication of SMA[73], and this SAE is unlikely related to nusinersen.

In Pool F (all nusinersen-treated subjects), 1 additional subject had an SAE in the Nervous system disorders SOC:

- **SAE PT Seizure:** Study CS3A Subject 1776-2306 (8 month old male; age of symptomatic onset 1 month; age at first nusinersen dose 2 months) had a history of acute respiratory failure diagnosed on Study days (b) (6). He received a tracheostomy on Study Day (b) (6) and received nighttime BiPAP. On Study Day (b) (6) he had an episode of right eye deviation with EEG showing left hemispheric seizures. He had no prior history of seizures. An MRI showed two sub-acute punctate cortical-based areas of restricted diffusion in the right frontal lobe, which were new compared to the prior MRI, likely representing acute or sub-acute infarcts (AE Cerebral infarction).
Reviewer comment: The etiology of this patient's seizures and cerebral infarction is unclear. These events are possibly related to nusinersen. There was no known risk factor or potential cause for cerebral infarction reported in this patient[74] (e.g., cardiac disease, sickle cell disease, vascular disease, head or neck trauma). Vasculitis is a possible cause for cerebral infarction. Cases of vasculitis or possible vasculitis are discussed in Section 8.5.4.

Headache was the most common adverse event PT in the Nervous system disorders SOC. It was reported in 28 of 56 (50%) of later onset SMA nusinersen-treated subjects

[73] Birnkrant, David J., et al. "Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding." *Pediatric neurology* 18.5 (1998): 407-410.
[74] Tsze DS, Valente JH. Pediatric Stroke: A Review. *Emergency Medicine International*. 2011;2011:734506.

(age range 2-16 years); 19 of these subjects reported headache within 5 days of lumbar puncture.[75] Because the controlled study CS3B included only infantile-onset SMA subjects, there were no adverse events of headache reported in the controlled data.

Reviewer comment: As seen with the reporting of headache AEs, the controlled study data do not capture events which rely on AE reporting from the subjects themselves.

Within the limited time frame of the clinical studies, the numbers for many Neurologic disorders SOC adverse events were too few to determine whether there was a relationship to study drug. Selected Neurologic disorder SOC AEs are discussed below:

- **Lethargy:**[76] A 7 month old female experienced lethargy in the setting of hyponatremia. *Reviewer comment: In this reviewer's opinion, this subject's hyponatremia with lethargy is drug related. For additional details on this and other cases of hyponatremia in nusinersen-treated subjects, see Section 8.4.6.*
- **Dyslexia:**[77] One case was reported in an 8-year-old female child with no relevant medical history or concomitant medications. The subject received the study drug (12 mg) on Study Days 1, 29, and 85 via intrathecal injection. On Study Day 150, 65 days following the latest dose and 149 days following the first dose of the study drug, the subject was diagnosed with dyslexia associated with attention deficit/hyperactivity disorder (ADHD). The subject's ADHD was treated with dexmethylphenidate hydrochloride. No treatment was reported for dyslexia. No action was taken with the study drug.
  Reviewer comment: The prevalence of dyslexia has been estimated at 5-10%[78]*, and the prevalence of ADHD has been estimated at 7%.*[79] *Findings in preclinical studies raise concern for neurocognitive changes after nusinersen treatment. However, it is unclear whether nusinersen had a role in this subject's dyslexia and ADHD.*

AEs that were likely to be complications of a lumbar puncture or related treatment included:

- Hyperreflexia:[80] Occurred 1 day after having AEs of epidural hemorrhage and spinal subarachnoid hemorrhage after failed lumbar puncture attempt.

[75] The International Classification of Headache Disorders Post-dural puncture headache (previously used term Post-lumbar puncture headache) as headache occurring within five days of a lumbar puncture, caused by cerebrospinal fluid (CSF) leakage through the dural puncture (3rd edition. Published in *Cephalalgia.* 2013 Jul;33(9):629-808) .
[76] CS3A Subject 1776-2305. Narrative on p. 17 of the information request response submitted to NDA 209531 on 10/14/2016.
[77] CS2 Subject 1776-4202. Narrative p. 63 of the IR response submitted to NDA 209531 on 10/14/2016.
[78] Siegel LS. "Perspectives on Dyslexia." *Paediatr Child Health*. 2006 Nov; 11(9): 581–587.
[79] Thomas R, et al. "Prevalence of Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis." *Pediatrics* 135.4 (2015): e994-e1001.
[80] Study 232SM201 Subject 511-002. Narrative p. 13 of the IR response submitted to NDA 209531 on 10/14/2016.

- Hypotonia:[81] Two week old male with presymptomatic SMA had 4 lumbar puncture attempts prior to his first nusinersen administration (Study Day 1) and was diagnosed with an epidural hematoma. He had hypotonia and reduced weight bearing on legs that resolved by Study Day 29.
- Cerebrospinal fluid leakage
- Aphonia:[82] Occurred after intubation during lumbar puncture and resolved after 2 days.

Neurologic SOC AEs in nusinersen subjects that are common manifestations of SMA included AEs coded to PTs Muscle contractions involuntary and Drooling. AEs of Syncope[83] and Tremor[84] were also likely related to SMA. A second AE of Syncope[85] in a 12 year old subject lasted 5 minutes and was "due to heat" during band practice.

Discussion

Neurologic toxicity can occur with intrathecal (spinal) drug delivery. Spinal cord or nerve root toxicity can manifest as histologic, physiologic, or behavioral/clinical derangements after exposure to a spinal drug.[86]

Evidence of neurotoxicity was reported in nonclinical studies of nusinersen in juvenile cynomolgus monkeys. Some animals showed dose-dependent hippocampal vacuolization and/or hippocampal cell necrosis.

Reviewer comment: Study 396443-AS11 was conducted to assess the effect of varying tissue preservative techniques on the microscopic appearance of nusinersen-associated vacuolization in the hippocampus of cynomolgus monkeys. Monkeys were administered nusinersen as six once-weekly 5 mg IT bolus injections (total dose of 30 mg). Minimal vacuolization in the hippocampus was observed in 3 of 6 (50%) of monkeys whose brain sections were fixed by immersion in 10% neutral buffered formalin (the standard fixation

[81] Study 232SM201 Subject 511-001. Narrative p. 27 of the IR response submitted to NDA 209531 on 10/14/2016
[82] Study CS1 Subject 1776-1004. Summary of Clinical Safety dataset ADAE submitted to NDA 209531 on 9/23/2016.
[83] Occurred in a 4 month old female with symptomatic infantile onset SMA with paradoxical breathing and choking. Study CS3A Subject 1776-2305. Narrative p. 17 of the IR response submitted to NDA 209531 on 10/14/2016.
[84] Tremor was present on Study Day 1 and reported to be a manifestation of SMA. Study CS12 Subject 1776-3202. Narrative p. 15 of the IR response submitted to NDA 209531 on 10/14/2016.
[85] Study CS12 Subject 1775-4002. AE of Syncope occurred 3 months after his first nusinersen dose. No treatment was given, and the subject's mental status was reported to be normal after the event. Narrative p. 14 of the information request response submitted to NDA 209531 on 10/14/2016.
[86] Hodgson, Peter S., et al. "The neurotoxicity of drugs given intrathecally (spinal)." *Anesthesia & Analgesia* 88.4 (1999): 797-809.

method for the nusinersen toxicology studies). No vacuolization was observed in monkeys whose brain sections were fixed by alternative methods.[87]

The Sponsor cites these study results as evidence that the hippocampal vacuolization is linked to the method of tissue preservation.[88] *However, hippocampal vacuolization In Studies 396443-AS03 and 396443-AS06 was dose-dependent and was not observed in low dose or control monkeys. This is consistent with the findings being drug-related and not solely a result of the tissue preservation method.*

Information on preclinical neurologic toxicity was described in informed consent documents for Studies CS3A and CS3B.[89]

We will pursue enhanced pharmacovigilance with detailed reporting of information related to potential neurologic toxicity. Assessment of this potential safety issue will be complicated by the neurologic and other medical changes that are often seen in spinal muscular atrophy patients. Also, it is expected that many patients will require sedation and/or anesthesia for intrathecal nusinersen administration. The effects of repeated exposure to anesthetic and sedative drugs in children are unclear,[90-91] and this exposure will likely confound the evaluation of neurologic effects of nusinersen.

Conclusion and Labeling Recommendation

There is preclinical evidence of neurologic toxicity with nusinersen. Neurologic toxicity has been reported with intrathecal (spinal) drug delivery.[92] There is no clear evidence of neurologic toxicity in clinical studies, but the currently available data are limited. The clinical development program included 83 and 54 patients exposed to nusinersen for 1 and 2 years, respectively. If nusinersen is approved for treatment of SMA, use in some patients will likely be considerably longer in duration.

Because of the seriousness of a potential neurotoxic effect of nusinersen, this reviewer recommends describing the preclinical neurologic toxicity with nusinersen in the

[87] Alternative methods included immersion fixation in Carnoy's solution, perfusion fixation with modified Karnovsky's solution, and fixation by freezing. P. 26 Study 396443-AS11 study report.
[88] P. 12 Summary of Clinical Safety.
[89] Submitted to NDA 209531 on 10/14/2016.
[90] SmartTots. Consensus Statement of the Use of Anesthetic and Sedative Drugs in Infants and Toddlers. October 2015. Accessed 11/12/2016 at: http://www.pedsanesthesia.org/wp-content/uploads/2015/12/ConsensusStatement.pdf
[91] Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology*. 2009;110(4):796-804.
[92] Hodgson, Peter S., et al. "The neurotoxicity of drugs given intrathecally (spinal)." *Anesthesia & Analgesia* 88.4 (1999): 797-809.

Warnings and Precautions Section of labeling. This issue meets the criteria described in the FDA guidance regarding the content of the Warnings and Precautions Section of labeling:[93]

> There are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur. The WARNINGS AND PRECAUTIONS section should include serious or otherwise clinically significant adverse reactions (as described in section II.A) that are anticipated to occur with a drug if:
>
> - It appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug (e.g., a drug with a large QT prolongation effect would be likely to cause Torsades des Pointes arrhythmia even if no cases have yet been seen).
>
> ***OR***
>
> - Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects)
>
> Generally, when deemed important for the prescriber, the labeling should acknowledge that the adverse reaction has not been observed with the subject drug, but may be anticipated to occur.

8.5.3. Safety Issues Related to Lumbar Puncture

The most frequent adverse events in the 120 hours[94-95] following nusinersen dosing are listed in the table below. Because infantile SMA subjects are generally unable to report adverse events, data from later onset SMA patients provide a more complete account of post-lumbar puncture adverse events.

[93] Section II. A. 3. Guidance from Industry. Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format. Accessed 11/12/2016 at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf

[94] In a published report (Haché 2015), which describes lumbar puncture experience in some nusinersen clinical studies, the majority of lumbar puncture-associated adverse events were reported within120 hours post-lumbar puncture.

[95] The International Classification of Headache Disorders Post-dural puncture headache (previously used term Post-lumbar puncture headache) as headache occurring within five days of a lumbar puncture, caused by cerebrospinal fluid (CSF) leakage through the dural puncture (3rd edition. Published in *Cephalalgia*. 2013 Jul;33(9):629-808).

Table 30. Most Frequent Adverse Events in the 120 hours Following Nusinersen Dosing

	Presymptomatic and Symptomatic Infantile SMA (N=117)	Later Onset SMA (N=56)	All Nusinersen subjects (N=173)
Back pain[a]	1 (<1)	29 (52)	30 (17)
Post lumbar puncture syndrome	0	21 (38)	21 (12)
Headache	1 (<1)	19 (34)	20 (12)
Vomiting	6 (5)	9 (16)	15 (9)
Nausea[b]	0	8 (15)	8 (5)

[a]Back pain includes events coded to Preferred Terms Back pain and Puncture site pain.

[b]Nausea includes events coded to Preferred Terms Nausea and Procedural nausea
Source: Tables 1 and 2 submitted to NDA 209351 on 10/26/2016

In clinical studies, 5 of 173 (3%) subjects had 6 events that were hemorrhagic complications of attempted or successful lumbar puncture.[96] These events included the following Preferred Terms: Injection site haemorrhage, Subdural haematoma, Spinal cord haematoma, Extradural haematoma, Epidural haemorrhage, and Spinal subarachnoid haemorrhage (one event each). All but one of the clinical study patients with hemorrhagic complications of lumbar puncture participated in Study SM201 and were 2 months of age or less at the time of study entry. The Sponsor reviewed the medical records and determined that no subject required surgical removal of a hematoma.

Use of radiologic guidance, sedation, and anesthesia for lumbar puncture in nusinersen clinical studies is summarized in the table below. Some patients received anesthesia or sedation for the lumbar puncture procedure.

[96] P. 6 of the information request response submitted to NDA 209531 on 11/7/2016.

Table 31. Use of Radiologic Guidance, Sedation, and Anesthesia for Lumbar Puncture in Nusinersen Clinical Studies

	Pool A	Pool B: Nusinersen	Pool B: Control	Pool C	Pool D	Pool E	Pool F
Studies	SM201	CS3B	CS3B	CS3B + CS3A	SM201, CS3A, CS3B	CS1/2/10/12	SM201, CS3B, CS3A, CS1/2/10/12
Sample size	17	80	41	100	117	56	173
Patient Demographics at Baseline							
Mean age at first dose	21.9 days	163.4 days	180.5 days	160.9 days	140.7 days	7.19 years	951.8 days
Mean weight	3.9 kg	6.6 kg	6.7 kg	6.6 kg	6.2 kg	26.2 kg	12.7 kg
Ambulatory at time of first dose, n (%)	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	23 (41%)	NA[a]
History of scoliosis, n (%)[b]	0 (0%)	2 (3%)	1 (2%)	2 (2%)	2 (2%)	24 (43%)	26 (15%)
Spinal rods, n (%)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
Lumbar Puncture Procedural Characteristics							
Patients who received at least 1 intrathecal injection placed under fluoroscopy, n (%)	1 (6%)	NA[d]	NA[d]	NA[d]	NA[d]	25 (45%)	NA[d]
In patients who received at least 1 intrathecal injection placed under fluoroscopy, the median (min, max) times that each patient had an intrathecal injection placed under fluoroscopy	1.0 (1, 1)	NA[d]	NA[d]	NA[d]	NA[d]	6.0 (1, 8)	NA[d]
Patients who received at least 1 intrathecal injection placed using ultrasound guidance, n (%)	7 (41%)	79 (99%)	NA	80 (80%)	87 (74%)	CS12 (n=47) 6 (13%)[e]	NA[e]
Patients who received inhalational anesthesia, n (%)	3 (18%)	6 (8%)	2 (5%)	10 (10%)	13 (11%)	50 (89%)	63 (36%)
List which inhalational anesthetic drugs were used[f]	NITROUS OXIDE SEVOFLURANE	NITROUS OXIDE	NITROUS OXIDE	NITROUS OXIDE	NITROUS OXIDE SEVOFLURANE	ISOFLURANE NITROUS OXIDE SEVOFLURANE	ISOFLURANE NITROUS OXIDE SEVOFLURANE
Patients who received intravenous sedation, n (%)	3 (18%)	2 (3%)	0 (0%)	3 (3%)	6 (5%)	55 (98%)	61 (35%)
List which intravenous sedation drugs were used[f]	DEXMEDETOMIDINE PROPOFOL	ATROPINE KETAMINE	NA	ATROPINE KETAMINE PROPOFOL	ATROPINE KETAMINE DEXMEDETOMIDINE PROPOFOL	DEXMEDETOMIDINE EPHEDRINE FENTANYL KETAMINE KETOROLAC	ATROPINE DEXMEDETOMIDINE EPHEDRINE FENTANYL KETAMINE

	Pool A	Pool B: Nusinersen	Pool B: Control	Pool C	Pool D	Pool E	Pool F
						MIDAZOLAM PROPOFOL	KETOROLAC MIDAZOLAM PROPOFOL
Patients who received local anesthesia, n (%)	12 (71%)	62 (78%)	37 (90%)	82 (82%)	94 (80%)	45 (80%)	139 (80%)
List which local anesthetic drugs were used[f]	ANESDERM LIDOCAINE EMLA	EMLA LIDOCAINE TETRACAINE	EMLA LIDOCAINE	EMLA LIDOCAINE TETRACAINE	ANESDERM LIDOCAINE EMLA TETRACAINE	EMLA LIDOCAINE XILONIBSA	ANESDERM LIDOCAINE EMLA TETRACAINE XILONIBSA

[a] Ambulatory status at baseline not assessed for infants.
[b] Patients were identified through a CRF review and a review of medical history data for the terms "scoliosis", "scoliosis surgery", "kyphoscoliosis", and "spinal fusion surgery"
[c] There was no field on the medical history CRF specifically for "spinal rods." A review of medical history data revealed 2 subjects who reported either scoliosis surgery or spinal fusion surgery as medical history prior to receiving the first dose of nusinersen. One additional patient had scoliosis surgery after participation in CS1, prior to enrolling in CS2, and two patients had spinal surgery while participating in CS12.
[d] Fluoroscopy was not captured on the administration CRF for Studies CS3B and CS3A. A medical review of ancillary procedures was performed for these studies, and no relevant procedures were identified.
[e] Ultrasound was not captured on the administration CRF for Studies CS1, CS2, or CS10. A medical review of ancillary procedures was performed for these studies, and no relevant procedures were identified.
[f] Concomitant medications were not designated as "anesthetics" or "sedatives" by the investigator. Review of all concomitant medications (including route of administration) was performed and medications that could be considered anesthetics or sedatives, and were administered on the same day as a dose, were identified.

Source: P. 4-5 Sponsor submission to NDA 209531 on 10/25/2016

Conclusion and Labeling Recommendation

Because of the risk of thrombocytopenia from nusinersen and the potential coagulation abnormalities as seen in some oligonucleotides, patients may be at increased risk for adverse reactions after lumbar puncture for intrathecal administration of nusinersen. I recommend advising prescribers to perform a complete blood count and coagulation laboratory testing at baseline and prior to each maintenance dose of nusinersen.

8.5.4. Rash and Possible Vasculitis

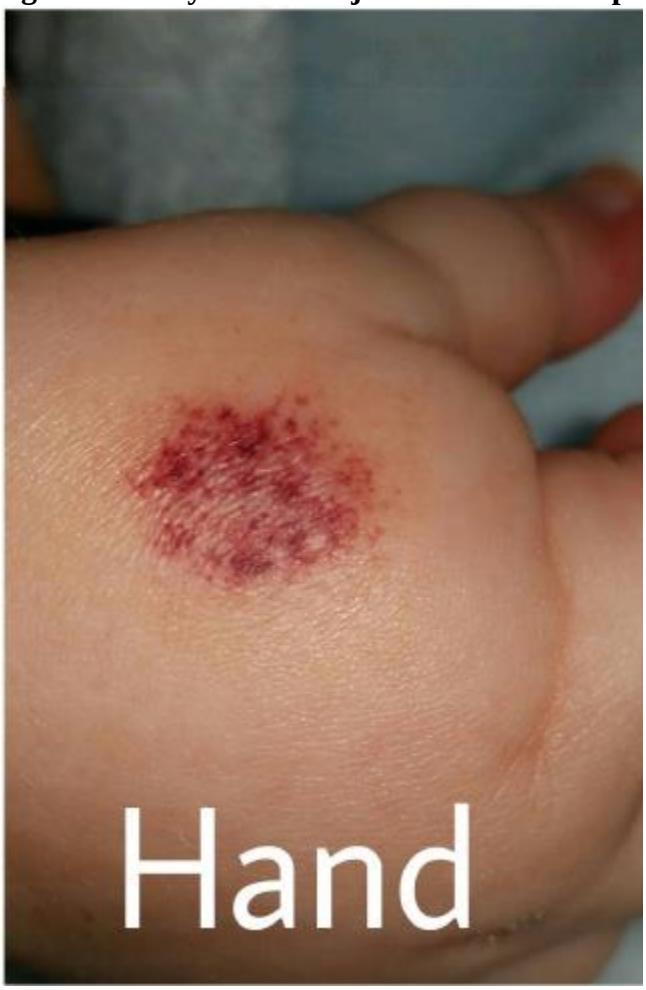
Proinflammatory effects of antisense oligonucleotide drugs have been described in the published literature.[97]

There were 3 cases of possible vasculitis with nusinersen:

- **Study CS3B Subject 2010-5026 (AE PT Vasculitis):**[98] 14 month old male developed "suspected vasculitis" of the right hand (see figure below) on the day of his sixth nusinersen injection (10 months after the first dose). Suspected vasculitis of the left hand reported 30 days later. The skin findings resolved after 3 months. No treatment was reported and no biopsy was done. No nusinersen was administered after these AEs, because it was the end of the study.

[97] Crooke, ST, ed. Antisense Drug Technology. CRC Press 2007.
[98] Narrative submitted to NDA 209531 on 10/17/2016.

Figure 2. Study CS3B Subject 2010-5026. Suspected Vasculitis Right Hand



Source: Appendix A submitted to NDA 209531 on 11/8/2016

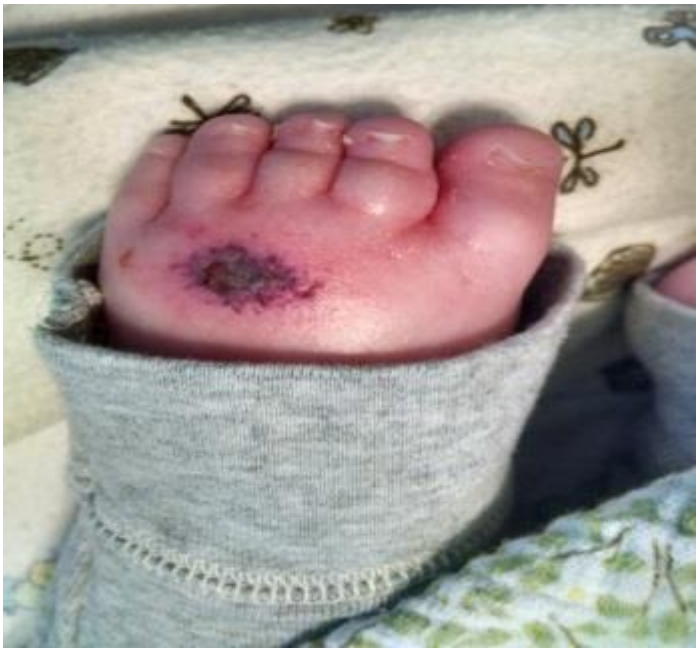
- **Study CS3A Subject 1776-2306 (AE PT Cerebral infarction):**[99] This 8 month old male (age of symptomatic onset 1 month; age at first nusinersen dose 2 months) had a history of acute respiratory failure diagnosed on Study days (b) (6). He received a tracheostomy on Study Day (b) (6) and received nighttime BiPAP. On Study Day (b) (6) nusinersen doses, respectively), he had an episode of right eye deviation with EEG showing left hemispheric seizures. He had no prior history of seizures. An MRI showed two sub-acute punctate cortical-based areas of restricted diffusion in the right frontal lobe, which were new compared to the prior MRI, likely representing acute or sub-acute infarcts.
  Reviewer comment: The etiology of this patient's seizures and cerebral infarction is unclear. These events are possibly related to nusinersen. There was no known risk factor

[99] Narrative submitted to NDA 209531 on 9/23/2016.

or potential cause for cerebral infarction reported in this patient[100] (e.g., cardiac disease, sickle cell disease, vascular disease, head or neck trauma). Vasculitis is a possible cause for cerebral infarction.

- **Study CS3B Subject 2002-5370 (AE PT Rash):[101]** 13 month old male who, 8 and 2 months after his first and fifth nusinersen doses, respectively, developed painless lesions on the forearm, leg, and foot over 8 weeks. The red macular lesions ulcerated and scabbed over within 4 weeks. Microscopic description of a left leg skin biopsy: "several thin-walled vessels in the superficial dermis demonstrating occlusion with red blood cells and amorphous eosinophilic material. There is early necrosis of some of the vessel lumens, without leukocytoclasia or significant inflammation." Post-op diagnosis was Vasculitis vs. Vascular occlusion. However, the biopsy report included a comment "There are no features of vasculitis." Laboratory tests for coagulopathy and immune disorders were unremarkable. He received one additional SPINRAZA dose after the rash started. The lesions resolved without treatment over several months.

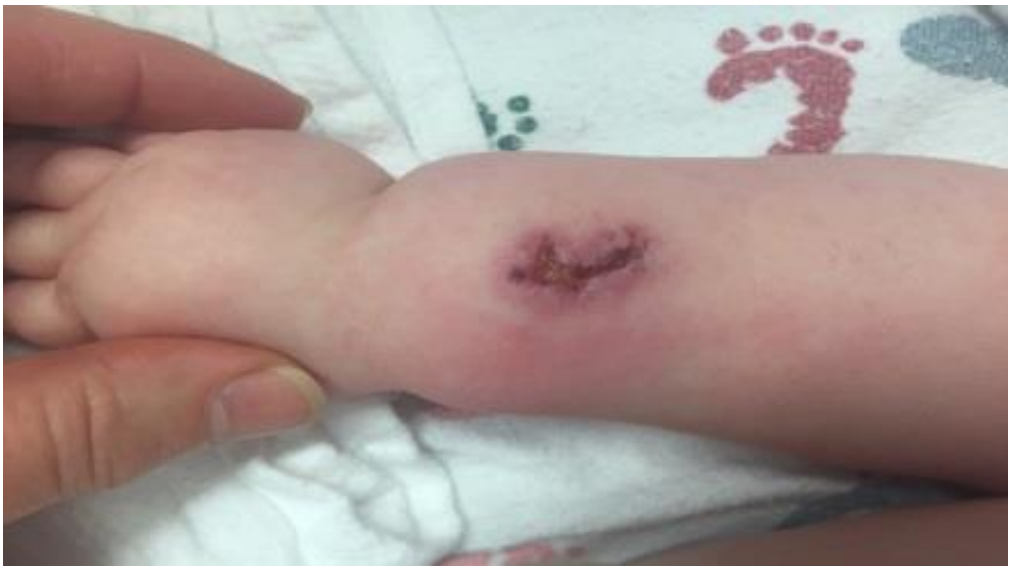
Figure 3. Study CS3B Subject 2002-5370. Foot lesion.



Source: Appendix B. 11/8/2016 submission to NDA 209531

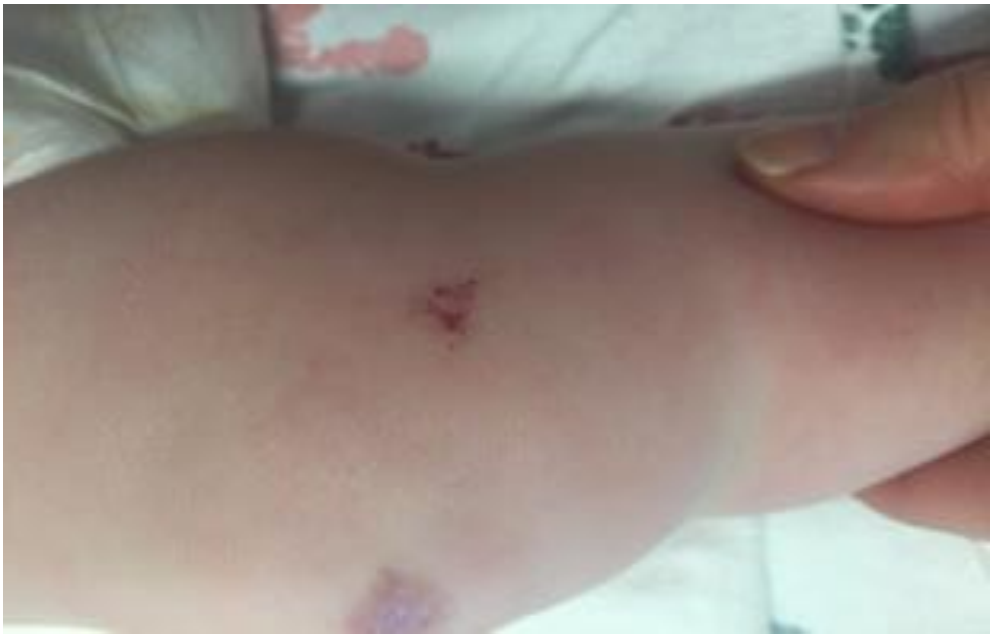
[100] Tsze DS, Valente JH. Pediatric Stroke: A Review. *Emergency Medicine International*. 2011;2011:734506.
[101] Narrative submitted to NDA 209531 on 10/17/2016.

Figure 4. Study CS3B Subject 2002-5370. Forearm Lesion.



Source: Appendix B. 11/8/2016 submission to NDA 209531

Figure 5. Study CS3B Subject 2002-5370. Leg Lesion (Site of Biopsy)

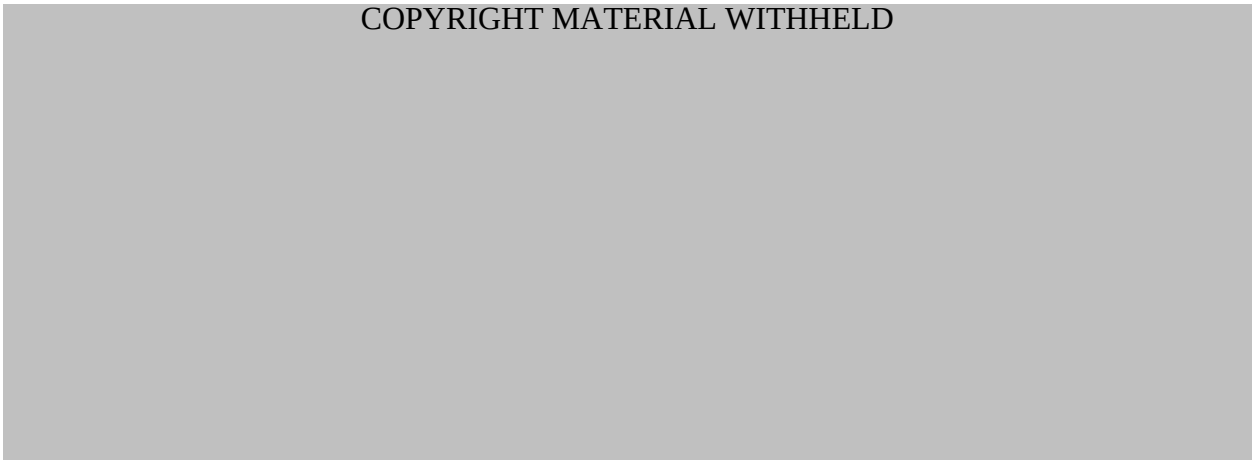


Source: Appendix B. 11/8/2016 submission to NDA 209531

Conclusion and Labeling Recommendation

Cases of distal necrosis have been described in SMA patients not treated with nusinersen. However, the lesion descriptions are different from the skin lesions in nusinersen subjects. Araujo[102] describes 2 cases in which started with bluish discoloration and evolved to red, then purple, then black, then to tissue necrosis (see figure below). Rudnik-Schöneborn[103] provides similar photographic documentation of 2 other cases but does not provide details of the lesions' evolution. Also, the published cases of distal necrosis are rare (a total of 4), while 2 cases of possible vasculitis occurred in the 173 nusinersen clinical study subjects.

Figure 6. Digital Necrosis in a Patient with SMA (Not Nusinersen-Treated)



Source: Araujo, Mario, and Kathryn J. Swoboda. *The Journal of pediatrics* 155.2 (2009): 292-294.

Cases of rash and possible vasculitis have been described in nusinersen subjects. I recommend describing these cases in the Warnings and Precautions section of labeling.

[102] Araujo, Mario, and Kathryn J. Swoboda. "Vascular perfusion abnormalities in infants with spinal muscular atrophy." *The Journal of pediatrics* 155.2 (2009): 292-294.
[103] Rudnik-Schöneborn, Sabine, et al. "Digital necroses and vascular thrombosis in severe spinal muscular atrophy." *Muscle & nerve* 42.1 (2010): 144-147.

8.6. Safety Analyses by Demographic Subgroups

Age

In infants diagnosed with SMA, the number and percentage of subjects who experienced at least 1 AE were 22 subjects (81%) in the <90 days of age subgroup and 83 subjects (92%) in the ≥90 days of age subgroup.[104] Overall, the incidence of AEs by SOC was higher in the ≥90 days of age subgroup than the <90 days of age subgroup. The overall lower incidence of AEs in the <90 days of age subgroup is likely influenced by the presence of the presymptomatic subjects, who generally do not have AEs related to manifestations of SMA, contributing to this cohort.

In subjects with Later-onset SMA (Pool E), at least 1 AE was experienced by all subjects in each age subgroup analyzed (28 subjects < 6 years old and 28 subjects ≥ 6 years old).[105] The AE incidence was generally similar between the 2 age subgroups. However, LP-related events were more commonly reported in the older age group (e.g., post lumbar puncture syndrome 21% in the <6 years of age subgroup versus 61% in the ≥6 years of age subgroup).

Sex

Of the 117 infants diagnosed with SMA, 60 were male and 57 were female. AE incidences were similar between the subgroups categorized by sex, and the most common SOCs were the same (e.g., infections and infestations and respiratory, thoracic, and mediastinal disorders).[106]

Of the 56 subjects in the Later-onset SMA subject group (Pool E), 26 were male and 30 were female. There was no difference in AE incidence between the subgroups, and the most common SOCs were the same (e.g., infections and infestations and musculoskeletal and connective tissue disorders).[107]

Race

Of the 113 infants with SMA who reported race, 93 were White and 20 were non-White. AE incidences between the subgroups were similar, and the most common SOCs were the same (e.g., infections and infestations; respiratory, thoracic and mediastinal disorders; and gastrointestinal disorders).[108]

[104] Table 96 Summary of Clinical Safety Source Tables
[105] Table 97 Summary of Clinical Safety Source Tables
[106] Table 101 Summary of Clinical Safety Source Tables
[107] Table 102 Summary of Clinical Safety Source Tables
[108] Table 107 Summary of Clinical Safety Source Tables

In the Later-onset SMA subject group (Pool E; N=56), the non-White subgroup had relatively few subjects (n = 7) compared with the White subgroup (n = 49), thereby limiting meaningful comparisons between the 2 subgroups. All subjects in both subgroups had at least 1 AE.[109]

8.7. Specific Safety Studies/Clinical Trials

No specific clinical safety studies were performed in the nusinersen development program.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There were 4 subjects with adverse events of benign neoplasms[110] reported in nusinersen clinical studies. Otherwise, no neoplasms were reported in the NDA submission.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported in nusinersen clinical studies. There were 10 female subjects who were over age 12 at the time of study entry.

8.8.3. Pediatrics and Assessment of Effects on Growth

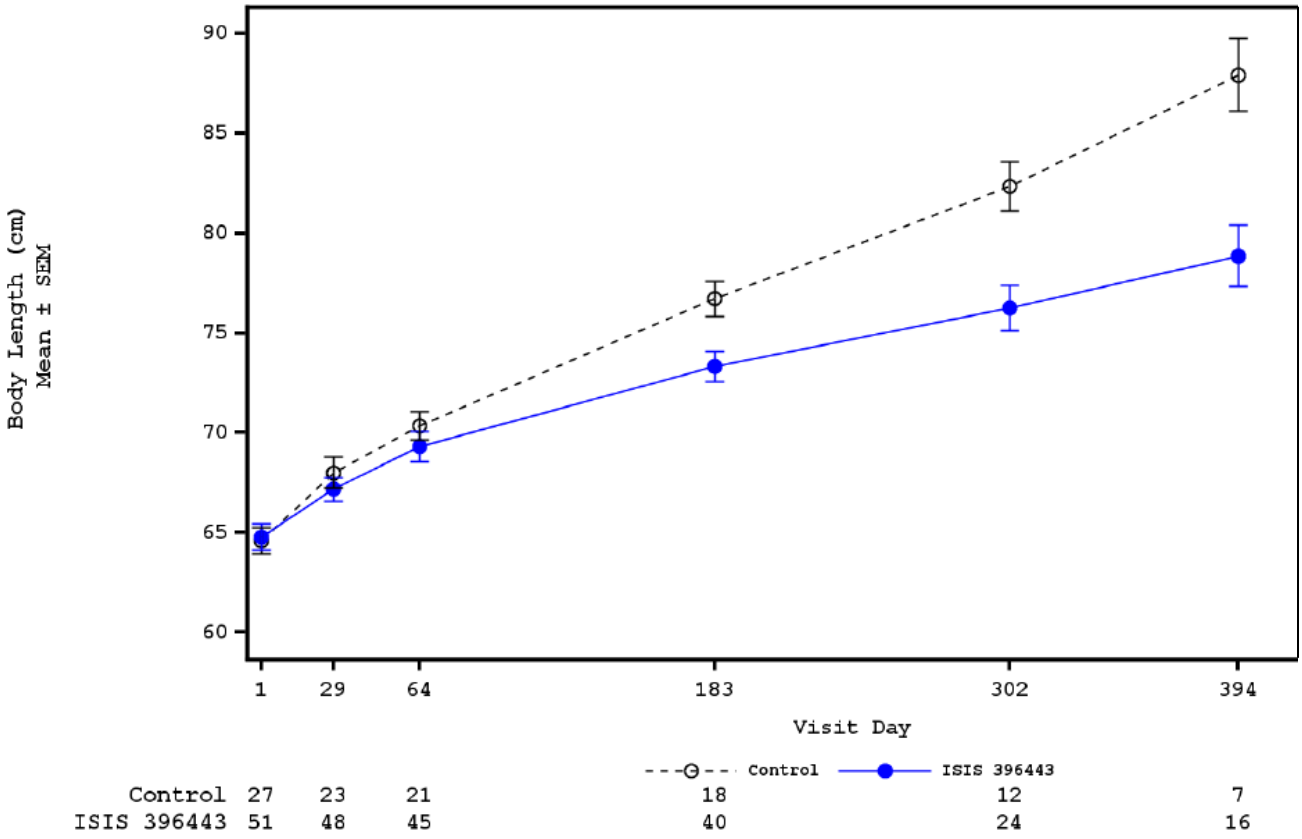
In Study CS3B, nusinersen subjects had reduced growth compared to sham procedure control subjects (see figures below). At Study Day 394: mean change from baseline in height/length was 13 cm for nusinersen subjects, compared to 21 cm in sham procedure control subjects;[111] mean change from baseline in height/length percentile for age was -26 for nusinersen subjects, compared to 26 in sham procedure control subjects;[112] mean change from baseline in weight was 3.1 kg for nusinersen subjects, compared to 3.9 kg in sham procedure control subjects;[113]

[109] Table 108 Summary of Clinical Safety Source Tables
[110] The following benign neoplasms were reported in nusinersen-treated subjects:
- PT Benign vascular neoplasm: Study CS3A Subject 1834-1301 (7 month old female from the United States) had swelling in the right arytenoid, which was biopsied and had a pathological diagnosis of "benign submucosal vascular proliferation". (P. 11 of the 10/25/2016 submission to NDA 209531)
- PT Skin papilloma (Study CS1 Subject 1780-1003)
- Pt Acrochordon (skin tag) (Study CS3A Subject 1835-2308)
- PT Seborrheic keratosis (Study 232SM201 Subject 510-001)

[111] CS3B Study Report p. 344.
[112] CS3B Study Report p. 342.
[113] CS3B Study Report p. 349.

and mean change from baseline in weight for age percentile was 0 in nusinersen subjects, compared to 27 in sham procedure control subjects.[114]

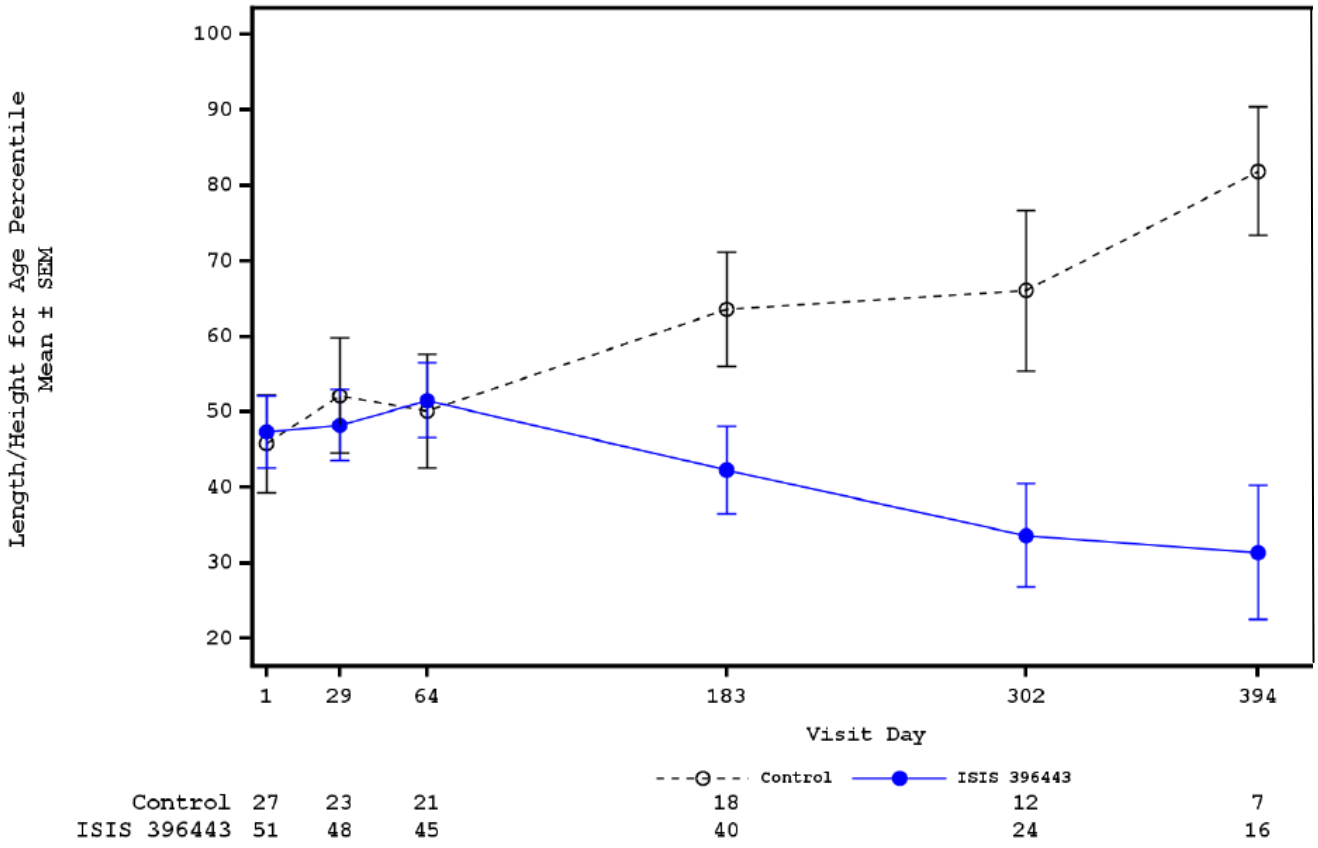
Figure 7. Study CS3B. Height/length over Time. Mean Results.



Source: CS3B Study Report p. 363
ISIS 396443 = nusinersen

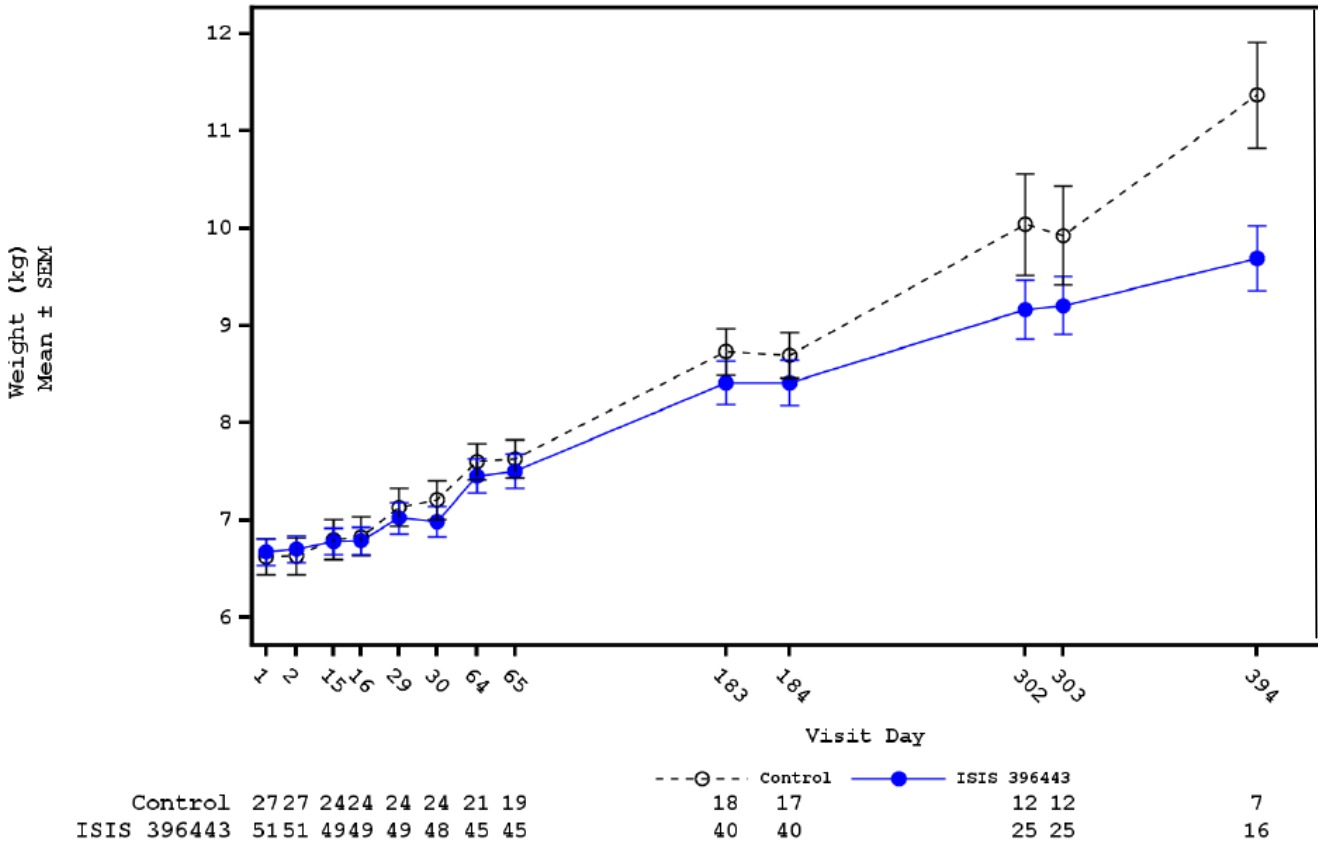
[114] CS3B Study Report p. 354.

Figure 8. Study CS3B. Height/length for Age Percentile over Time. Mean Results.



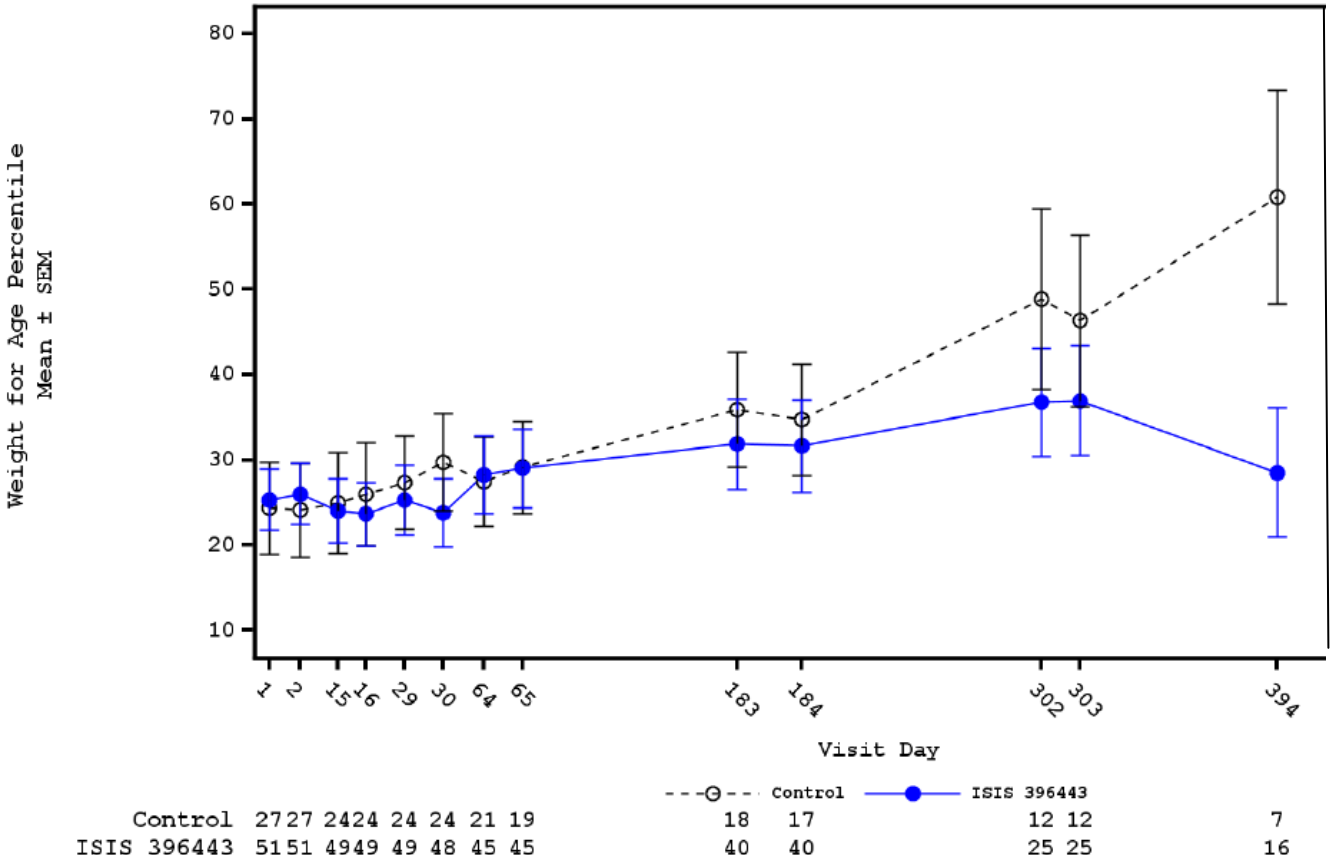
Source: CS3B Study Report p. 362
ISIS 396443 = nusinersen

Figure 9. Study CS3B. Weight over Time. Mean Results.



Source: CS3B Study Report p. 364
ISIS 396443 = nusinersen

Figure 10. Study CS3B. Weight for Age Percentile over Time. Mean Results.



Source: CS3B Study Report p. 365
ISIS 396443 = nusinersen

Reviewer comment: In Study CS3B, nusinersen subjects had reduced growth compared to sham procedure control subjects. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment. I recommend describing this issue in the Warnings and Precautions section of the nusinersen label.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

There were no adverse events of overdose in the clinical program.

Drug abuse potential

In a consult regarding NDA 209531, the FDA Controlled Substance Staff, in a review dated 11/30/16, found no issues related to drug abuse potential and provided the following conclusions and recommendations:

Conclusions

1. Nonclinical studies demonstrate that nusinersen does not signal abuse potential. Based on its structure as an oligonucleotide and its specificity of binding to mRNA to modulate splicing of the SMN2 gene, nusinersen should not bind to receptors known to be involved in drug abuse. The IT route of administration is unlikely to have a potential for abuse, and nusinersen does not cross the Blood Brain Barrier (BBB) when administered IV or SQ.

2. No abuse-related AEs were found in the clinical trials involving children and adolescents.

Recommendations

1. The label for Spinraza should not include Section 9 Abuse and Dependence, given that there are no data showing that the drug has abuse potential or induces physical dependence.

2. Spinraza should not be recommended for scheduling under the Controlled Substances Act.

Reviewer comment: This reviewer agrees with the Controlled Substance Staff conclusions. The Sponsor's proposed label does not include a Section 9 (Abuse and Dependence).

Withdrawal and Rebound

This reviewer performed a search using the MedDRA Drug Withdrawal SMQ. No drug withdrawal or rebound adverse events were found in nusinersen clinical studies.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. There is no previous postmarket experience.

8.9.2. Expectations on Safety in the Postmarket Setting

Additional information regarding nusinersen known clinical safety issues will be obtained and new safety issues likely identified as there are more patients exposed for increasing durations of treatment.

If it is approved, nusinersen will be administered by a health professional, in a way similar to administration in clinical studies. Because its mechanism of action is specific to the treatment of SMA, we do not anticipate significant off-label use of nusinersen.

8.10. Additional Safety Issues From Other Disciplines

The reader is referred to Section 4 of this review.

8.11. Integrated Assessment of Safety

The main safety concerns with nusinersen are thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, effect on growth, rash and possible vasculitis, neurologic toxicity in animal studies, and hepatic effects.

Six of 56 (11%) nusinersen patients had a platelet level below the lower limit of normal, compared to 0 of 28 sham procedure control patients in controlled study CS3B. No patient had a platelet count less than 50,000 cells per microliter in that study. Five of 173 (3%) nusinersen patients had a hemorrhagic complication of lumbar puncture. Coagulation abnormalities have been observed after administration of some antisense oligonucleotides. Low platelet levels or coagulation abnormalities may increase the risk of adverse outcomes after intrathecal administration of nusinersen. Monitoring hematologic and coagulation parameters at baseline and prior to each maintenance dose may help mitigate this risk.

Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile onset SMA, compared to 5/25 (20%) sham control subjects. Proteinuria occurred in 26 of 52 (69%) of later-onset SMA subjects with a longer duration of treatment. Treatment-emergent low serum bicarbonate occurred in 32 of 48 (67%) of nusinersen subjects in whom it was measured; measurements from a control group were not performed. Low serum bicarbonate levels are characteristic of proximal renal tubular acidosis. Nusinersen accumulates in the kidney and renal toxicity is a class effect of oligonucleotides. Monitoring for proteinuria and monitoring serum electrolytes including bicarbonate at baseline and prior to each maintenance dose may help mitigate a risk of an adverse clinical outcome.

Severe hyponatremia occurred in a patient treated with nusinersen. Monitoring serum electrolytes at baseline and before each maintenance dose may help to mitigate this risk. Decreased growth (height and weight) was observed in nusinersen subjects compared to sham control subjects in Study CS3B. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment.

Rash and possible vasculitis were reported in 2 patients treated with nusinersen. A third subject had new onset seizures and cerebral infarction after starting nusinersen, with no known risk factor or potential cause for cerebral infarction; the etiology in this case is unknown, but vasculitis is a possible cause of cerebral infarction.

Nusinersen, like other phosphorothioate oligonucleotides, accumulates in the liver. In Study CS3B, 2 of 55 (4%) nusinersen subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects. Monitoring hepatic tests, including gamma-glutamyl transferase (GGT) and bilirubin at baseline and before each maintenance dose may help to mitigate the risk of hepatotoxicity.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Labeling Recommendations

10.1. Prescribing Information

This reviewer recommends describing several issues in the Warnings and Precautions section of labeling, including thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, effect on growth, rash and possible vasculitis, neurologic toxicity, and hepatic effects.

10.2. Patient Labeling

We will use the label Section 17 (Patient Counseling) to provide information for clinicians to communicate to the patients and caregivers, including information about the Warnings, the need for laboratory monitoring, and symptoms for which patients should monitor between visits (e.g., symptoms of thrombocytopenia).

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Safety issues that warrant consideration of a REMS include:

- Thrombocytopenia
- Renal toxicity

11.2. Conditions of Use to Address Safety Issue(s)

Thrombocytopenia

Laboratory monitoring of a complete blood count at baseline and every 4 months (prior to each maintenance dose) will be necessary to mitigate the risk of complications related to thrombocytopenia from nusinersen. Health care providers who care for SMA patients are highly specialized and will educate patients and caregivers on symptoms of thrombocytopenia for which patients should monitor.

Renal Toxicity

Measurement of a quantitative urine protein and a general metabolic panel (including electrolytes and serum creatinine) at baseline and every 4 months (prior to each maintenance dose) will be necessary to mitigate the risk of complications related to renal toxicity from nusinersen. Health care providers who care for SMA patients are highly specialized and will educate patients and caregivers on symptoms of thrombocytopenia for which patients should monitor.

11.3. Recommendations on REMS

At the time of this review, I do not recommend a REMS for this NDA. Factors influencing this decision include:

- Spinal muscular atrophy (SMA) is mainly treated in specialty centers with detailed knowledge of SMA and its treatment.
- Patients are scheduled to see a medical professional at least every 4 months for administration of nusinersen, which will facilitate risk mitigation.
- The SMA community is active in educating patients and families regarding SMA treatment.

The Division of Neurology Products (DNP) met with the Division of Risk Management (DRISK) on 10/19/16 and agreed that a REMS would not be recommended at this time.

12 Postmarketing Requirements and Commitments

At the time of this review, we plan no postmarketing requirements or commitments related to clinical safety. We plan to have enhanced pharmacovigilance to assess cases of thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, effects of nusinersen on growth, rash and possible vasculitis, neurologic toxicity, and hepatotoxicity.

13 Appendix

Appendix 1. Routine laboratory tests measured in the nusinersen development program

Panel	Lab parameter(s)	CS1 Cohorts 1 & 2	CS1 Cohorts 3 & 4	CS2 Cohorts 1, 2, & 4	CS2 Cohort 3	CS10	CS12	CS3A	CS3B	SM201 (Nurture)
Chemistry	sodium, potassium, chloride, total protein, albumin, calcium, phosphorus, bicarbonate, glucose, blood urea nitrogen, creatinine, total serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and creatinine phosphokinase	Screening (Day -28 to -1), Days 1, 2, 29	Screening (Day -28 to -1), Days 1, 2, 29, 85	Screening (Day -28 to -1), Days 1, 2, 29, 36, 85, 92, 169	Screening (Day -28 to -1), Days 1, 2, 36, 85, 92, 169, 253	Screening (Day -28 to -1), Days 1, 8, 85, 169	Screening (Day -28 to -1), Days 1, 85, 92, 169, 351, 533, 715	Screening (Day -21 to -1), Days 29, 92, 169, 253, 337, 442, 568, 694, 820, 946, 1072, 1198, 1352	Screening (Day -21 to -1), Days 64, 183, 394	Screening (Day -21 to -1), Days 29, 64, 183, 302, 365, 421, 540, 659, 700, 778, 868
Chemistry	Cystatin C	none	none	Screening (Day -28 to -1), Days 1, 2, 29, 36, 85, 92, 169	Screening (Day -28 to -1), Days 1, 2, 36, 85, 92, 169, 253	Screening (Day -28 to -1), Days 1, 8, 85, 169	Screening (Day -28 to -1), Days 1, 85, 92, 169, 351, 533, 715	Screening (Day -21 to -1), Days 92, 169, 253, 337, 442, 568, 694, 820, 946, 1072, 1198, 1352 (no Day 29)	Screening (Day -21 to -1), Days 64, 183, 394	Screening (Day -21 to -1), Days 64, 183, 302, 365, 421, 540, 659, 700, 778, 868 (no Day 29); Cystatin C was not assessed in subjects weighing less than 3 kg at screening

Panel	Lab parameter(s)	CS1 Cohorts 1 & 2	CS1 Cohorts 3 & 4	CS2 Cohorts 1, 2, & 4	CS2 Cohort 3	CS10	CS12	CS3A	CS3B	SM201 (Nurture)
Hematology	hematocrit, hemoglobin, platelets, red blood cells (RBCs), white blood cells (WBCs), and WBC differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)	Screening (Day -28 to -1), Days 1, 2, 29	Screening (Day -28 to -1), Days 1, 2, 29, 85	Screening (Day -28 to -1), Days 1, 2, 29, 36, 85, 92, 169	Screening (Day -28 to -1), Days 1, 2, 36, 85, 92, 169, 253	Screening (Day -28 to -1), Days 1, 8, 85, 169	Screening (Day -28 to -1), Days 1, 85, 92, 169, 351, 533, 715	Screening (Day -21 to -1), Days 29, 92, 169, 253, 337, 442, 568, 694, 820, 946, 1072, 1198, 1352	Screening (Day -21 to -1), Days 64, 183, 394	Screening (Day -21 to -1), Days 29, 64, 183, 302, 365, 421, 540, 659, 700, 778, 868
Coagulation	prothrombin time, activated partial thromboplastin time, and international normalized ratio	Screening (Day -28 to -1), Day 1	Screening (Day -28 to -1), Day 1	Screening (Day -28 to -1), Days 1, 85	Screening (Day -28 to -1), Days 1, 85	Screening (Day -28 to -1), Day 1	Screening (Day -28 to -1)	Screening (Day -21 to -1)	Screening (Day -21 to -1)	Screening (Day -21 to -1)
Urinalysis	specific gravity, pH, protein, glucose, ketones, bilirubin, RBCs, WBCs, epithelial cell, bacteria, casts, and crystals	Screening (Day -28 to -1), Days 1, 2	Screening (Day -28 to -1), Days 1, 2	Screening (Day -28 to -1), Days 1, 2, 29, 36, 85, 92	Screening (Day -28 to -1), Days 1, 2, 36, 85, 92, 253	Screening (Day -28 to -1), Days 1, 8, 85	Screening (Day -28 to -1), Days 1, 85, 92, 169, 351, 533, 715	Screening (Day -21 to -1), Days 29, 92, 169, 253, 337, 442, 568, 694, 820, 946, 1072, 1198, 1352	Screening (Day -21 to -1), Days 64, 183, 394	Screening (Day -21 to -1), Days 29, 64, 183, 302, 365, 421, 540, 659, 700, 778, 868
Urinalysis	blood	Screening (Day -28 to -1), Days 1, 2	Screening (Day -28 to -1), Days 1, 2	Screening (Day -28 to -1), Days 1, 2, 29, 36, 85, 92	Screening (Day -28 to -1), Days 1, 2, 36, 85, 92, 253	Screening (Day -28 to -1), Days 1, 8, 85	Screening (Day -28 to -1), Days 1, 85, 92, 169, 351, 533, 715	Screening (Day -21 to -1), Days 29, 92, 169, 253, 337, 442, 568, 694, 820, 946, 1072, 1198, 1352	Screening (Day -21 to -1), Days 64, 183, 394	not required

Panel	Lab parameter(s)	CS1 Cohorts 1 & 2	CS1 Cohorts 3 & 4	CS2 Cohorts 1, 2, & 4	CS2 Cohort 3	CS10	CS12	CS3A	CS3B	SM201 (Nurture)
CSF	RBC, WBC, glucose, and protein	Days 1, 8	Day 1; Day 8 AND Day 29 (Cohort 3); Day 8 OR Day 29 (Cohort 4)	Days 1, 29, 85	Days 1, 85	Day 1	Days 1, 169, 351, 533	Days 1, 15, 85, 253, 379, 505, 631, 757, 883, 1009, 1135, 1261	none	none
Plasma cytokine and CSF cytokine	interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemotactic protein-1 (MCP-1)	Days 1, 8	Day 1; Day 8 AND Day 29 (Cohort 3); Day 8 OR Day 29 (Cohort 4)	none	none	none	none	none	none	none

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/s/

EVELYN K MENTARI
12/14/2016

SALLY U YASUDA
12/14/2016

CLINICAL EFFICACY REVIEW

Application Type	NDA
Application Number(s)	209531
Priority or Standard	Priority
Clinical Submit Date(s)	9/23/2016
Received Date(s)	9/23/2016
PDUFA Goal Date	5/23/2017
Division/Office	DNP/OND
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Review Completion Date	12/1/2016
Established Name	Nusinersen
(Proposed) Trade Name	Spinraza
Applicant	Biogen, Inc.
Formulation(s)	Intrathecal injection
Dosing Regimen	12mg (5mL) loading dose on days (b) (4) followed by maintenance dose every 4 months. (b) (4)
Applicant Proposed Indication(s)/Population(s)	Spinal muscular atrophy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Spinal muscular atrophy

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HFMSE	Hammersmith Functional Motor Scale - Expanded
HINE	Hammersmith Infant Neurological Examination
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IT	intrathecal
ITT	intent to treat

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MUNE	Motor unit number estimation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SGE	special government employee
SMA	Spinal muscular atrophy
SOC	standard of care
TEAE	treatment emergent adverse event
ULMT	Upper Limb Module Test
6MWT	6-minute Walk Test

1 Executive Summary

1.1. Product Introduction

APPEARS THIS WAY ON ORIGINAL

Nusinersen (called ISIS 396443 in clinical trials, Spinraza is proposed proprietary name) is an antisense oligonucleotide administered intrathecally that binds to pre-mRNA to increase the production of normal SMN protein.

Nusinersen is a new molecular entity (NME) containing no previously approved active ingredient (including any ester or salt of the active ingredient).

Note that reviewer commentary throughout the text is presented in *italics*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sham-procedure controlled study CS3B is the one adequate and well-controlled efficacy study that can support approval of nusinersen for the treatment of infantile-onset SMA patients, with confirmatory evidence from 6 open-label studies as well as a report of a statistically significant result ($p=0.0000002$) assessing motor function in a sham-procedure controlled study (CS4 in Section 6.3, data not available for review) in later-onset SMA patients.

Study CS3B is a single well-designed multicenter study that has provided reliable and statistically strong ($p<0.0001$) evidence of an important clinical benefit, motor milestone development that is inconsistent with the natural course of this terminal disease, with a numerical trend suggesting a beneficial effect on survival. A confirmatory sham-procedure controlled study in infantile-onset SMA infants, who typically die by 2 years of age, would have been difficult to conduct on ethical grounds.

Based on the results of all available studies, the fact that a deficiency of SMN protein causes disease across all SMA types, and nusinersen's demonstrated ability to increase the amount of full-length SMN2 mRNA for translation to SMN protein, it is reasonable to extrapolate that nusinersen can provide benefit both to patients with infantile-onset and later-onset SMA.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Nusinersen (called ISIS 396443 in clinical trials, Spinraza is the proposed proprietary name) is an antisense oligonucleotide administered intrathecally that binds to pre-mRNA to increase the production of normal SMN protein. Nusinersen is intended to treat patients with spinal muscular atrophy (SMA). Based on the positive results of a single adequate and well-controlled study and confirmatory evidence from 6 open-label studies as well as the reported results of an additional sham-procedure controlled study (data not available for review) in later-onset SMA patients, it is the conclusion of this reviewer that nusinersen should be approved for the treatment of SMA.

Spinal muscular atrophy (SMA) is an autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to respiratory failure and infection. It is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births.

There are no FDA-approved treatments for SMA and there is no effective clinical treatment generally. Current medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery. Although the lifespan of the most severely affected SMA patients can be increased through invasive mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection. There is a significant unmet clinical need for effective treatments for SMA patients.

A 13-month sham-procedure controlled multicenter study of nusinersen in infantile-onset SMA infants (80 nusinersen, 41 control) has provided reliable and statistically strong evidence that nusinersen can help these infants achieve motor milestone development that they would otherwise not achieve due to the disease. This milestone development includes infants attaining the ability to sit and even to stand, which type 1 SMA patients normally never can do. Attaining motor milestone development is clinically meaningful because infants become able to perform basic motor skills needed for normal life, such as controlling head movements,

sitting, rolling over, crawling, and standing.

Although there is some evidence to suggest that nusinersen might have a beneficial effect on survival, the study's statistical plan for interim analysis allowed only a descriptive report of this result. No conclusion regarding a beneficial effect of nusinersen on the long-term survival of infantile-onset SMA patients can be reached from the available data.

Further confirmation of the benefit of nusinersen in treating patients with SMA is provided by the results of six open-label studies (four in later-onset SMA, one in presymptomatic infants with genetic diagnosis of SMA, and one in infants with infantile-onset SMA) as well as a reported statistically significant result assessing motor function by the Hammersmith Functional Motor Scale - Expanded score in a sham-procedure controlled study (data not available for review) in later-onset SMA patients (types 2 and 3).

Based on the results of all available studies, the fact that a deficiency of SMN protein causes disease across all SMA types, and nusinersen's demonstrated ability to increase the amount of full-length SMN2 mRNA for translation to SMN protein, it is reasonable to extrapolate that nusinersen can provide benefit both to patients with infantile-onset and later-onset SMA.

As described in the separate safety review by Dr. Evelyn Mentari, the following common adverse events occurred in the 13-month sham-procedure controlled multicenter study of nusinersen in infantile-onset SMA infants: upper respiratory infection (44%); lower respiratory infections (43%); and constipation (30%). QT prolongation of at least 500 msec with at least a 60 msec increase from baseline was also observed on the ECG in 4 of 80 (5%) nusinersen subjects in the study. Safety issues that occurred at the proposed dose of nusinersen include thrombocytopenia, proteinuria, hyponatremia, decreased growth, and rash and possible vasculitis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Spinal muscular atrophy (SMA) is a genetic disease that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. • There are different types of SMA (types 0, 1, 2, 3 and 4). Classification	• Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to weakening of the muscles needed for breathing and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	into SMA types used to be based only on the age when symptoms began and the kinds of movements patients could achieve. Today we also have genetic testing to help classify the different types of SMA. • In general, the more copies of the survival motor neuron 2 gene (SMN2) that a patient has, the better the prognosis is. • Affected infants have impaired motor milestone development. For example, they remain unable to lift the head, sit, stand, or walk. Following the initial weakness and impaired motor development, there is a long-term decline or a plateau in strength and movement ability. • Type 1 (infantile-onset) SMA is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births.	infections that occur when babies become too weak to cough and clear their lungs. • Genetic testing alone can't always tell one exactly which type of SMA will develop in all patients. • Different patients with the same SMN2 gene copy number can have different severities of symptoms.
Current Treatment Options	• There are no FDA-approved treatments for SMA and there is no effective clinical treatment generally. Current medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery.	Although the lifespan of the most severely affected SMA patients can be increased through permanent mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection. There is a significant unmet clinical need for effective treatments for SMA patients.
Benefit	• In the 13-month sham-procedure controlled multicenter study of nusinersen in infantile-onset SMA infants (80 nusinersen, 41 control), 40% of infants who received nusinersen had an improvement in motor milestone development, compared to 0% of infants who received the sham-procedure ($p<0.0001$).	The results of the 13-month sham-procedure controlled multicenter study of nusinersen in infantile-onset SMA infants provide reliable and statistically strong evidence

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Of the infants who received nusinersen, 18% achieved full head control, 10% achieved independent sitting, and 1 subject (2%) achieved standing. None of the subjects in the control group achieved any of these milestones. • Although there is no formal statistical comparison, there is some evidence to suggest that nusinersen might have a beneficial effect on survival. During the study, 15% of infants in the nusinersen group died compared to 32% in the control group. • Although there is no formal statistical comparison, neuromuscular function as measured by the CHOP INTEND score and motor nerve function as measured by the Compound Muscle Action Potential (CMAP) amplitude also improved in the infants who received nusinersen. 65% of infants who received nusinersen had at least a 4-point improvement in CHOP INTEND score compared to 4% of infants in the control group. 43% of infants who received nusinersen had at least a 0.5mV increase in peroneal nerve CMAP amplitude compared to 0% in the control group. • Further confirmation of the benefit of nusinersen in treating patients with SMA is provided by the results of six open-label studies (four in later-onset SMA, one in presymptomatic infants with genetic diagnosis of SMA, and one in infants with infantile-onset SMA) as well as a statistically significant result assessing motor function by HFMSE score in a sham-procedure controlled study (data not available for review) in later-onset SMA patients (types 2 and 3). The results of these latter studies (described in Sections 6.2, 6.3, 7.1.2, and 13.8) do not contradict the results of the main sham-procedure control study in	that nusinersen can help these infants achieve motor milestone development that they would not otherwise achieve due to the disease. Attaining motor milestone development is clinically meaningful because infants become able to perform basic motor skills needed for normal life, such as controlling head movements, sitting, rolling over, crawling, and standing. No conclusion regarding a beneficial effect on the long-term survival of infantile-onset SMA patients can be reached from the available data. Based on the results of all available studies, the fact that a deficiency of SMN protein causes disease across all SMA types, and nusinersen's demonstrated ability to increase the amount of full-length SMN2

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infantile-onset SMA described above.	mRNA for translation to SMN protein, it is reasonable to extrapolate that nusinersen can provide benefit both to patients with infantile-onset and later-onset SMA.
Risk	As described in the separate safety review by Dr. Evelyn Mentari, the safety database for nusinersen includes all patients from the Phase 3 controlled study and the Phase 2 open-label study in patients with symptomatic infantile-onset SMA, the Phase 2 open-label study in infants with presymptomatic SMA, and open-label studies in subjects with later-onset SMA In Study CS3B, the Phase 3 controlled study in symptomatic infantile onset SMA patients, common AEs were: upper respiratory infection (44%); lower respiratory infections (43%); and constipation (30%). QT prolongation of at least 500 msec with at least a 60 msec increase from baseline was also observed on the ECG in 4 of 80 (5%) nusinersen subjects in the study. Safety issues that occur at the proposed dose of nusinersen include thrombocytopenia, proteinuria, hyponatremia, decreased growth, and rash and possible vasculitis. .	Nusinersen accumulates in the kidney in humans and accumulation in proximal tubule cells has been described in nonclinical studies. Coagulation laboratory abnormalities, renal accumulation, and hepatic accumulation are class effects of phosphorothioate antisense oligonucleotides. Monitoring for proteinuria and monitoring serum electrolytes including bicarbonate at baseline and prior to each maintenance dose may help mitigate a risk of an adverse clinical outcome. Laboratory values as markers of renal, hepatic, and thrombocytopenia adverse events would be useful at baseline and prior to each maintenance dose. In

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		cases of severe hyponatremia, the sodium level normalized after salt supplementation treatment, which continued for 14 months. Clinical studies did not evaluate whether the effect of nusinersen on growth is reversible with cessation of treatment and a thorough QT study was not performed. No conclusion may be drawn on reversibility for those adverse events. Consider the risk of concomitant use of drugs that prolong the QT interval.
Risk Management	Strong product labeling with recommendations for monitoring of laboratory parameters may help to mitigate the risks of renal, hepatic, and thrombocytopenia adverse events. However, even with adequate monitoring, some patients may experience serious adverse events.	WARNINGS and PRECAUTIONS should be included in labeling to describe the risks of renal and hepatic adverse events and thrombocytopenia and to provide recommendations for monitoring. I also recommend informing prescribers about hyponatremia, decreased growth, rash and possible vasculitis, and QT prolongation in WARNINGS and PRECAUTIONS.

2 Therapeutic Context

2.1. Analysis of Condition

Spinal muscular atrophy (SMA) is an autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to respiratory failure and infection. It is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births (Arkblad 2009; Jedrzejowska 2010; Prior 2010; Sugarman 2012).

There are multiple types of SMA (0-4), as shown in the table "Classification of Spinal Muscular Atrophy" in Section 6.1.1. Classification into SMA types has historically been based on the age of symptom onset and the maximal achieved motor abilities (Finkel 2015). In general, the severity of symptoms decreases and the age of onset is delayed with increasing survival motor neuron 2 gene (SMN2) copy number and correspondingly increasing amounts of SMN protein (Arnold, 2015), although different patients with the same SMN2 copy number can have different clinical phenotypes.

Affected infants have impaired motor milestone development, e.g., lift the head, sit, stand, or walk. Following the initial acute weakness and impaired motor development, there is a chronic decline or plateau in functional capabilities (Crawford 2004; Swoboda et al. 2007).

2.2. Analysis of Current Treatment Options

There are no FDA-approved treatments for SMA and there is no effective clinical treatment generally. Current medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery (Wang 2007). Although the lifespan of the most severely affected SMA patients can be increased through invasive mechanical ventilation (Gregoretti et al., 2013), the quality of such a life is poor and most patients eventually succumb to respiratory infection. There is a significant unmet clinical need for effective treatments for SMA patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nusinersen is a new molecular entity (NME) that is not currently marketed in the United States or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The FDA granted ISIS 396443 Fast Track (11/29/2011), Orphan Drug, Priority review, and Rolling submission designations.

Breakthrough designation was denied on 9/11/2014.

Rare Pediatric Disease Designation was granted on October 21, 2016.

Type C Meeting: September 15, 2015

The sponsor presented results from a Phase 2, open-label, historical control trial in 20 infants with SMA type I as the potential basis for an NDA. A Phase 3 double-blind, sham-procedure controlled trial was also ongoing.

The sponsor asserted that the Phase 2 study results indicated a benefit on survival times and clinical assessments relative to natural history. However, confounding factors such as more intensive supportive care or differences in patient selection made them very difficult to interpret.

Over the subsequent months, the Division had multiple iterative interactions (both written and by teleconference) with the sponsor to help develop and refine its interim analysis plan.

The result of the interim analysis of the Phase 3 trial, provided to the Division on July 30, 2016, strongly supported the efficacy of nusinersen.

The Division initiated a teleconference with the sponsor on August 4, 2016, to discuss the findings and actively encourage the submission of an NDA.

During this call, the Division also supported the sponsor's proposal to submit an intermediate-sized patient population expanded access protocol for Type I SMA patients (submitted on August 17, 2016).

Part 1 of the rolling submission (CMC and nonclinical) was received on August 9, 2016, with the complete application submitted on September 23, 2016.

3.3. Foreign Regulatory Actions and Marketing History

Nusinersen has not been marketed previously in any country

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three clinical study sites have been inspected in the United States. No problems were found.

4.2. Product Quality

The applicant states that "ISIS 396443 will be provided as a single use, sterile, isotonic solution containing no preservatives for intrathecal administration. ISIS 396443 drug product is formulated and packaged for single use as a 5.0 mL deliverable volume in a 6 mL vial containing 2.4mg/mL of ISIS 396443" (Introduction, p. 2).

Analysis and discussion of the acceptability of product quality is deferred to the chemistry, manufacturing, and controls (CMC) reviewer.

4.3. Clinical Microbiology

Not applicable. Nusinersen is not an antimicrobial or antiviral drug.

4.4. Nonclinical Pharmacology/Toxicology

The applicant reports the following results of nonclinical studies, including hippocampal vacuolation findings in monkeys without any apparent accompanying neurobehavioral effects. The applicant attributes this vacuolation to the method of tissue preservation. The reader is referred to the separate nonclinical review for further details and analysis.

"In the 14-week and 53-week juvenile cynomolgus monkey studies, observed microscopic changes were limited to the inferior hippocampal region of the brain, where the primary finding was slight to mild focal neuronal vacuolation. The incidence of vacuolation was greatest in the 14-week study which had the most intensive dosing schedule (a total dose of 45 mg over 14 weeks compared to 52 mg over 53 weeks for the highest dose groups). Furthermore, the highest concentrations were measured in animals dosed at 3 mg per week in the 14-week study (169 and 166 µg/g in lumbar spinal cord and cerebral cortex, respectively). Based on a 5-point microscopic rating scale, the hippocampal vacuolation findings ranged from slight to mild, and in the opinion of the study pathologist, were unlikely to cause any clinical signs or negatively influence the animals' ability to function normally. This interpretation, based on the microscopic rating scale, was supported by the lack of effects on neurobehavioral assessments in these animals. Supporting information for this conclusion was provided by an investigational study conducted in cynomolgus monkeys using 6 weekly IT doses sections from these animals were fixed by immersion in 10% neutral buffered formalin (10% NBF, the standard fixation method for the toxicology studies) and by alternative methods (immersion fixation in Carnoy's solution, perfusion fixation with modified Karnovsky's solution, and fixation by freezing). Vacuolation was seen in the hippocampal region in brain sections processed using 10% NBF while vacuolation was not observed microscopically in the hippocampal sections fixed by the alternative methods. Based on this investigational study, vacuoles in the hippocampus do not represent an adverse toxicological finding. The observation of vacuoles is linked to the method of tissue preservation and the presence of ASO in endosomes or lysosomes...

Results of the 2 developmental and reproductive toxicity studies using SC dosing were negative for drug-related effects on fertility or embryo-fetal development.

In safety pharmacology studies, no pulmonary or cardiovascular effects were found in rats following continuous IT infusion for 25 days, and there were no effects on electrocardiogram (ECG) in the repeat-dose IT toxicology studies in monkeys" (Summary of Clinical Safety, p. 13).

4.5. Clinical Pharmacology

The key outcomes of the clinical pharmacology discipline review are summarized below. The reader is referred to the full review of the Office of Clinical Pharmacology (OCP) for further details.

"Clinical pharmacology studies in healthy subjects were not conducted given the intrathecal route of administration of nusinersen. Drug-drug interaction studies were not conducted given the lack of any significant in vitro findings on nusinersen as an inducer or inhibitor of CYP enzymes or transporters. Renal and hepatic impairment studies were not conducted as concomitant renal or hepatic disease is not likely to be found in the SMA population.

OCP recommends a fixed-dose of 12 mg/5 mL for all subjects with loading doses at days (b) (4) followed by the same maintenance dose every 4 months thereafter. We considered the following when recommending fixed dosing versus age based dosing:

- PK simulations of fixed dosing demonstrate that the mean nusinersen exposures (AUCinf and Cmax) will be ~25% higher in 0-3 month age group compared to age-based dosing. The mean difference in nusinersen exposures between dosing regimens for other age groups (>3 months to 2 years) will be less than 25%. The variability in data suggests considerable overlap in nusinersen CSF levels between age-based and fixed dosing.
- Nusinersen was well-tolerated and there was no evidence for any serious adverse events (SAEs) related to exposure.
- Exposure-response findings from a phase 2 study indicate higher proportion of motor milestone responders in the infantile-onset SMA population at the higher end of the dose response curve.
- (b) (4)

4.5.1. Mechanism of Action

Nusinersen in an 18-mer 2'-MOE phosphorothioate antisense oligonucleotide that is intrathecally injected. Nusinersen acts as a splice-altering oligonucleotide designed to displace heterogeneous ribonucleoproteins (hnRNPs) at the intronic splice silencing site-1 (ISS-1), present in all SMA patients, downstream of exon 7 on the *SMN2* pre-mRNA to promote the inclusion of exon 7 in the SMN2 mRNA transcript and enhance the production of full length SMN protein (OCP review & Introduction, p.1).

4.5.2. **Pharmacodynamics**

The applicant reports the following pharmacodynamics information for nusinersen.
The reader is referred to review of the Office of Clinical Pharmacology (OCP) for analysis and discussion.

"The PD of ISIS 396443 was characterized by the following, generally consistent with the drug's mechanism of action:

SMN2 splicing in autopsy CNS tissue samples:

SMA infants treated with ISIS 396443 have higher levels of SMN2 mRNA containing exon 7 in the thoracic spinal cord compared to untreated SMA infants and similar high levels of exon 7 transcripts in other regions of the spinal cord and brain, consistent with distribution and the proposed mechanism of action of the drug. Autopsy samples showed that SMA infants treated with ISIS 396443 had 50 to 69% full-length SMN2 mRNA that included exon 7 from the thoracic spinal cord, compared to 15 to 26% from untreated SMA controls

SMN protein localization in autopsy CNS tissue samples:

SMN protein was detected in thoracic spinal cord motor neurons from subjects treated with ISIS 396443 as well as in neurons and other cell types (such as glial, Purkinje, endothelial) in spinal cord tissues and other regions of the CNS. However, quantitative conclusions could not be reached due to limitations in the immunohistochemistry methodology used to localize the protein.

SMN protein concentration in CSF:

Although ISIS 396443 likely increases SMN protein levels at the site of action within the neuron, a measurement of the increase in tissue in subjects is not feasible. The closest concentrations that can be measured are CSF concentrations, which are highly variable in the infant population due to marked changes in SMN protein in utero and early neonatal period. In addition, since no data are available from control subjects, the actual change in SMN protein concentrations in CSF could not be assessed. In light of these limitations, no relationship was observed between CSF concentrations of ISIS 396443 and SMN protein concentrations in the CSF" (Summary of Clinical Pharmacology, p. 15)

4.5.3. **Pharmacokinetics**

"**Absorption:** Nusinersen is administered as an intrathecal injection.
Distribution: Nusinersen distributes rapidly to the CNS and the plasma. Plasma concentrations peak at 1-6 hours and decline rapidly due to extensive tissue distribution.
Metabolism: Nusinersen is metabolized by exonucleases primarily at the 3' end of the oligonucleotide. N-1 metabolites were found in the cerebrospinal fluid (CSF), while N-1,2,3 metabolites were found in the plasma.
Elimination: The mean terminal half-life in the CSF ranges from 135-177 days. It is mainly excreted in the urine as chain-shortened metabolites (N-1,2,3) that are not considered active. Urinary excretion of intact nusinersen represented only a small fraction of the dose (0.5%) at day 85 following a third dose of the drug" (OCP Review, p. 5).

4.6. **Devices and Companion Diagnostic Issues**

Not applicable to this application.

4.7. **Consumer Study Reviews**

Not applicable to this application.

5 Sources of Clinical Data and Review Strategy

5.1. **Table of Clinical Studies**

An overview of the clinical studies performed by the applicant is shown in the figure below, copied from the applicant. Note that data from studies CS4 and CS11 were not submitted for this NDA, although the applicant did provide a summary of results for CS4 that is described in Section 6.3. Summaries of the studies submitted to support efficacy are in the table of clinical studies below.

Figure 1: Overview of ISIS 396443 Clinical Development Program. Source: Summary of Clinical Efficacy, p. 18

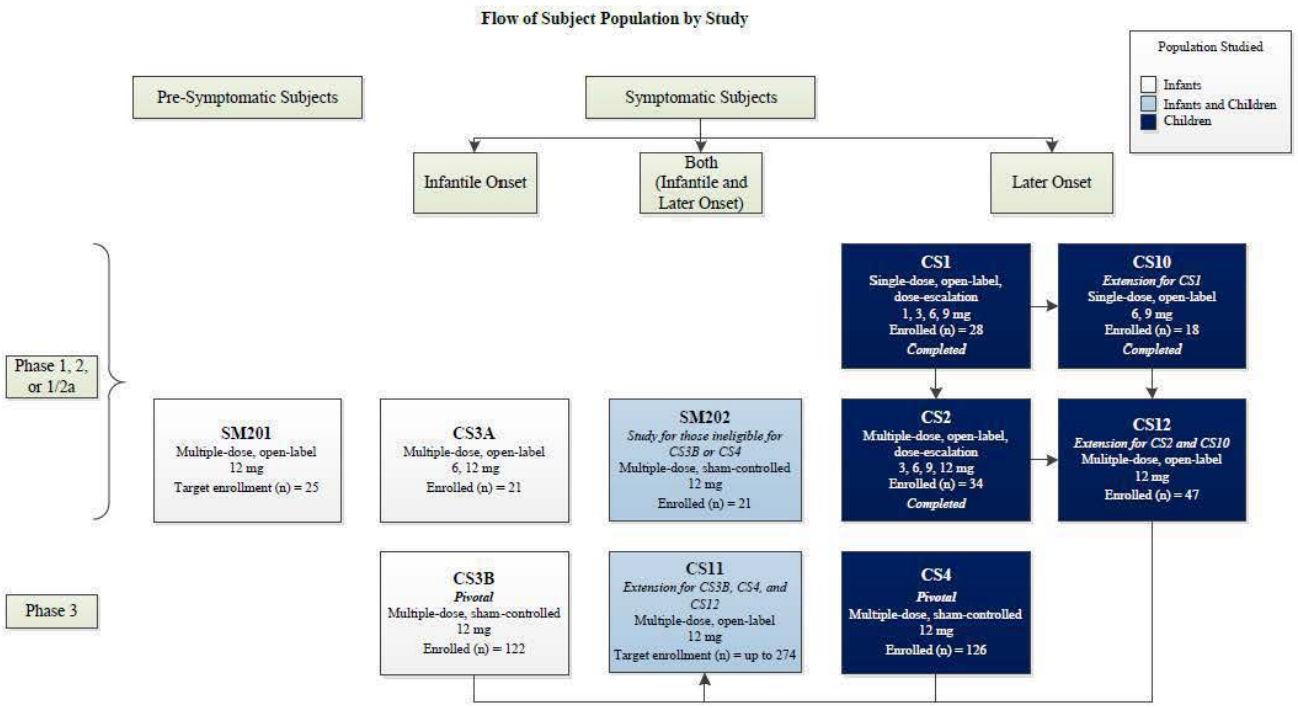


Table 1: Clinical Studies in Subjects with SMA Contributing Efficacy Data. Source: Summary of Clinical Efficacy, p. 35

Study ID	Study CS3B	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Study Type/Design	Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled	Phase 2, Open-label, multiple-dose	Phase 2, Open-label, multiple-dose, single-arm	Phase 1, Open-label, escalating dose	Phase 1, Open-label, single dose	Phase 1, open-label, dose-escalation, multiple dose	Phase 1, Open-label, multiple-dose, single-arm
Study population	Subjects with symptomatic infantile-onset SMA	Subjects with symptomatic infantile-onset SMA	Presymptomatic subjects with genetically diagnosed SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA
Number of Study Centers that enrolled subjects Number of Subjects Enrolled by Location	31 centers Australia: 5 Belgium: 1 Canada: 6 France: 8 Germany: 10 Italy: 9 Japan: 3 South Korea: 1 Spain: 11 Sweden: 3 Turkey: 5 UK: 5 US: 54	4 centers US: 18 Canada: 3	10 centers Australia: 1 Germany: 1 Italy: 2 Taiwan: 1 US: 12	4 centers US: 28	4 centers US: 18	4 centers US: 34	4 centers US: 47
Study Start **Enrollment Status** Total Enrolled as of Data Cutoff Date[a] (Planned)	August 2014 Completed 122 subjects (111 subjects)	May 2013 Completed 21 subjects (20 subjects)	20 May 2015 Ongoing 11 subjects (25)	05 Dec 2011 Completed 28 subjects (NA)	10 Jan 2013 Completed 18 subjects (NA)	12 Oct 2012 Completed 34 subjects (NA)	30 January 2014 Completed 47 subjects (NA)

Study ID	Study CS3B	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Study Objectives	Efficacy, safety, tolerability, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, dose finding, efficacy	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy and PK
Primary efficacy endpoint	Motor milestones (HINE Section 2)	Motor milestones (HINE Section 2)	Time to death or respiratory intervention	HFMSE	HFMSE	HFMSE	HFMSE
Secondary efficacy endpoints	CHOP INTEND, CMAP, overall and event-free survival, growth	CHOP INTEND, CMAP, overall and event-free survival, growth	Development of clinically manifested SMA, motor milestones, CHOP INTEND, CMAP, overall and event-free survival, growth	PedsQL™, CMAP, MUNE	PedsQL™ CMAP, MUNE	PedsQL™, CMAP, MUNE, ULM, myometry, 6MWT, ACEND	6MWT, ULM, CMAP
Test Product, Route of Administration **Dosage Regimen** Duration of Treatment	ISIS 396443: 12 mg scaled equivalent dose IT injection by LP or sham-procedure (2:1) Loading dose: Days 1, 15, 29, 64 Maintenance dose: Days 183 and 302 Total duration: approximately 14 months	ISIS 396443 IT injection by LP: Cohort 1: • 6 mg scaled equivalent loading dose and 12 mg maintenance dose Cohort 2: • 12 mg scaled equivalent loading dose and 12 mg maintenance dose Loading dose: Days 1, 15, and 85 Maintenance dose: Day 253 and every 4 months thereafter.	ISIS 396443: 12 mg (scaled equivalent) IT injection by LP Loading dose: Days 1, 15, 29, and 64 Maintenance dose: Days 183, 302, 421, 540, 659, and 778 Total duration: approximately 2.4 yrs	ISIS 396443 1, 3, 6, and 9 mg single dose IT injection by LP	ISIS 396443 IT injection by LP Cohort 1: 6 mg on Day 1 Cohort 2: 9 mg on Day 1	ISIS 396443 IT injection by LP: Cohort 1: 3 mg on Days 1, 29, 85 Cohort 2: 6 mg on Days 1, 29, 85 Cohort 3: 9 mg on Days 1, 85 Cohort 4: 12 mg on Days 1, 29, 85 Total Duration: approximately 8 months	ISIS 396443: 12 mg IT injection by LP Doses on Days 1, 169, 351, and 533 Total duration: approximately 1.5 yrs

Study ID	Study CS3B	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Number of Subjects by Arm Dosed	ISIS 396443: 80 Sham procedure: 41 1 subject withdrew before dosing	Cohort 1: 4 Cohort 2: 16 1 subject withdrew before dosing	12 mg: 17	1 mg cohort: 6 3 mg cohort: 6 6 mg cohort: 6 9 mg cohort: 10	Cohort 1: 4 Cohort 2: 14	Cohort 1: 8 Cohort 2: 8 Cohort 3: 9 Cohort 4: 9	12 mg: 47
Sex	45% male 55% female	60% male 40% female	65% male 35% female	39% male 61% female	28% male 72% female	59% male 41% female	49% male 51% female
Mean (median) Age at baseline	153 (166) days (20 to 211 days)	155 days (36 to 210 days)	21.9 (19) days (8 to 42 days)	Mean 6.1 yrs (2-14 yrs)	Mean 6.6 yrs (2-11 yrs)	Mean 7.4 yrs (2-15 yrs)	8 years (3-17 yrs)
Mean (median) Age at symptom onset	8.4 (8.0) weeks	Median 56 days	NA (presymptomatic)	Not summarized	Not summarized	Not summarized	Not summarized
Number *SMN2* Copies	2 (n=118) 3 (n=2) Unknown (n=2)	2 (n=17) 3 (n=2) Unknown (n=1)	2 (n=12) 3 (n=5)	3 (n=25) 4 (n=2) 5 (n=1)	3 (n=17) 4 (n=1)	2 (n=1) 3 (n=25) 4 (n=8)	3 (n=39) 4 (n=8)

[a] As of 26 January 2016 for Study CS3A, 15 June 2016 for Study CS3B, 08 June 2016 for Study SM201, and 07 April 2016 for CS12.
6MWT = six-minute walk test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; CSR = clinical study report; IT = intrathecal; LP = lumbar puncture; MUNE = motor unit number estimation; NA = not applicable; PedsQL™ = Pediatric Quality of Life Inventory; PK = pharmacokinetic; SMA = spinal muscular atrophy; ULM = Upper Limb Module; UK = United Kingdom; US = United States; yrs = years.

5.2. **Review Strategy**

An efficacy determination was made by evaluating the interim results from the sham-procedure controlled study CS3B in infantile-onset SMA patients. This reviewer assessed the primary endpoint, motor milestone response, by examining the source data provided by the applicant. Statistical analysis of the data was performed and reported by a separate statistical reviewer.

The 6 open-label studies submitted (CS1, CS2, CS3A, CS10, CS12, and SM201) were evaluated for their potential to provide confirmatory evidence of efficacy.

The results of the sham-procedure controlled study CS4 in later-onset type 2 and 3 SMA patients were assessed for their potential to provide additional confirmatory evidence of efficacy to support the results of study CS3B. Although CS4 appears to be a well-controlled study based on the summary provided by the applicant, no data for CS4 were available at the time of NDA submission so CS4 cannot be reviewed.

Note that this review focuses solely on clinical efficacy. This application is being reviewed separately for safety by Dr. Evelyn Mentari.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. **ISIS 396443-CS3B. A Phase 3, Randomized, Double-Blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients With Infantile-Onset Spinal Muscular Atrophy**

6.1.1. **CS3B Study Design**

Overview and Objective

Study CS3B is a Phase 3, multicenter, randomized, double-blind, sham-procedure controlled study of nusinersen (ISIS 396443) in subjects with symptomatic infantile-onset SMA.

The objectives of the study are described by the applicant as follows.

"The primary objective of the study is to examine the clinical efficacy of ISIS 396443 administered intrathecally to patients with infantile-onset SMA.

The secondary objective of the study is to examine the safety and tolerability of ISIS 396443 administered intrathecally to patients with infantile-onset SMA.

The tertiary objective of the study is to examine the cerebrospinal fluid (CSF) and plasma PK of ISIS 396443 administered intrathecally to patients with infantile-onset SMA" (CS3B CSR, p. 28).

Trial Design

- **Basic study design:**

  This was a Phase 3, multicenter, double-blind, randomized, sham-procedure controlled study of ISIS 396443 conducted at 31 centers worldwide. Approximately 111 subjects were to be enrolled into the study. This study was conducted to test the clinical efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 administered as IT injections by lumbar puncture (LP) to subjects with infantile-onset SMA. The study was stopped following an interim analysis of the data.

  The total duration of subject participation in the study was approximately 14 months. The study consisted of a Screening Period, a Treatment Period, and a Post-treatment Follow-up Period.

- **Choice of control group:**
  A double-blinded placebo-control study is a rigorous and readily interpretable study design. It is ethically acceptable for this indication given the unknown effect of the study drug and the lack of any effective treatment that might otherwise have served as an active control. Placebo (sham procedure) group patients continued to receive the standard of care for SMA.

- **Diagnostic criteria:**
  SMA diagnosis was based on genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote with an SMN2 copy number = 2, and the onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age. *Note that SMA was historically diagnosed based on clinical phenotype prior to the availability of genetic testing, as described in the following table. There may be phenotypic overlap between patients with different SMN2 copy number, and patients with the same SMN2 copy number may have more or less severe phenotypes. It is therefore possible that some patients who would historically have been classified as type 2 SMA based solely on phenotype could initially be called type 1 given current genetic testing capability. Based on the age of symptom onset and SMN2 copy number, the patients in study CS3B are classified as type 1 (severe) SMA.*

Table 2: Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	SMN copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..	Four or more copies of *SMN2*

- **Key inclusion/exclusion criteria:**

  The criteria listed below from the submitted protocol appear adequate to enroll infantile-onset SMA patients representative of the U.S. population.

Inclusion Criteria

To participate in this study, candidates were required to meet the following eligibility criteria at Screening:

1. Signed informed consent of parent(s) or guardian(s).
2. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
3. SMN2 copy number = 2.
4. Onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age.
5. Males and females ≤7 months (210 days) of age at Screening.
6. At study entry, receiving adequate nutrition and hydration (with or without gastrostomy), in the opinion of the Site Investigator.
7. Body weight ≥3rd percentile for age using appropriate country-specific guidelines.
8. Medical care, such as routine immunizations (including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis (palivizumab) if available), meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA (Appendix D of the protocol), in the opinion of the Site Investigator.
9. Gestational age of 37 to 42 weeks.
10. Reside within approximately 9 hours ground-travel distance from a participating study

center for the duration of the study. Residence >2 hours ground-travel distance from a study center must obtain clearance from the Investigator and the study Medical Monitor.

11. Able to complete all study procedures, measurements and visits and parent or guardian/subject has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator.

Exclusion Criteria

Subjects meeting any of the following criteria were not eligible for the study:

1. Hypoxemia (O2 saturation awake <96% or O2 saturation asleep <96%, without ventilation support) during screening evaluation.
2. Signs or symptoms of SMA present at birth or within the first week after birth.
3. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening Period of ISIS 396443-CS3B.
4. History of brain or spinal cord disease that would interfere with the LP procedures, CSF circulation, or safety assessments.
5. Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter.
6. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Site Investigator, at screening that would render the subject unsuitable for inclusion.
7. Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/ salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological agent, or device within 30 days prior to screening or anytime during the study. Any history of gene therapy, prior ASO treatment, or cell transplantation.
8. The subject's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study, or does not agree to comply with the protocol defined schedule of assessments.
9. Subject's caregiver is not willing to continue to meet standard of care guidelines for care (including vaccinations and respiratory syncytial virus prophylaxis if available), nutritional, and respiratory support throughout the duration of the study (see Appendix D of the protocol).
10. Ongoing medical condition that according to the Site Investigator would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures. (CS3B CSR, pp. 33-34)

- **Dose selection:**

The applicant reports that the dose level selected for this multiple-dose clinical study (12 mg ISIS 396443) was predicted to achieve levels of approximately 10 µg/g lumbar spinal cord tissue and 3 µg/g cervical spinal cord tissue following the first dose based on nonclinical studies in juvenile monkeys. Pharmacology and PK results in SMA transgenic mice led to estimates that the target tissue concentration needed to produce 50% to 90% SMN2 exon 7 inclusion is between 1 and 10 µg/g in spinal cord tissue. The loading dose interval (i.e., doses on Study Days 1, 15, 29, and 64) was selected based on nonclinical PK and pharmacology data to achieve and maintain ISIS 396443 spinal cord tissue levels within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical spinal cord tissue concentrations). The maintenance dose interval (once every 4 months on Study Days 183 and 302) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range (CS3B CSR, pp. 37-38).

Reviewer Comment: Doses of 1, 3, 6, 9, and 12 mg of nusinersen were studied by the applicant in prior open-label studies. 12mg was selected based on the positive preliminary efficacy results of those studies, which are discussed in more detail later in Section 6.

- **Study treatments:**

Subjects randomized to the ISIS 396443 treatment group received a single IT LP injection of study drug as a slow bolus (1 to 3 minutes) using a spinal anesthesia needle and 5-mL syringe on Study Days 1, 15, 29, 64, 183, and 302. As shown in the table below, the volume of injection was adjusted based on the subject's age on the day of dosing such that each subject received a 12-mg scaled equivalent dose based on CSF volume scaling. Younger subjects were given a lower dose of drug, achieved by injecting a smaller volume that was proportional to estimated CSF volume for age, such that dose volume was equivalent to 5 mL for age 2 years to adult.

As described by the applicant (CS3B CSR, p. 36), the sham procedure chosen for the control group consisted of a small superficial needle puncture on the lower back where the LP injection was normally made. The needle broke the skin but no LP injection or needle insertion occurred. The needle prick was covered with the same bandage that was used to cover the LP injection normally, thus simulating the appearance of an LP injection. The study subject was kept in the procedure room for the same amount of time that subjects administered study drug were kept, simulating the time period of a study drug administration procedure.

Please refer to the Office of Pharmaceutical Quality (OPQ) review for discussion of the

product formulation used for the active study arm.

Table 3: ISIS 396443 Dose Volume to be Injected

Age	Estimated CSF Volume	Injection Volume	Dose
0 to 3 months (0 to 90 days)	120 mL	4 mL	9.6 mg
3 to 6 months (91 to 180 days)	130 mL	4.3 mL	10.3 mg
6 to 12 months (181 to 365 days)	135 mL	4.5 mL	10.8 mg
12 to 24 months (366 to 730 days)	140 mL	4.7 mL	11.3 mg

CSF = cerebrospinal fluid
Source: [Matsuzawa 2001]

- **Assignment to treatment:**

The applicant states that "subjects were considered enrolled in the study after parental informed consent was obtained. At the time of consent, a subject was assigned a unique screening number before any study procedures were performed. The screening number remained constant throughout the study. If the subject was reconsented and rescreened, a new screening number was to be assigned. Once assigned, screening numbers were not reused. Subjects were randomized after all screening assessments were completed and study eligibility criteria were satisfied. In this double-blind study, an Interactive Voice/Web Response System was used to randomize subjects in a 2:1 ratio to receive either ISIS 396443 or a sham procedure, respectively. Randomization was stratified based on disease duration (i.e., subject's age at screening minus age at symptom onset) of ≤12 weeks versus >12 weeks, with a randomization block size of 3. The randomization was performed globally, except that a separate randomization list was used in Japan. No separate randomization list was used for individual study sites. Subjects were not to begin treatment prior to randomization and assignment of a unique randomization number. If a subject did not successfully receive the first dose of ISIS 396443 or sham procedure, they were to be replaced" (CS3B CSR, p. 37).

- **Blinding:**

The applicant reports the following methods of blinding, in addition to those described in the sham procedure description above. These methods appear adequate. The primary endpoint of motor milestone achievement could potentially be influenced by unblinding in that an unblinded investigator might be biased toward reporting a higher milestone rating, especially in cases where a patient appeared borderline between two milestone categories.

"The Sponsor, parents of the subjects, and key study site personnel were blinded throughout the study. The evaluator (i.e., physical therapist) who performed efficacy evaluations was blinded to study treatment and was not involved in decisions about the subjects' ventilation. Clinicians who were making decisions regarding subjects' ventilation were blinded throughout the study, and did not have access to study treatment assignments or efficacy evaluation results. Study personnel involved in processing and analyzing study samples (e.g., blood, urine) were blinded to treatment assignment. To protect against unblinding when analyzing blood and CSF samples for drug concentrations and anti-ISIS 396443 antibodies, dummy identification numbers were assigned by vendors. There were both blinded and unblinded monitors in the study. Data collected during administration of ISIS 396443 and performance of the sham procedure were documented in an unblinded source packet that was kept separate and secured from all other source documents and was accessible only to unblinded study staff. Unblinded monitors verified all information in the unblinded source packets and transmitted a copy of the packet to unblinded personnel at Bioclinica. Only the unblinded personnel assigned to the study had access to the information. The unblinded personnel entered the data into unblinded electronic CRFs within the Electronic Data Capture (EDC) system for the study. No site staff had access to the unblinded electronic CRFs. The unblinded monitor verified all unblinded data entered into the ECD against the source packet filed on site. Unblinded datasets were only exported from the EDC and transferred to unblinded personnel by unblinded personnel at Bioclinica. Ionis Pharmaceuticals Data Management had to request the transfer and confirm that the receiver was unblinded before delivery occurred. All physical and electronic copies of unblinded data were protected. Electronic files were either password protected or located in a secure area with limited access and, if transferred between parties, was done in a secure manner such as by secure File Transfer Protocol or using some other method approved by each party's information technology department" (CS3B CSR, p. 38).

- **Dose modification, dose discontinuation**

"No adjustment of dose was to be permitted. If a concurrent illness prevented the dosing procedure from being performed safely, an adjustment in the dose schedule could have been permitted, but must have been approved by the Medical Monitor in advance. In general, each scheduled dose could have been delayed by up to 8 weeks" (CS3B CSR, p. 38).

This modification plan is acceptable. A dose delay beyond the drug half-life of 4-6 months could allow drug concentrations in the spinal cord tissue to drop below predicted therapeutic levels and might diminish efficacy.

- **Administrative structure:**

Investigators at 36 study centers worldwide received IRB/IEC approval to participate in this study, and 31 centers enrolled and treated subjects. Safety data were reviewed on an ongoing basis by the Sponsor's Medical Monitor and by an independent Data and Safety Monitoring Board (DSMB). The primary efficacy endpoint events of death or permanent ventilation were reviewed in a blinded fashion by the Endpoint Adjudication Committee (EAC). The Sponsor, in collaboration with (b) (4), identified the potential efficacy events and prepared case packets for adjudication. (CS3B CSR, p. 20)

- **Procedures and schedule:**

The following table from the applicant summarizes the schedule of study visits, screening periods, treatment periods, treatment withdrawal periods, and follow-up periods.

Figure 2: Study CS3B Schedule of Treatment and Efficacy Assessments. Source: Summary of Clinical Efficacy, p. 38.

	Screening	Treatment Phase						Follow-Up
		Loading Dose Period				Maintenance Dose Period		
		ISIS 396443: 12 mg IT						
		Sham procedure						
Day	-21 to -1	1	15	29	64	183	302	394
Dosing		+	+	+	+	+	+	
HINE	+				+	+	+	+
CHOP INTEND	+				+	+	+	+
Overall and event-free survival	←							→
Growth	+				+	+	+	+
CMAP	+				+	+	+	+

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; HINE = Hammersmith Infant Neurological Examination; IT = intrathecal.
Source: CSR CSB, Table 5

- **Dietary restrictions/instructions:**

As described in the inclusion criteria, study patients were required to be receiving adequate nutrition and hydration (with or without gastrostomy) at study entry with a body weight greater than or equal to the 3rd percentile for age using appropriate country-specific guidelines. Patients were excluded from the study if their caregivers were not willing to continue to meet standard of care guidelines for nutritional support. Recommended appropriate nutritional support included orally or via a feeding tube, hydration management, and medical or surgical gastroesophageal reflux disease management.

The dietary restrictions/instructions described above applied to both the treatment and sham-procedure arms of the study and seem reasonable.

- **Concurrent medications:**

Throughout the study, investigators or designated licensed physicians involved in the study were permitted to prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care (CS3B CSR, p. 39). Study subjects were prohibited from receiving other experimental agents during the study. This included marketed agents at experimental doses that were being tested for the treatment of SMA (e.g., valproate, riluzole, creatine, sodium phenylbutyrate, hydroxyurea, and salbutamol).

- **Treatment compliance:**

Treatment compliance was determined by having dedicated study personnel administer each dose of ISIS 396443 or perform each sham procedure in a dedicated room to ensure blinding. The time, date, and volume of each study treatment was recorded on the CRF.

- **Rescue medication:**

  There were no applicable rescue medications for this trial.

- **Subject completion, discontinuation, or withdrawal:**

  Subjects who terminated early from the study were encouraged to complete assessments per the Day 394 Visit. Subjects who were randomized but did not successfully receive the first dose of ISIS 396443 or undergo the first sham procedure were replaced.

  After completion of the Day 303 Visit, subjects entered the 3-month Post-treatment Follow-up Period. This period consisted of a study center visit on Study Day 394 and follow-up phone assessments on a weekly basis. If a subject had reached ≥16 hours/day of ventilation within the last 3 weeks prior to their Day 394 Visit, they were followed by phone contact until the primary endpoint was confirmed.

As a result of the decision by the study Sponsor to terminate the study earlier based on the assessment of risk-benefit of ISIS 396443, all subjects were invited to complete the End of Double Blind Period (EODBP) Visit, during which all Day 394 assessments were conducted. The EODBP visit occurred no less than 2 weeks from the most recently administered dosing or sham procedure. After completing the EODBP Visit, subjects enrolled in the study at that time were considered study completers.

Following treatment and the Day 394 follow-up evaluation, eligible subjects could elect to enroll in an open-label extension study without unblinding to the subject's treatment group. (CS3B CSR, p. 30-31)

Study treatment was to be permanently discontinued for any of the following reasons:

- The subject's parent/guardian withdrew consent.
- The subject experienced an AE that necessitated permanent discontinuation of study treatment.
- In the event of treatment discontinuation, the reason for discontinuation of study treatment was to be recorded in the Case Report Form (CRF) and source documentation. Subjects who discontinued treatment were to enter the Post-treatment Follow-up Period unless consent was withdrawn.

Subjects were to be withdrawn from the study for any of the following reasons:

- Withdrawal of consent.
- The subject or the subject's parents/guardians were unwilling or unable to comply with the protocol.
- The subject experienced a medical emergency that necessitated unblinding of the subject's treatment assignment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.
- Significant protocol deviation.
- Decision by the Investigator or Sponsor.

All information, including the reason for withdrawal from the study, was to be recorded in the CRF (CS3B CSR, pp. 34-35).

Reviewer Comment: The above criteria for completion, discontinuation, or withdrawal appear reasonable. "Decision by the investigator or Sponsor" is vague, but details of the reason for withdrawal would be included in the CRF.

Study Endpoints

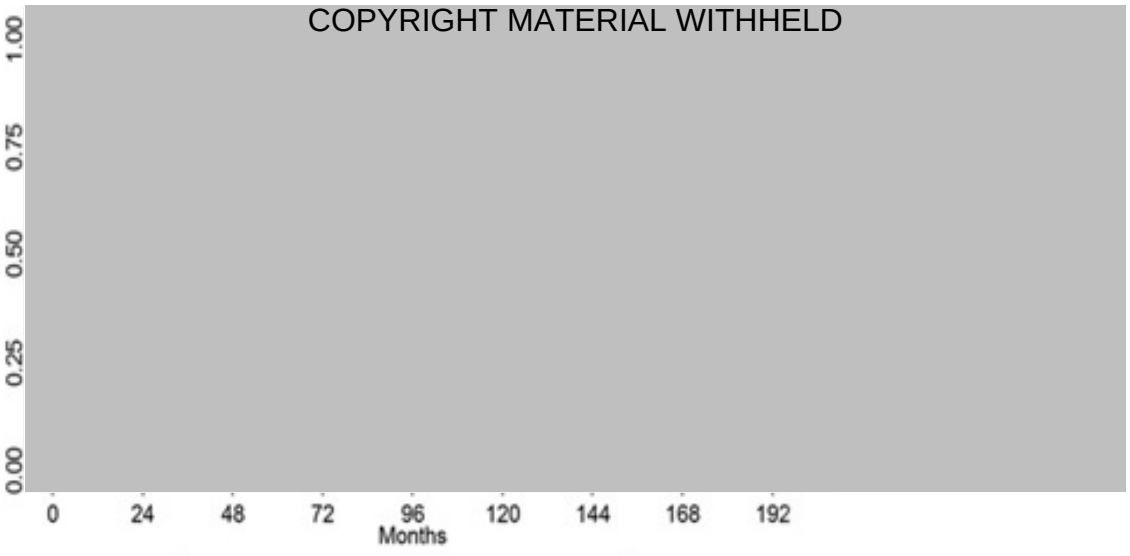
Primary Efficacy Endpoints

Primary efficacy endpoints of the study are as follows:

- Proportion of motor milestone responders (Section 2 of the Hammersmith Infant Neurological Examination [HINE])
- Time to death or permanent ventilation (≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event OR tracheostomy).

Reviewer Comment: Only the first primary efficacy endpoint, proportion of motor milestone responders, was tested statistically for the interim analysis of study CS3B, as described in the statistical analysis plan below. All other endpoints were descriptively reported. Survival as an endpoint is less interpretable because it can be strongly affected by the type and quality of respiratory support provided to SMA infants, as shown in the figure below comparing survival with no respiratory support, non-invasive ventilation, and invasive ventilation/tracheostomy (Gregoretti et al., 2013).

Figure 3: Kaplan-Meier survival curves in type 1 SMA infants as a function of type of respiratory support. Patients with Tracheostomy/Invasive Mechanical Ventilation (top, n=42); Non-invasive bilevel ventilation and mechanically assisted coughing (middle; n=31); Untreated (bottom, n=121). Source: Gregoretti et al., 2013



In the September 15 meeting with the applicant, the Agency responded that it appeared reasonable, based on the effect size suggested by the phase 2 study CS3A, to revise the phase 3 study (ISIS 396443-CS3B) to include an interim analysis based on function, not survival. Motor milestone development was chosen as the functional endpoint based on the known clinical course of type 1 SMA, in which there is progressive loss of motor milestones through the course of the disease. Patients with type 1 SMA never sit, stand, or walk. As discussed later in Section 6.2.1, there had also been a positive signal suggesting motor milestone improvement in the phase 2 open-label study, CS3A.

The HINE (scoring sheet shown in the figure below) evaluates the neuromuscular development of infants in 8 motor milestone categories (head control, sitting, grasping, ability to kick in supine position, rolling, crawling, standing and walking) with 3 to 5 progressively more difficult items for each milestone category, as shown in the figure below. Scoring proceeds from left to right, with 0 meaning inability to perform a task and 3 or 4 (depending on the task) meaning full milestone development. The HINE has been assessed in a retrospective multicentric study of 33 type I SMA infants (De Sanctis et al., 2016). The authors reported that "all [type 1 SMA] patients studied had a score of 0 out of a scale of 4 on items assessing sitting, rolling, crawling, standing or walking. A score of more than 0 was only achieved in three items: head control (n = 13), kicking (n = 15) and hand grasp (n = 18). In these items, the maximal score achieved was 1 out of a scale of 4, indicating only partial achievement of the milestone."

For study CS3B, motor milestone assessments were performed at Screening, Day 64 pre-dose, Day 183 pre-dose, Day 302 pre-dose, and Day 394.

A motor milestone responder was defined by the applicant as follows.
"The definition of a motor milestones responder is based on the motor milestones categories in Section 2 of the Hammersmith Infant Neurological Exam with the exclusion of voluntary grasp using assessment at the later of the Day 183, Day 302, or Day 394 study visits as follows:

> (i) subject demonstrates at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking, AND
> (ii) among the motor milestone categories with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening. Note: for the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least 1-point decrease" (CS3B documentation of statistical methods, pp. 21-22). "Voluntary grasp, a category in which none of the milestones require movement against gravity, was excluded from the analysis as some infants with SMA can acquire all milestones in this

category" (CS3B CSR, p. 86).

Reviewer Comment: Based on the above descriptions of the HINE and the progressive loss of motor milestones in type 1 SMA patients, the choice of motor milestone development as measured by the HINE is an acceptable primary endpoint for the interim analysis of study CS3B.

In order to assess the second primary endpoint of time to death or permanent ventilation, a subject's ventilator or BiPAP use (number of hours/day) was recorded daily by the caregivers using a daily ventilator use diary for the duration of the study. This information was obtained during study visits and weekly telephone contacts (CS3B CSR, p. 43).

Figure 4: Hammersmith Infant Neurological Examination Section 2 – Motor Milestones. Source: CS3B CSR, p. 44

Scoring:	**0**	**1**	**2**	**3**	**4**
Motor Milestone Category	**Milestone Level Progression [age expected in heathy infants*]** →				
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb; immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) (3 months)	Touches leg (4-5 months)	Touches toes (5-6 months)
Head control	Unable to maintain upright (<3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolling to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sit with support at hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) (10 months)
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4-5 months)	Crawling flat on abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4-5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) (11 months)	Walking independently (15 months)	

* Values for healthy infants in [Haataja 1999].

Secondary Efficacy Endpoints

Secondary efficacy endpoints of the study are as follows:

- 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.
- Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration.
- Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration.

CHOP INTEND

The applicant reports that "Evaluations using the CHOP INTEND motor function scale were performed by physical therapists at the study centers. These evaluations were scheduled at Screening (2 assessments, baseline assessment), Day 64 predose, Day 183 predose, Day 302 predose, and Day 394. The CHOP INTEND is a validated 16-item, 64-point motor assessment designed specifically to evaluate the motor skills of infants with symptomatic SMA and to accommodate their fragile nature and observed tolerance to item administration [Glanzman 2010]. The test was designed by an expert panel that was guided in item selection by the statistical characteristics of each item as well as by clinical judgment concerning the item's ability to quantify motor behavior in Type I SMA. The test captures neck, trunk, proximal, and distal limb strength in 14 elicited and 2 observational items and has been established as a safe, reliable, and clinically meaningful measure of motor function in infants with SMA" (CS3B CSR p. 44).

Reviewer Comment: The CHOP INTEND appears to be an acceptable neuromuscular evaluation for use as a secondary endpoint. See the CHOP INTEND scoring sheet in Appendix 13.3.

CMAP

The applicant states that compound muscle action potential (CMAP) "measurements of ulnar nerve function in the abductor digiti minimus muscle and peroneal nerve function in the anterior tibialis muscle were performed or supervised by a clinical electromyographer at the study center. Measurements were made at Screening (baseline assessment), Day 64 predose, Day 183 predose, Day 302 predose, and Day 394... CMAP is a well validated method for tracking disease progression in neuromuscular disorders such as SMA [Lewelt 2010; Swoboda 2005] and amyotrophic

lateral sclerosis [Shefner 2011] and has been proposed as a potential biomarker of a therapeutic effect in SMA" (CS3B CSR pp. 44-45).

Reviewer Comment: Review of the medical literature supports the use of CMAP to monitor disease progression in type 1 SMA patients. Swoboda et al. 2005 reported a rapid and sustained age-dependent decline in the CMAP amplitudes of SMA1 and SMA2 patients. CMAP may be more difficult to interpret in type 2 SMA because Kang et al. (2014) found a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in SMA2 patients, appearing to contradict the finding of Swoboda et al. 2005 for type 2 SMA patients.

Tertiary Efficacy Endpoints

The tertiary efficacy endpoints are as follows:

- Change from baseline in growth parameters (weight for age/length, chest circumference, head to chest circumference ratio, and arm circumference).
- Number of serious respiratory events.
- Number of hours of ventilation support.
- Number and length of hospitalizations.

Growth Parameters

Growth parameters were assessed by trained site staff at the study centers. The assessments were performed at Screening, Day 29 pre-dose, Day 64 pre-dose, Day 183 pre-dose, Day 302 pre-dose, and Day 394. Body length, head circumference, chest circumference, and arm circumference were measured. Ratios of weight-for-age, weight-for-length, and head-to-chest circumference were also calculated.

Reviewer Comment: The Secondary and Tertiary efficacy endpoints are acceptable. Their results are reported descriptively in Section 6.1.2.

Safety Endpoints

Safety endpoints are as follows:

- AEs, including SAEs
- Vital signs and weight
- Neurological examinations
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)

- Electrocardiograms
- Use of concomitant medications

Safety evaluations include the following parameters:

- Assessment of AEs and SAEs
- Vital signs: resting blood pressure, pulse, respiratory rate, temperature, and pulse oximetry awake.
- Neurological examinations: assessment of mental status, level of consciousness,
- sensory function, motor function, cranial nerve function, and reflexes.
- Physical examinations and weight

Clinical laboratory tests included (CS3B CSR, pp. 45-46):

- Serum chemistry: sodium, potassium, chloride, total protein, albumin, calcium, phosphorus, glucose, blood urea nitrogen, creatinine, cystatin C, total serum bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine phosphokinase
- Hematology: red blood cells (RBCs), hemoglobin, hematocrit, platelets, white blood cells (WBCs), and WBC differential (% and absolute neutrophils, lymphocytes, eosinophils, basophils, and monocytes)
- Coagulation: aPTT, PT, and INR
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, blood, RBCs, WBCs, epithelial cell, bacteria, casts, and crystals
- Immunogenicity evaluation: ISIS 396443 plasma antibodies
- Electrocardiograms (ECGs)
- Assessment of concomitant medications and concomitant procedures

Reviewer Comment: See the separate clinical safety review for discussion of the adequacy of the safety endpoints.

Figure 5: Schedule of procedures including safety monitoring. Source: CS3B CSR pp. 41-42

* The study center will monitor the subject's condition through telephone contact on a weekly basis[12] (excluding weeks in which there is a study visit) throughout the duration of the study

Study Period	Screen[1]	Treatment/Follow-up															
Study Day	D -21 to D -1	D1			D2	D15 (±1D)			D16	D29 (±1D)			D30	D64, D183 and D302 (±7D)			D65, D184, and D303	D394[15] (±7D) and early term
		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP /SP	Post-dose		
Study Drug Injection/Sham Procedure[10]			X				X[9]				X[9]				X[9]			
In-Patient Stay (24 hours)				X														
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical History	X																	
Vital Signs[2]	X	X		4X[3]	X[5]	X		4X[3]	X	X		4X[3]	X	X		4X[3]	X	X
Weight	X	X			X	X			X	X			X	X			X	X
Growth Parameters[4]	X									X				X[14]				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
Neurological Examination	X	X		2X[6]	X[5]	X		2X[6]	X	X		2X[6]	X	X		2X[6]	X	X
ECG	X				X							X						X
Safety Labs[7]	X													X[14]				X
Coagulation Labs	X																	
Immunogenicity		X												X[14]				X
CSF PK[11]		X				X				X				X				
Plasma PK[11]		X		3X	X					X		X		X[14]				
CHOP INTEND	X[8, 13]													X[14]				X
Motor Milestones	X[8]													X[14]				X

Study Period	Screen[1]	Treatment/Follow-up																
Study Day	D -21 to D -1	D1			D2	D15 (±1D)			D16	D29 (±1D)			D30	D64, D183 and D302 (±7D)			D65, D184, and D303	D394[15] (±7D) and early term
		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP/ SP	Post-dose		Pre-dose	LP /SP	Post-dose		
CMAP	X[8]													X[14]				X
Con Med Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CHOP INTEND = Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; CMAP = compound muscle action potential; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; LP = lumbar puncture; PK = pharmacokinetics

1 For those subjects who do not have documented evidence of *SMN2* copy number, this must be obtained during the Screening Period. For those subjects who have documented evidence of *SMN2* copy number of 2 but do not have testing results from the central diagnostic laboratory, this may be obtained during the Screening Period or the Treatment Period.
2 Resting blood pressure, pulse, respiratory rate, temperature, and pulse oximetry awake. Pulse oximetry asleep will also be assessed at Screening only.
3 Vital signs performed 1, 2, 4, and 6 hours after dosing.
4 Length, weight for age/length, head circumference, chest circumference, head to chest circumference ratio, and arm circumference.
5 Conducted within 20 to 24 hours after dosing.
6 Neurological exams at 3 and 6 hours after dosing.
7 Serum chemistry, hematology, and urinalysis panels (see Appendix B of the protocol for analytes). Safety laboratories not performed at Study Day 302.
8 CHOP-INTEND, CMAP, and Motor Milestone assessments do not form part of the screening assessment or inclusion/exclusion criteria but are baseline measurements taken during the screening phase of the study.
9 Overnight stay is optional on Day 15, Day 29, Day 64, Day 183, and Day 302 if needed.
10 Injections may not occur within 72 hours after an immunization.
11 Refer to Table 6 for PK sampling schedule.
12 At telephone contact, changes in concomitant medications and adverse events will be recorded as well as daily ventilator/Bi-PAP use and health status.
13 CHOP-INTEND will be performed 2 times during the Screening/Baseline Period (baseline assessment).
14 These assessments may be performed up to 7 days prior to dosing, if necessary.
15 If a subject has reached ≥16 hours/day ventilation within the last 3 weeks prior to their Day 394 Visit, they will continue to be followed by phone contact until the outcome of the primary endpoint is confirmed.

Pharmacokinetic Endpoints

The PK endpoints are as follows:

- CSF levels of ISIS 396443
- Plasma levels of ISIS 396443

Figure 6: Pharmacokinetic sampling schedule. Source: CS3B CSR p. 43

Treatment Period	Study Day	Timepoints	Blood Collection	CSF Collection
Multiple Dose: LP Injection	D1	Predose	0.35 mL	0.5 mL
		1 hr	0.35 mL	NA
		2 hr	0.35 mL	NA
		4 hr	0.35 mL	NA
	D2	20 to 24 hr	0.35 mL	NA
	D15	Predose	NA	0.5 mL
	D29	Predose	0.35 mL	0.5 mL
		4 hr	0.35 mL	NA
	D64	Predose	0.35 mL	0.5 mL
	D183	Predose	0.35 mL	0.5 mL
	D302	Predose	0.35 mL	0.5 mL

CSF = cerebrospinal fluid; hr = hour; LP = lumbar puncture; mRNA = messenger ribonucleic acid; miRNA = micro ribonucleic acid; NA = Not applicable (No collection scheduled); PK = pharmacokinetic; SMA = spinal muscular atrophy.
Details on sampling, preparation, and shipment are included in the study laboratory manual.
Any of the collected PK plasma and CSF samples from the study subjects may also be used for investigation of possible biomarkers of SMA disease or the pharmacodynamic effects of ISIS 396443 (e.g., CSF mRNA, CSF protein, CSF miRNA panel) or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or to assess other actions of ISIS 396443 with plasma and CSF constituents.

Immunogenicity Endpoint

- The immunogenicity endpoint is the incidence and titer of plasma antibodies to nusinersen. (CS3B CSR, pp. 28-29; Statistical methods, p. 13).

Statistical Analysis Plan

Reviewer Comment: Please refer to the statistical review for detailed evaluation of the applicant's planned statistical analysis. The null hypothesis for the primary endpoint is that there is no difference in the proportion of responders between nusinersen and the sham-procedure groups. Only the interim analysis was conducted because the study was subsequently stopped due to the positive results of the interim analysis. Note that the statistical plan for the interim analysis was made in consultation with the Agency. For the interim analysis there was no adjustment for multiplicity because only the primary endpoint was analyzed statistically. All other endpoints were reported descriptively.

An interim efficacy analysis took place with a targeted clinical cut-off date of June 15, 2016. The study was then terminated on the grounds that conducting a sham-controlled study was no longer deemed ethical or feasible given the positive results of the interim analysis. At the interim analysis, the first primary efficacy endpoint, proportion of motor milestones responders, was tested at an alpha of 0.035 using Logistic regression (Fisher's exact test in the situation of less than 5 responders in either group) of the ITT/(Interim) Efficacy population. If the first primary endpoint of motor milestones was statistically significant at the interim analysis, then the second primary endpoint and all secondary endpoints were to be descriptively reported. No formal statistical comparison would be performed and no p-values would be calculated for statistical inference for those endpoints.

The applicant had the following statistical analysis plan in the event that the primary efficacy endpoint, proportion of motor milestone responders, was not significant at the interim analysis.

"In this case, at the final analysis, the primary efficacy endpoint, proportion of motor milestones responders will be tested at an alpha of 0.03. If the proportion of motor milestones responders is not significant at the final analysis, then the testing of the secondary primary, time to death or permanent ventilation, and all secondary endpoints will be considered exploratory. If the proportion of subjects who achieve improvement in motor milestones is significant at the final analysis, then the second primary endpoint and all secondary endpoints will be tested using the following strategy:

- The second primary efficacy endpoint, time to death or permanent ventilation, will be tested at an alpha of 0.05. If it is significant, proceed to the next step; otherwise all subsequent tests are considered exploratory.

  The proportion of CHOP INTEND responders will be tested at an alpha of 0.05. If it is significant, proceed to the next step; otherwise all subsequent tests are considered exploratory.
- Test time to death at an alpha of 0.05. If it is significant, proceed to the next step; otherwise all subsequent tests are considered exploratory.

• Test percentage of subjects not requiring permanent ventilation at an alpha of 0.05. If it is significant, proceed to the next step; otherwise all subsequent tests are considered exploratory.
• Test proportion of CMAP responders at an alpha of 0.05.
• Test time to death or permanent ventilation in subgroup of subjects with disease duration at Screening below or at study median at an alpha of 0.05. If it is significant, proceed to the next step; otherwise all subsequent tests are considered exploratory.
• Test time to death or permanent ventilation in subgroup of subjects with disease duration at Screening above study median at an alpha of 0.05. If it is significant, proceed to the next step; otherwise the subsequent test is considered exploratory.

Subjects who die or withdraw from the study will be counted as non-responders and will be included in the denominator for the calculation of the proportion. As a result, mortality will be accounted for in the motor milestone analysis" (Statistical Methods, pp. 21, 44).

Populations for the analyses
"The Intent-to-treat (ITT) Set, (Interim) Efficacy Set, and the Per-protocol Set (PPS) will be used for efficacy analyses. The ITT Set is defined as all subjects who are randomized and receive at least one dose of study drug/sham procedure. Subjects will be analyzed in the treatment group to which they were randomized. This will be the primary population for the analysis of time-to event (e.g., time to death or permanent ventilation) endpoints.

For the interim analysis of functional endpoints such as motor milestones, the Interim Efficacy Set will be used. The Interim Efficacy Set is defined as the subset of subjects in the ITT Set who have the opportunity to be assessed at the Day 183 visit. Specifically, the Interim Efficacy Set will include all subjects with Day 183, Day 302, or Day 394 visit and all subjects with time difference of at least 190 days (183 plus 7 day window) between date of first dose and the targeted clinical cut-off date of June 15, 2016 for the interim analysis (i.e., dosed on or before December 09, 2015). However, a subject who has died or withdrawn will be included provided that there is a time difference of at least 176 days (183 minus 7 day window) between the date of first dose and the targeted clinical cut-off date of June 15, 2016 for the interim analysis (i.e., dosed on or before December 23, 2015)" (Statistical Methods, p. 14).

Pre-specified methods of handling missing data
"Missing data will be imputed on an individual motor milestone level. If a motor milestone is missing at screening, then the missing value will be imputed as the median of the non-missing values of the stratum to which the subject belongs to: age at symptom onset (≤12 weeks, >12 weeks) by disease duration (≤12 weeks, >12 weeks).

Specifically, the four strata are:

- Age at symptom onset ≤12 weeks and disease duration ≤12 weeks
- Age at symptom onset ≤12 weeks and disease duration >12 weeks
- Age at symptom onset >12 weeks and disease duration ≤12 weeks
- Age at symptom onset >12 weeks and disease duration >12 weeks

In the event of no observed data for imputation, disease duration will be used as the classification factor for the purpose of identifying non-missing data for imputation. If for the subject with missing motor milestones at a particular visit, the corresponding visit is flanked by visits with non-missing Motor Milestones, the missing value for those motor milestones will be imputed using linear interpolation with the result rounded to the nearest integer score. Otherwise, if the missing visit is the last visit, missing motor milestone value will be imputed as the lowest value in the stratum (age at symptom onset by disease duration) to which the subject belongs within the same treatment group at the same visit only in the two situations below:

1. Only a subset of motor milestones was assessed during the visit.
2. The subject is in the (interim) efficacy set, but the subject has neither died nor withdrawn from the study with no assessment at Day 183, Day 302, or Day 394. In this case, only the Day 183 assessment will be imputed.

In the event of no observed data for imputation, disease duration by treatment will be used as the classification factor for the purpose of identifying non-missing data for imputation. Of note, only observed data will be utilized for imputation purposes. Missing motor milestone items will be imputed first prior to any analysis" (Statistical methods, p. 21).

Subgroup Analysis

"The main analyses of time to death or permanent ventilation, motor milestones, CHOP INTEND, and overall survival results will be presented for the following subgroups:

- age at symptom onset (<=12 weeks, >12 weeks)
- disease duration at Screening (<=12 weeks, >12 weeks)
- geographic region (North America, Europe, Asia-Pacific). Region is based not only on considerations of geography but also on the type of health care system and access to health care in each country" (Statistical Methods, p. 42)

Protocol Amendments

The protocol and statistical plan were amended for the interim analysis, which changed the primary endpoint, as discussed above in Section 6.1.1, Primary Efficacy Endpoints and Statistical Analysis Plan. See Appendix 13.4 for a table of all protocol amendments.

Data Quality and Integrity: Sponsor's Assurance

The applicant reports the following methods for assuring data quality and integrity, which appear adequate.

"To ensure the quality of clinical data, a clinical data management review was performed on the subject data received by the Sponsor, Ionis Pharmaceuticals. During this review, subject data was checked for consistency, omissions, and any apparent discrepancies. In addition, the data was reviewed for adherence to the protocol and GCP... During the course of the study, Clinical Research Associates visited each study center at regular intervals. All monitoring visits were conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the study center and its facilities. During these visits, data were source verified... As part of the Sponsor's quality assurance program, as of 15 August 2016, 3 study centers and 1 central laboratory facility were audited for compliance with GCP... Protocol deviations identified during site monitoring were captured in a protocol deviation log and categorized as major or minor deviations. These deviations were listed and major protocol deviations were summarized for both the ITT and Interim Efficacy sets" (CS3B CSR, pp. 50, 52).

6.1.2. CS3B Study Results

Compliance with Good Clinical Practices

All clinical studies were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and local requirements, and in consideration of applicable regulatory guidance. (Clinical Overview, p. 8)

Financial Disclosure

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Twenty-three sub-investigators for the main efficacy study, CS3B, had missing financial disclosure forms. This lack of disclosure does not raise serious questions about the integrity of the data because the study design minimizes bias through randomization and blinding.

Patient Disposition

Patient disposition is described in the following table, copied from the applicant.
Note that 29% of control group patients discontinued treatment due to the "adverse event" of death, compared to 15% of the nusinersen group.

Table 4: Patient Disposition. Source: CS3B CSR, p. 63

	Control	ISIS 396443	Total
Number of subjects screened			149
Number of screen failures			27
Number of subjects randomized	41	81	122
Number of subjects who withdrew prior to dosing	0	1	1
Number of subjects dosed (ITT set)	41 (100)	80 (100)	121 (100)
Number of subjects who completed the study	7 (17)	15 (19)	22 (18)
Number of subjects who discontinued treatment	12 (29)	13 (16)	25 (21)
Adverse Event	12 (29)	12 (15)	24 (20)
Voluntary Withdrawal	0	1 (1)	1 (<1)
Ineligibility	0	0	0
Investigator Judgment	0	0	0
Not Reported	0	0	0
Other	0	0	0
Protocol Deviation	0	0	0

	Control	ISIS 396443	Total
Number of subjects who withdrew from study	13 (32)	13 (16)	26 (21)
Adverse Event	12 (29)	12 (15)	24 (20)
Voluntary Withdrawal	1 (2)	1 (1)	2 (2)
Ineligibility	0	0	0
Investigator Judgment	0	0	0
Not Reported	0	0	0
Other	0	0	0
Protocol Deviation	0	0	0

NOTE: Numbers in parentheses are percentages.
NOTE: All adverse events leading to treatment discontinuation or study withdrawal were deaths.

Protocol Violations/Deviations

A summary of major protocol deviations is in the following table, copied from the applicant. Note that the same proportion (15%) of control and nusinersen subjects had major protocol deviations. The "other" category consisted of miscalculations of disease duration by the study sites. The applicant reports that these errors did not affect its statistical analyses because analyses using disease duration were made using actual dates of symptom onset and not study

site calculations. The "enrollment criteria" deviation was from a patient who was born 1 week earlier (36 weeks gestation) than permitted in the enrollment criteria (37 to 42 weeks).

Reviewer Comment: These deviations do not appear likely to have significantly affected the study results.

Table 5: Summary of Major Protocol Deviations - ITT Set. Source: CS3B CSR, p. 263

	Control	ISIS 396443	Total
Number of subjects	41 (100)	80 (100)	121 (100)
Number with at least one major deviation	6 (15)	12 (15)	18 (15)
ENROLLMENT CRITERIA	0	1 (1)	1 (<1)
OTHER	6 (15)	9 (11)	15 (12)
VISIT PROCEDURE	0	1 (1)	1 (<1)
VISIT SCHEDULE	0	1 (1)	1 (<1)

Table of Demographic Characteristics

Study patient demographics are described in the following table, copied from the applicant. *Overall, there appears to be an acceptable balance of demographic characteristics between the control and treatment groups which adequately represents the demographics of the intended patient population.*

Table 6: Demography at Screening - ITT Set. Source: CS3B CSR, p. 67

	Control	ISIS 396443	Total
Number of subjects	41	80	121
Age at screening (days)			
<30 days (less than 1 month)	1 (2)	0	1 (<1)
>=30 days to <90 days (1 to 3 months)	3 (7)	10 (13)	13 (11)
>=90 days to <180 days (3 to 6 months)	15 (37)	47 (59)	62 (51)
>=180 days (6 months or older)	22 (54)	23 (29)	45 (37)
Age at screening (days)	41	80	121
Mean	164.7	147.2	153.1
SD	48.54	46.85	47.95
Median	190.0	151.5	166.0
25^{th},75^{th} percentiles	131.00, 201.00	111.50, 190.00	112.00, 199.00
Min, Max	20, 211	32, 210	20, 211
Age at first dose (days)			
<30 days (less than 1 month)	0	0	0
>=30 days to <90 days (1 to 3 months)	2 (5)	6 (8)	8 (7)
>=90 days to <180 days (3 to 6 months)	14 (34)	43 (54)	57 (47)
>=180 days (6 months or older)	25 (61)	31 (39)	56 (46)

	Control	ISIS 396443	Total
Age at first dose (days)			
n	41	80	121
Mean	180.5	163.4	169.2
SD	50.92	49.57	50.48
Median	205.0	164.5	175.0
25^{th},75^{th} percentiles	143.00, 215.00	118.00, 208.50	132.00, 213.00
Min, Max	30, 262	52, 242	30, 262
Sex			
n	41	80	121
Male	17 (41)	37 (46)	54 (45)
Female	24 (59)	43 (54)	67 (55)
Ethnicity			
n	41	80	121
Hispanic or Latino	4 (10)	12 (15)	16 (13)
Not Hispanic or Latino	37 (90)	68 (85)	105 (87)
Race			
n	41	80	121
American Indian or Alaska Native	0	0	0
Asian	1 (2)	5 (6)	6 (5)
Black	0	3 (4)	3 (2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	36 (88)	68 (85)	104 (86)
Multiple	2 (5)	1 (1)	3 (2)
Other	1 (2)	3 (4)	4 (3)
Not Reported	1 (2)	0	1 (<1)

	Control	ISIS 396443	Total
Geographic Region			
North America	22 (54)	38 (48)	60 (50)
Europe	17 (41)	30 (38)	47 (39)
Asia-Pacific	2 (5)	12 (15)	14 (12)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline clinical characteristics of study patients are described in the following table copied from the applicant. At baseline, subjects in the ISIS 396443 treatment group had a younger age of SMA symptom onset than the sham-procedure control group (median of 6.5 weeks vs. 8 weeks) and required more ventilatory support (26% vs. 15%). A greater percentage of infants in the ISIS 396443 group had a history of paradoxical breathing (ISIS 396443 vs. control: 89% vs. 66%), pneumonia or respiratory symptoms (35% vs. 22%), and swallowing or feeding difficulties (51% vs. 29%). (CS3B CSR, p. 65)

Reviewer Comment: The relatively more severe baseline SMA-related symptoms in the infants of the nusinersen group could potentially predispose them to more complications as the disease progresses which would have made it more difficult to show a benefit from nusinersen.

Table 7: SMA History - ITT Set. Source: CS3B CSR, p. 70

Parameter Statistics	Control	ISIS 396443	Total
Number of subjects	41	80	121
Gestational age (weeks)			
n	41	80	121
Mean	39.3	38.9	39.0
SD	1.33	1.30	1.32
Median	40.0	39.0	39.0
25^{th},75^{th} percentiles	38.00, 40.00	38.00, 40.00	38.00, 40.00
Min, Max	37, 42	36, 41	36, 42
Birth weight (kg)			
n	41	80	121
Mean	3.480	3.281	3.349
SD	0.7411	0.4413	0.5659
Median	3.380	3.273	3.300
25^{th},75^{th} percentiles	2.9500, 3.8800	2.9350, 3.5350	2.9400, 3.6290
Min, Max	2.13, 6.13	2.41, 4.74	2.13, 6.13
Age at symptom onset (weeks)			
<= 12 weeks	32 (78)	72 (90)	104 (86)
> 12 weeks	9 (22)	8 (10)	17 (14)
n	41	80	121
Mean	9.6	7.9	8.4
SD	4.66	3.95	4.27
Median	8.0	6.5	8.0
25^{th},75^{th} percentiles	6.00, 12.00	4.50, 11.00	5.00, 12.00
Min, Max	1, 20	2, 18	1, 20

NOTE: Numbers in parentheses are percentages.
NOTE: SMN2 gene copy number is based on the central lab testing. For the subject with 3 copies based on the central lab result, at screening the copy number is 2 based on the local lab result. For all subjects with missing central lab results, the copy number is 2 based on the local lab results at the time of the screening.

Parameter Statistics	Control	ISIS 396443	Total
Disease duration (weeks)			
<= 12 weeks	18 (44)	34 (43)	52 (43)
> 12 weeks	23 (56)	46 (58)	69 (57)
n	41	80	121
Mean	13.920	13.205	13.447
SD	5.6578	5.4579	5.5133
Median	12.714	13.143	13.143
25^{th},75^{th} percentiles	10.1429, 18.4286	8.9286, 17.7143	9.4286, 17.8571
Min, Max	0.00, 23.14	0.00, 25.86	0.00, 25.86
Age SMA diagnosed (weeks)			
n	41	80	121
Mean	17.5	12.6	14.2
SD	7.47	6.63	7.28
Median	20.0	11.0	12.0
25^{th},75^{th} percentiles	12.00, 22.00	8.00, 18.00	8.00, 20.00
Min, Max	2, 30	0, 29	0, 30

Parameter Statistics	Control	ISIS 396443	Total
Number of subjects who experienced			
Hypotonia	41 (100)	80 (100)	121 (100)
Developmental motor delay	39 (95)	71 (89)	110 (91)
Paradoxical breathing	27 (66)	71 (89)	98 (81)
Pneumonia or respiratory symptoms	9 (22)	28 (35)	37 (31)
Limb weakness	41 (100)	79 (99)	120 (99)
Swallowing or feeding difficulties	12 (29)	41 (51)	53 (44)
Other	14 (34)	20 (25)	34 (28)
SMN2 gene			
2 copies	40 (98)	78 (98)	118 (98)
Other than 2 copies	1 (2)	0	1 (<1)
Unknown	0	2 (3)	2 (2)

Baseline characteristics of motor milestone achievement, used for the primary endpoint of the efficacy evaluation, are described in the following table. *The control and nusinersen groups appear to be adequately balanced.*

Table 8: Motor milestones at baseline. Source: CS3B CSR p. 191

Parameter Category	Control	ISIS 396443	Total
Number of subjects	27	51	78
Head control			
n	27 (100)	51 (100)	78 (100)
Unable to maintain head upright	22 (81)	41 (80)	63 (81)
Wobbles	4 (15)	10 (20)	14 (18)
All the time maintained upright	1 (4)	0	1 (1)
Sitting			
n	27 (100)	51 (100)	78 (100)
Cannot sit	27 (100)	48 (94)	75 (96)
Sits with support at hips	0	2 (4)	2 (3)
Props	0	1 (2)	1 (1)
Stable sit	0	0	0
Pivots (rotates)	0	0	0
Voluntary grasp			
n	27 (100)	51 (100)	78 (100)
No grasp	7 (26)	16 (31)	23 (29)
Uses whole hand	18 (67)	31 (61)	49 (63)
Index figure and thumb but immature grasp	1 (4)	3 (6)	4 (5)
Pincer grasp	1 (4)	1 (2)	2 (3)

NOTE: Numbers in parentheses are percentages.

Parameter Category	Control	ISIS 396443	Total
Ability to kick			
n	27 (100)	51 (100)	78 (100)
No kicking	21 (78)	35 (69)	56 (72)
Kick horizontally, legs do not lift	5 (19)	15 (29)	20 (26)
Upward (vertically)	0	1 (2)	1 (1)
Touches leg	1 (4)	0	1 (1)
Touches toes	0	0	0
Rolling			
n	27 (100)	51 (100)	78 (100)
No rolling	23 (85)	50 (98)	73 (94)
Rolling to side	4 (15)	1 (2)	5 (6)
Prone to supine	0	0	0
Supine to prone	0	0	0
Crawling			
n	27 (100)	51 (100)	78 (100)
Does not lift head	27 (100)	51 (100)	78 (100)
On elbow	0	0	0
On outstretched hand	0	0	0
Crawling flat on abdomen	0	0	0
Crawling on hands and knees	0	0	0
Standing			
n	27 (100)	51 (100)	78 (100)
Does not support weight	27 (100)	51 (100)	78 (100)
Supports weight	0	0	0
Stands with support	0	0	0
Stands unaided	0	0	0

Parameter Category	Control	ISIS 396443	Total
Walking			
n	27 (100)	51 (100)	78 (100)
No walking	27 (100)	51 (100)	78 (100)
Bouncing	0	0	0
Cruising (walks holding on)	0	0	0
Walking independently	0	0	0

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There are no documented differences in treatment compliance between the treatment and control groups.

The most commonly used concomitant medications are listed in the following table, copied from the applicant. A smaller percentage of subjects treated with ISIS 396443 were administered the H2 blocker ranitidine (28% vs. 39%). A greater percentage of subjects receiving ISIS 396443 received amoxicillin with clavulanate potassium and azithromycin (13% vs. 7%), while a smaller percentage of these subjects received nystatin (15% vs. 20%) and vancomycin (4% vs. 20%). *The reported medication differences do not appear to have the potential to affect the trial efficacy analyses.*

Table 9: Concomitant Medication Taken by 5% or More of Subjects – Safety Set. CS3B CSR, p. 79

Preferred Term	Control	ISIS 396443	Total
Number of subjects dosed	41 (100)	80 (100)	121 (100)
Number of subjects taking any concomitant medication	41 (100)	80 (100)	121 (100)
PARACETAMOL	31 (76)	57 (71)	88 (73)
POVIDONE-IODINE	27 (66)	53 (66)	80 (66)
EMLA /00675501/	31 (76)	41 (51)	72 (60)
SALBUTAMOL	21 (51)	42 (53)	63 (52)
PNEUMOCOCCAL VACCINE	14 (34)	41 (51)	55 (45)
SODIUM CHLORIDE	17 (41)	38 (48)	55 (45)
IBUPROFEN	21 (51)	30 (38)	51 (42)
PALIVIZUMAB	15 (37)	35 (44)	50 (41)
LIDOCAINE	14 (34)	33 (41)	47 (39)
AMOXICILLIN	13 (32)	27 (34)	40 (33)
INFLUENZA VACCINE	12 (29)	28 (35)	40 (33)
RANITIDINE	16 (39)	22 (28)	38 (31)
OXYGEN	15 (37)	19 (24)	34 (28)
CEFTRIAXONE	10 (24)	21 (26)	31 (26)
HAEMOPHILUS INFLUENZA TYPE B VACCINE	11 (27)	20 (25)	31 (26)
CHLORHEXIDINE	10 (24)	20 (25)	30 (25)
MORPHINE	14 (34)	14 (18)	28 (23)
VACCIN IPAD D.T.C.	10 (24)	18 (23)	28 (23)
FENTANYL	11 (27)	16 (20)	27 (22)
MIDAZOLAM	11 (27)	16 (20)	27 (22)
MACROGOL	12 (29)	14 (18)	26 (21)
SUCROSE	3 (7)	23 (29)	26 (21)
AUGMENTIN	7 (17)	18 (23)	25 (21)

Preferred Term	Control	ISIS 396443	Total
DEXTROSE AND SODIUM CHLORIDE INJECTION	9 (22)	15 (19)	24 (20)
GLYCEROL	9 (22)	15 (19)	24 (20)
HEPATITIS B VACCINE	6 (15)	18 (23)	24 (20)
ROTAVIRUS VACCINE	5 (12)	19 (24)	24 (20)
MEASLES MUMPS & RUBELLA LIVE ATTENUATED (FREE	5 (12)	16 (20)	21 (17)
CLINDAMYCIN	7 (17)	13 (16)	20 (17)
COLECALCIFEROL	7 (17)	13 (16)	20 (17)
NYSTATIN	8 (20)	12 (15)	20 (17)
VARICELLA ZOSTER VACCINE	7 (17)	12 (15)	19 (16)
VITAMIN D NOS	7 (17)	12 (15)	19 (16)
PIP/TAZO	5 (12)	13 (16)	18 (15)
BUDESONIDE	5 (12)	12 (15)	17 (14)
CEFAZOLIN	6 (15)	10 (13)	16 (13)
GLYCOPYRRONIUM	4 (10)	12 (15)	16 (13)
OSMOTAN	6 (15)	10 (13)	16 (13)
PROPOFOL	7 (17)	9 (11)	16 (13)
CETIRIZINE	5 (12)	10 (13)	15 (12)
INFANRIX IPV+HIB	2 (5)	12 (15)	14 (12)
POLIO VACCINE	5 (12)	9 (11)	14 (12)
ROCURONIUM	7 (17)	7 (9)	14 (12)
AMOXICILLIN W/CLAVULANATE POTASSIUM	3 (7)	10 (13)	13 (11)
ATROPINE	6 (15)	7 (9)	13 (11)
AZITHROMYCIN	3 (7)	10 (13)	13 (11)
CIPROFLOXACIN	4 (10)	9 (11)	13 (11)
DEXMEDETOMIDINE	6 (15)	7 (9)	13 (11)
DORNASE ALFA	2 (5)	11 (14)	13 (11)
ACETYLCYSTEINE	3 (7)	9 (11)	12 (10)
FAMOTIDINE	6 (15)	6 (8)	12 (10)
HEPATITIS A VACCINE	2 (5)	10 (13)	12 (10)

Preferred Term	Control		ISIS 396443		Total	
HYDROCORTISONE	5	(12)	7	(9)	12	(10)
IPRATROPIUM	3	(7)	9	(11)	12	(10)
LANSOPRAZOLE	4	(10)	8	(10)	12	(10)
POTASSIUM	6	(15)	6	(8)	12	(10)
ERYTHROMYCIN	4	(10)	7	(9)	11	(9)
FUROSEMIDE	4	(10)	7	(9)	11	(9)
VANCOMYCIN	8	(20)	3	(4)	11	(9)
HIBISOL	2	(5)	8	(10)	10	(8)
LORAZEPAM	2	(5)	8	(10)	10	(8)
NITROUS OXIDE	3	(7)	7	(9)	10	(8)
OMEPRAZOLE	3	(7)	7	(9)	10	(8)
PREDNISOLONE	3	(7)	7	(9)	10	(8)
DOCUSATE	5	(12)	4	(5)	9	(7)
GLUCOSE	4	(10)	5	(6)	9	(7)
INFANRIX HEXA	1	(2)	8	(10)	9	(7)
LACTULOSE	3	(7)	6	(8)	9	(7)
MULTIVITAMINS	2	(5)	7	(9)	9	(7)
SIMETICONE	4	(10)	5	(6)	9	(7)
BACITRACIN	5	(12)	3	(4)	8	(7)
BACTRIM	3	(7)	5	(6)	8	(7)
CEFDINIR	2	(5)	6	(8)	8	(7)
ESOMEPRAZOLE	3	(7)	5	(6)	8	(7)
FLEBOBAG RING LACT	4	(10)	4	(5)	8	(7)
KETAMINE	4	(10)	4	(5)	8	(7)
MUPIROCIN	4	(10)	4	(5)	8	(7)
PEDIARIX	3	(7)	5	(6)	8	(7)
SPEKTRAMOX	1	(2)	7	(9)	8	(7)
UNACID /00917901/	3	(7)	5	(6)	8	(7)
BARIUM	2	(5)	5	(6)	7	(6)
BISEPTINE /01186301/	2	(5)	5	(6)	7	(6)

Preferred Term	Control		ISIS 396443		Total	
CLAVULANIC ACID	6	(15)	1	(1)	7	(6)
DEXAMETHASONE	4	(10)	3	(4)	7	(6)
EPINEPHRINE	3	(7)	4	(5)	7	(6)
HEPARIN	3	(7)	4	(5)	7	(6)
IMMUNOGLOBULIN ANTI RESPIRATORY SYNCYTIAL VIR	2	(5)	5	(6)	7	(6)
PANTOPRAZOLE	1	(2)	6	(8)	7	(6)
SALINE /01783401/	3	(7)	4	(5)	7	(6)
TOBRAMYCIN	2	(5)	5	(6)	7	(6)

Efficacy Results – Primary Endpoint

The table below shows the applicant's report of the results of analysis of the primary endpoint, the proportion of motor milestone responders assessed by Section 2 of the Hammersmith Infant Neurological Examination. A statistically significantly greater proportion of subjects achieved a motor milestone response in the ISIS 396443 group (21/51; 41%) compared to the sham control group (0/27; 0%) ($p<0.0001$). During consultation with the Agency to develop the statistical analysis plan for the interim analysis, the Agency recommended expanding the set of subjects to be analyzed to include all infants who died and all who were withdrawn, resulting in 52 ISIS 396443-treated subjects being compared with 30 control subjects. The applicant reports that the motor milestone response was 40% of the ISIS 396443 group and 0% of the control group, $p<0.0001$. This result was confirmed by the FDA biostatistician, with a motor milestone response of 20/52=40.4% for nusinersen and 0/30 (0%) for the sham group, $p<0.0001$. Using a stricter definition of motor milestone responder, requiring at least a 2-point increase in total motor milestone score in order to be classified as a responder, the applicant reported response rates of 37% and 0% in the ISIS 396443 and control groups, respectively, $p<0.0001$.

Note that in the ISIS 396443 group, 9 subjects (18%) achieved full head control, 5 subjects (10%) achieved independent sitting, and 1 subject (2%) achieved standing with support. No subjects in the control group achieved any of these milestones.

Reviewer Comment: There is agreement between the applicant and the FDA (analysis of the biostatistician, see separate statistical review) that the primary efficacy endpoint result of a higher percentage of motor milestone responders in the nusinersen group compared to the sham-control group is statistically significant. The achievement of these motor milestones is not consistent with the natural history of type 1 SMA, in which patients never sit or stand, and represents a clinically meaningful improvement for these patients.

Table 10: Applicant's interim analysis of primary endpoint: Improvement in motor milestones from baseline: Control 0 % vs. Nusinersen 41%, p<0.0001. Source: CS3B CSR, p. 89.

	Control	ISIS 396443
Number of evaluable subjects (a)	27 (100)	51 (100)
Number of subjects who died (b)	10 (37)	11 (22)
Number of subjects withdrawn for reasons other than death (b)	1 (4)	1 (2)
Number of subjects with an improvement from baseline in motor milestones (c):		
Ability to kick:		
At least a 2-point increase	0	9 (18)
Achievement of touching toes	0	5 (10)
Head control: at least a 1-point increase	0	17 (33)
Rolling: at least a 1-point increase	1 (4)	18 (35)
Sitting: at least a 1-point increase	0	13 (25)
Crawling: at least a 1-point increase	0	4 (8)
Standing: at least a 1-point increase	0	4 (8)
Walking: at least a 1-point increase	0	0
Achievement of any of the above in which there are more categories with improvement than with worsening (d)	0	21 (41)

	Control	ISIS 396443
Difference in percentages (ISIS 396443 - control) (95% CI) (e)		41.18 (18.16, 61.20)
p-value (compared to control) (f)		<0.0001***

(a) Subjects with opportunity for at least a 6 month (Day 183) assessment.
(b) Subjects who died or who were withdrawn are considered non-responders.
(c) Subjects with 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) data. The last available assessment is used.
(d) Endpoint used for analysis. For category of ability to kick, similar to the definition of improvement, worsening is defined as at least 2 point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least 1-point decrease.
(e) Exact unconditional confidence interval.
(f) From Fisher's exact test.
Abbreviation: CI=confidence interval.

The following two figures of HINE motor milestone scores in the control and nusinersen groups are intended to demonstrate the relative magnitudes and temporal progression of scores in the two groups. In the nusinersen group, mean and median scores are higher at day 64 and continue to increase to day 302, compared to lower and stable or decreasing median and mean scores in the control group. Note that the maximum possible HINE score is 26.

Figure 7: HINE motor milestone scores: Sham-procedure control group evaluated at screening and at days 64, 183, 302, and 394. Median, Mean, and number of subjects (N) are shown in the captions for each time point. Box-and-whisker plot showing quartiles and outliers.

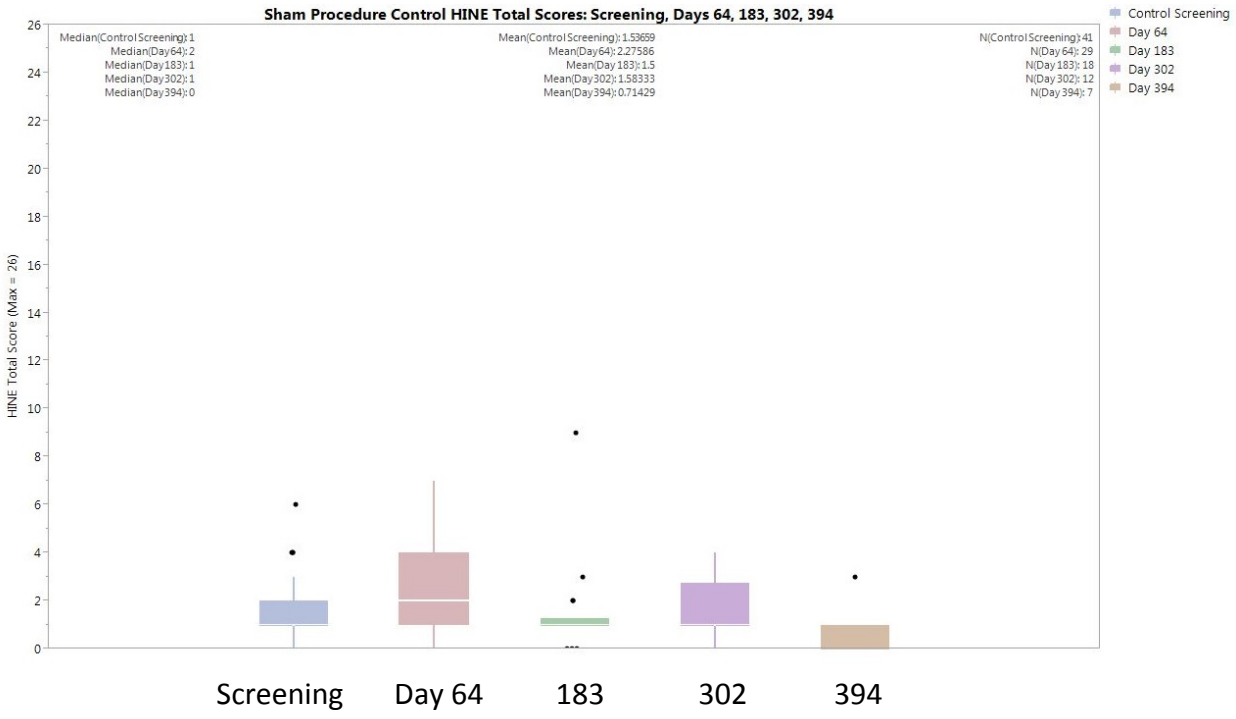
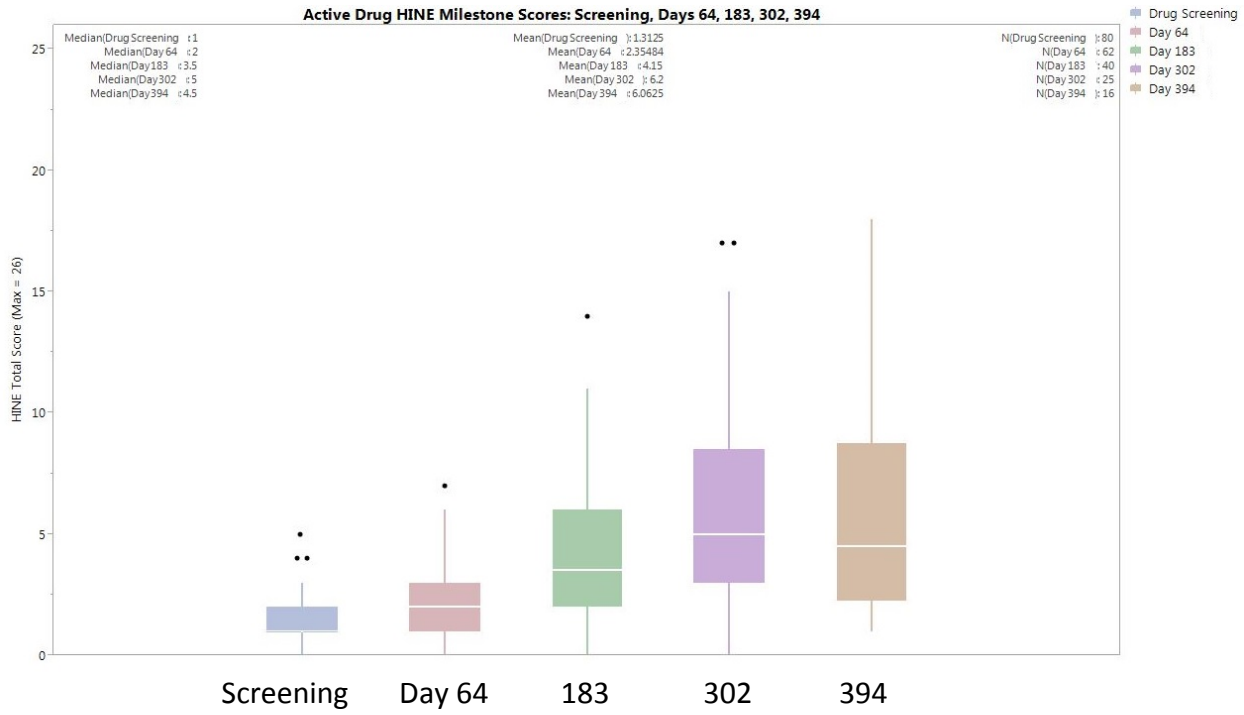


Figure 8: HINE motor milestone scores: Nusinersen group evaluated at screening and at days 64, 183, 302, and 394. Median, Mean, and number of subjects (N) are shown in the captions for each time point. Box-and-whisker plot showing quartiles and outliers.



Geographic region

As analyzed by the FDA biostatistician, forty two (42/78=54%) of the interim efficacy population were enrolled in the United States and 36 outside the US. Motor Milestone interim efficacy results within and outside the US were similar:

- 9/23 (39%) vs. 0/13 (0%) non-US and
- 12/28(43%) vs. 0/14 (0%) within the US.

The largest US site had 10 patients assigned to nusinersen and 1 to placebo; fifty percent of the nusinersen group responded in this site as compared to 0% of placebo.

Second Primary Endpoint, Time to death or permanent ventilation

The applicant reports the results for the second primary endpoint descriptively, as summarized in the Kaplan-Meier curves and the tables below. There is a numerical trend toward lower mortality in the nusinersen group (15%) compared to the sham-procedure group (32%), as reported by the applicant. Analysis by the FDA biostatistician found a Hazard Ratio = 0.5 with p = 0.09 for all causes of mortality, showing a numerically lower risk of mortality in the nusinersen group compared to the sham-procedure control group. The applicant reported similar rates of permanent ventilation in the nusinersen group (19%) compared to the sham-procedure group (22%). A subject was considered to have received permanent ventilation if a tracheostomy was performed or if a subject required at least 16 hours of ventilator support per day continuously for more than 21 days in the absence of an acute reversible event.

Reviewer Comment: The second primary endpoint of time to death or permanent ventilation is only reported descriptively. There appears to be a trend towards reduced mortality in the nusinersen group that may support, and does not contradict, the positive results of the first primary endpoint. The shorter study time (~13 months) of the interim analysis may make it more difficult to detect a survival difference because more than approximately 80% of type 1 SMA patients could be alive at that time if they received intensive mechanical respiratory support (Gregoretti et al., 2013).

The following five figures and tables depict Kaplan-Meier curves of time to death or permanent ventilation with supporting data tables copied from the applicant, as well as Kaplan-Meier survival curves based on mortality calculated by the FDA biostatistician.

Figure 9: Kaplan-Meier Curves for Time to Death or Permanent Ventilation (EAC-Adjudicated Events) ITT Set. Source: CS3B CSR, p. 104

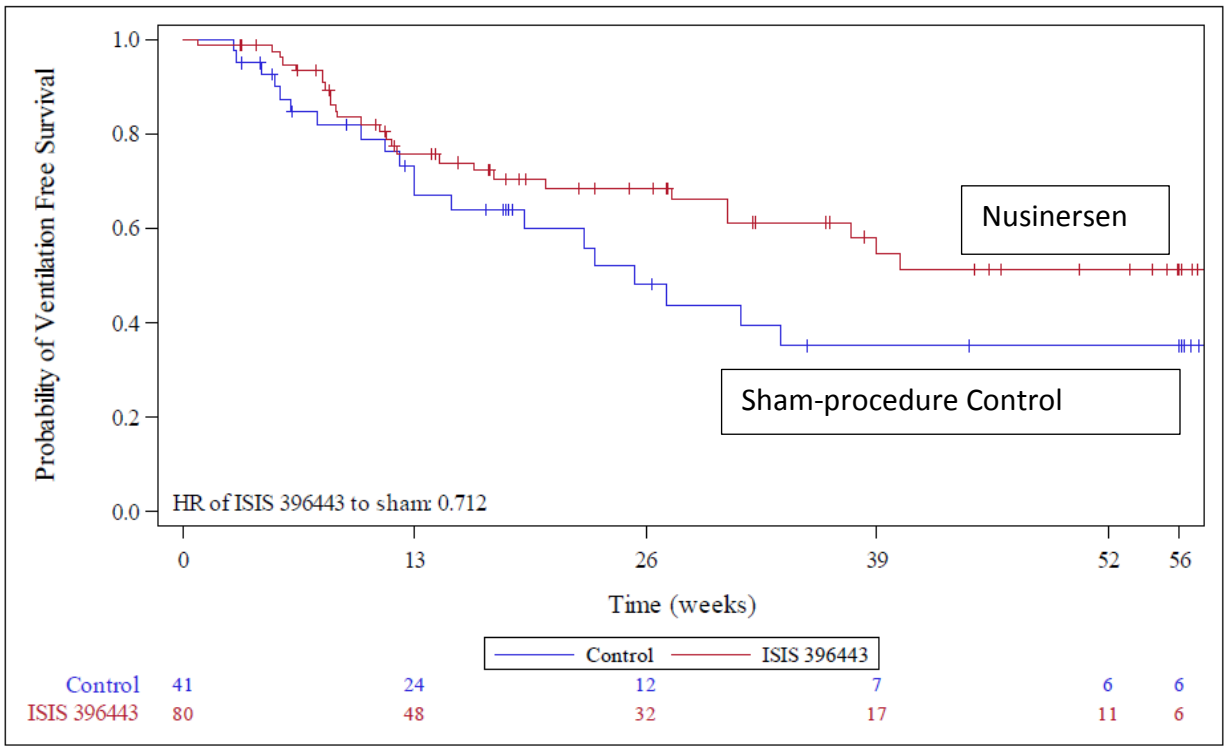


Figure 10: Summary of Time to Death or Permanent Ventilation (EAC-Adjudicated Events) - Descriptive Analysis, ITT Set. Source: CS3B CSR, p. 105

	Control	ISIS 396443
Number of subjects Dosed	41 (100)	80 (100)
Number of subjects who died or required permanent ventilation	20 (49)	27 (34)
Time (weeks) to death or permanent ventilation (a)		
10th percentile	5.1	8.0
25th percentile	12.1	14.4
50th percentile - median (95% CI)	25.4 (13.6, NA)	NA (30.6, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects who died or required permanent ventilation by		
Day 91 (13 weeks/3 months)	0.269	0.243
Day 182 (26 weeks/6 months)	0.520	0.315
Day 273 (39 weeks/9 months)	0.651	0.419
Day 364 (52 weeks/12 months)	0.651	0.487
Day 394 (13 months)	0.651	0.487
Hazard ratio of ISIS 396443 to control (b)		0.71

Table 11: Summary of Time to Death - Descriptive Analysis – ITT Set

	Control	ISIS 396443
Number of subjects Dosed	41 (100)	80 (100)
Number of subjects who died	13 (32)	12 (15)
Time (weeks) to death (a)		
10th percentile	5.1	16.1
25th percentile	17.4	NA
50th percentile - median (95% CI)	NA (23.1, NA)	NA (NA, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects who died by		
Day 91 (13 weeks/3 months)	0.213	0.100
Day 182 (26 weeks/6 months)	0.342	0.152
Day 273 (39 weeks/9 months)	0.386	0.198
Day 364 (52 weeks/12 months)	0.386	0.198
Day 394 (13 months)	0.386	0.198
Hazard ratio of ISIS 396443 to control (b)		0.44

Figure 11: Kaplan-Meier survival curves based on mortality from all causes in the ITT population. Hazard Ratio=0.5; p=0.09. Source: FDA biostatistician

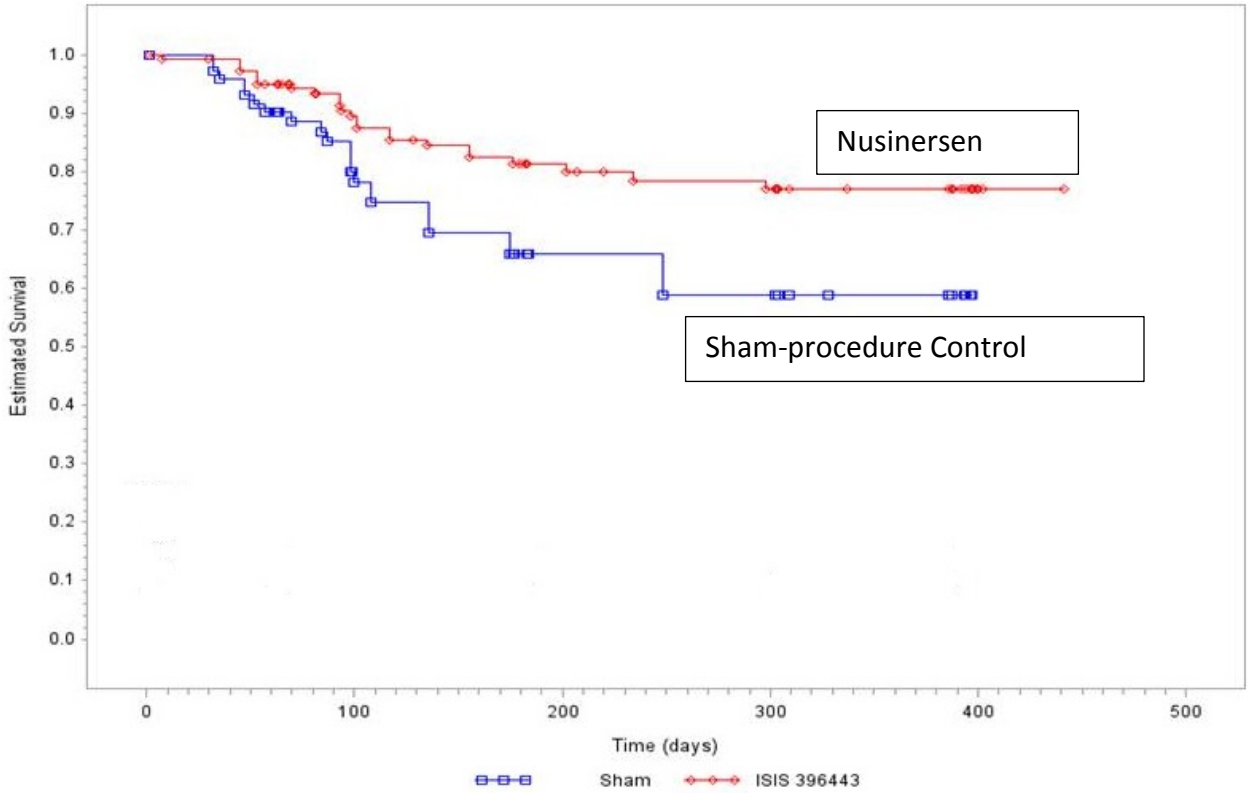


Table 12: Summary of Percentage of Subjects Requiring Permanent Ventilation – ITT Set. Source: CS3B CSR, p. 108.

	Control	ISIS 396443
Number of subjects Dosed	41 (100)	80 (100)
Number of subjects requiring permanent ventilation	9 (22)	15 (19)
Time (weeks) to permanent ventilation (a)		
10th percentile	13.6	8.3
25th percentile	25.4	39.1
50th percentile - median (95% CI)	NA (25.4, NA)	NA (40.3, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects requiring permanent ventilation by	0.062	0.149
Day 91 (13 weeks/3 months)		
Day 182 (26 weeks/6 months)	0.307	0.168
Day 273 (39 weeks/9 months)	0.433	0.239
Day 364 (52 weeks/12 months)	0.433	0.328
Day 394 (13 months)	0.433	0.328
Hazard ratio of ISIS 396443 to control (b)		0.90

Data Quality and Integrity – Reviewers' Assessment

No clinical research sites were identified by OSI as potentially fraudulent. No sites existed where investigators received significant financial compensation.

Efficacy Results – Secondary and other relevant endpoints

Reviewer Comment: All remaining efficacy endpoints for study CS3B are reported descriptively, as agreed with the Agency for the interim statistical analysis plan. There is no statistical adjustment for multiplicity.

Results of Secondary Efficacy Endpoints

- **Proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders.**

The applicant reports a numerical improvement in CHOP INTEND scores in the nusinersen-treated patients versus a decline in the sham-procedure controls as illustrated in the following figures and table copied from the applicant. The applicant defined a CHOP INTEND responder as a subject with an increase of 4 or more points from the baseline CHOP INTEND total score. This definition appears reasonable given that the mean rate of decline of CHOP INTEND scores in type 1 SMA patients was 1.27 points/year (95% confidence interval 0.21–2.33, p=0.02) in the

study by Finkel et al. (2014).

Figure 12: CHOP INTEND Total Score Over Time: Mean Results - Interim Efficacy Set. Maximum possible score = 64. Source: CS3B CSR, p. 114

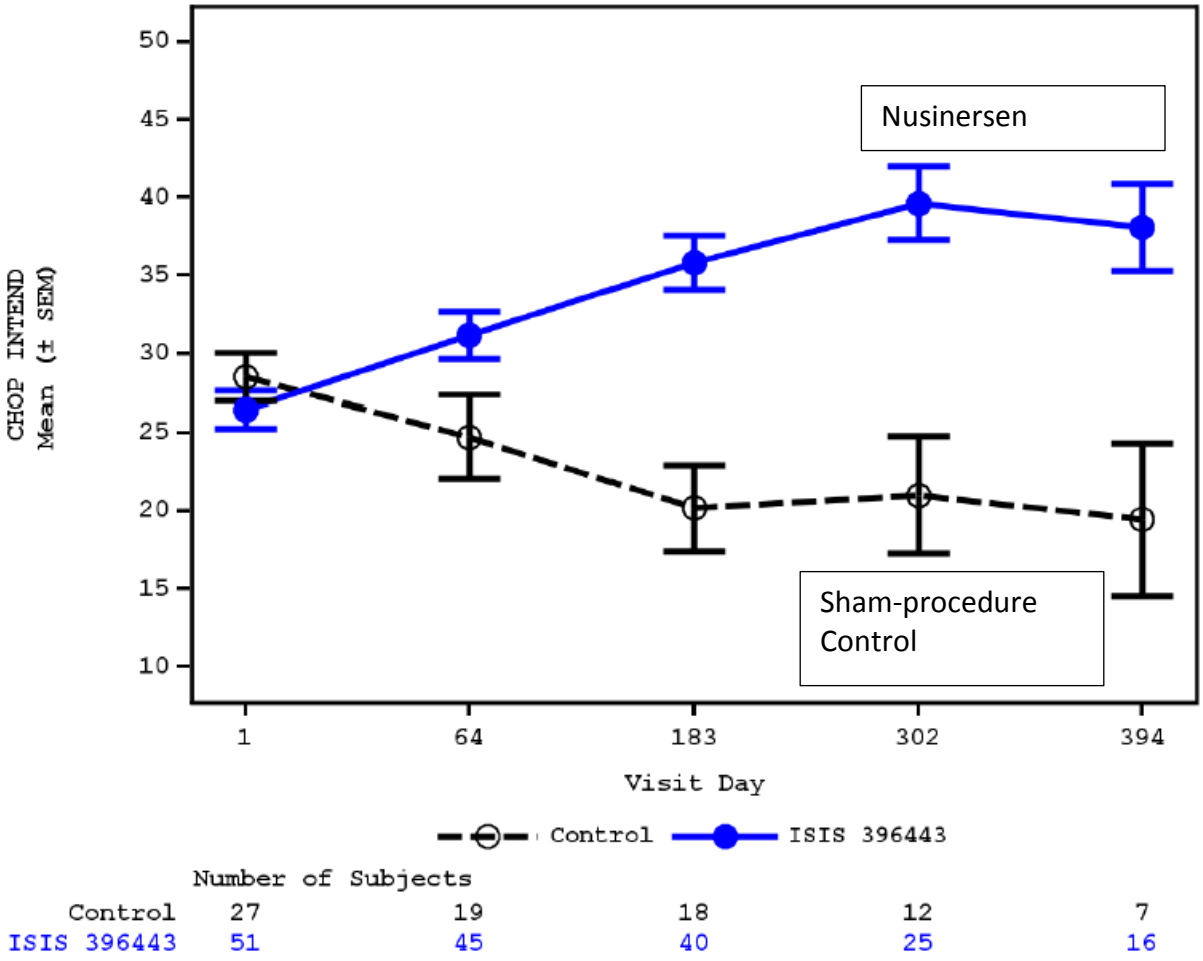


Figure 13: CHOP INTEND Total Score Over time: Mean Change from Baseline - Interim Efficacy Set. Source: CS3B CSR, p. 115

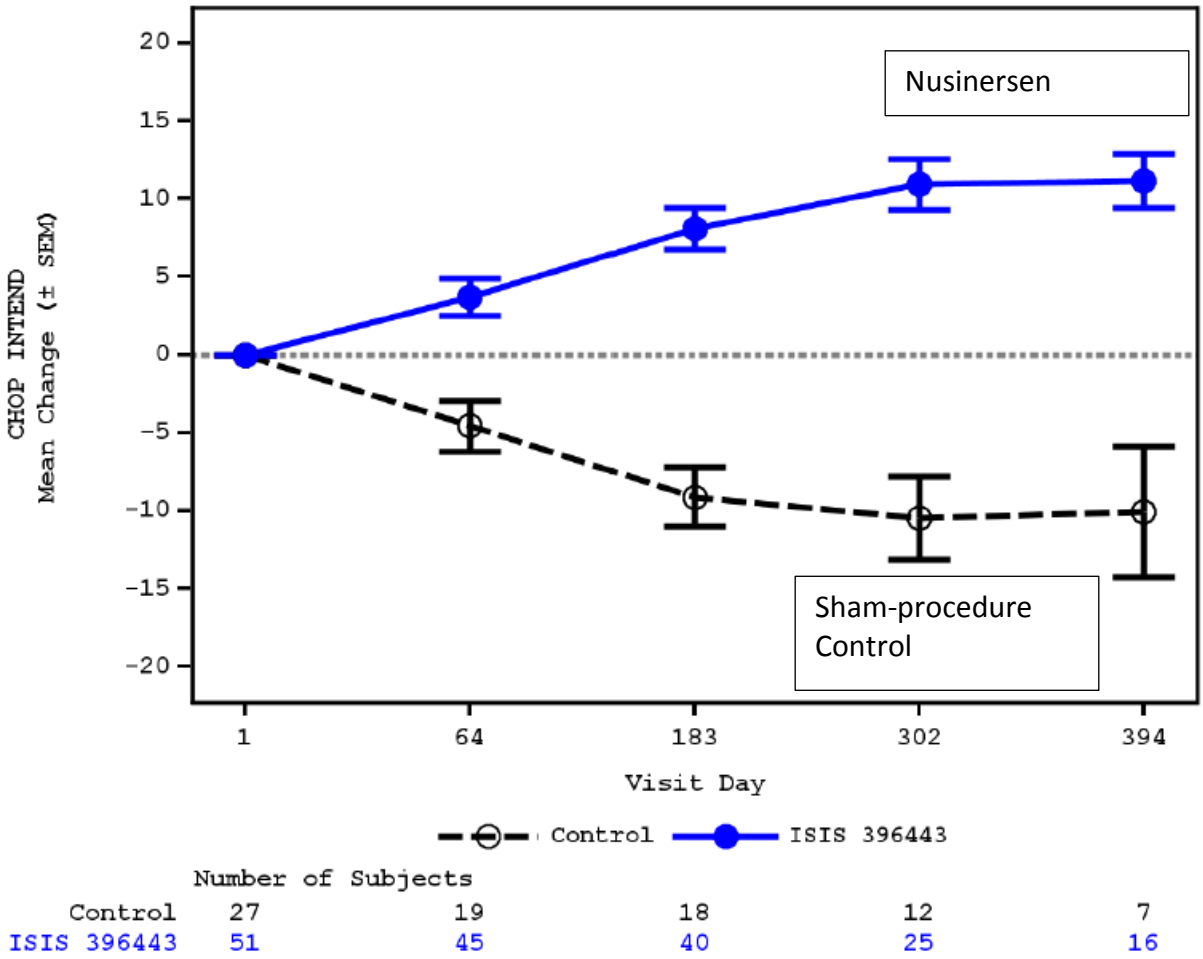


Table 13: CHOP INTEND: Change from Baseline to Day 394 Visit. Source: CS3B CSR, p. 310

	Control	ISIS 396443
Number of evaluable subjects (a)	11 (100)	23 (100)
Number of subjects who died before Day 394 visit	3 (27)	6 (26)
Number of subjects withdrawn for reasons other than death before Day 394 visit	1 (9)	1 (4)
Change from baseline CHOP INTEND total score (b):		
Worsening		
>=6 points	6 (55)	0
>=5 points	6 (55)	0
>=4 points	6 (55)	1 (4)
>=3 points	6 (55)	1 (4)
>=2 points	6 (55)	1 (4)
>=1 point	6 (55)	2 (9)
No change	0	0
Improvement		
>=1 point	1 (9)	14 (61)
>=2 points	1 (9)	14 (61)
>=3 points	1 (9)	14 (61)
>=4 points	1 (9)	14 (61)
>=5 points	1 (9)	14 (61)
>=6 points	1 (9)	14 (61)

- **Survival rate.**
  The applicant reports that 12 subjects (15%) in the ISIS 396443 group and 13 subjects (32%) in the control group had died by the data cutoff date, as shown in the following table copied from the applicant. See also the Kaplan-Meier survival curves shown in the discussion of the primary endpoint results above.

Table 14: Summary of Time to Death - Descriptive Analysis – ITT Set. Source: CS3B CSR, p. 109

	Control	ISIS 396443
Number of subjects Dosed	41 (100)	80 (100)
Number of subjects who died	13 (32)	12 (15)
Time (weeks) to death (a)		
10th percentile	5.1	16.1
25th percentile	17.4	NA
50th percentile - median (95% CI)	NA (23.1, NA)	NA (NA, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects who died by		
Day 91 (13 weeks/3 months)	0.213	0.100
Day 182 (26 weeks/6 months)	0.342	0.152
Day 273 (39 weeks/9 months)	0.386	0.198
Day 364 (52 weeks/12 months)	0.386	0.198
Day 394 (13 months)	0.386	0.198
Hazard ratio of ISIS 396443 to control (b)		0.44

NOTE: Results are based on all available data.
(a) Based on the Kaplan-Meier product-limit method.
(b) Based on Cox regression adjusting for each subject's disease duration at screening.
(b) An HR < 1 indicates lower risk of event for the ISIS 396443 group.
Abbreviation: CI=confidence interval.

- **Percent of subjects not requiring permanent ventilation.**
  The applicant reports that none of the subjects required permanent ventilation at baseline. Fifteen subjects (19%) in the ISIS 396443 group and 9 subjects (22%) in the control group had required permanent ventilation by the data cutoff date, as shown in the table below copied from the applicant. The applicant states that "of the 15 subjects in the ISIS 396443 group who required permanent ventilation, 8 (53%) were still within the loading dose period (up to Day 64) when permanent ventilation occurred, before maximal efficacy could be achieved" (CS3B CSR, p. 103).

  Reviewer Comment: There appears to be a similar rate of permanent ventilation in the nusinersen and control groups overall, with a numerically lower rate in the nusinersen group from day 182 to the end of the study.

Table 15: Summary of Percentage of Subjects Requiring Permanent Ventilation – ITT Set. Source: CS3B CSR, p. 108

	Control	ISIS 396443
Number of subjects Dosed	41 (100)	80 (100)
Number of subjects requiring permanent ventilation	9 (22)	15 (19)
Time (weeks) to permanent ventilation (a)		
10th percentile	13.6	8.3
25th percentile	25.4	39.1
50th percentile - median (95% CI)	NA (25.4, NA)	NA (40.3, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects requiring permanent ventilation by	0.062	0.149
Day 91 (13 weeks/3 months)		
Day 182 (26 weeks/6 months)	0.307	0.168
Day 273 (39 weeks/9 months)	0.433	0.239
Day 364 (52 weeks/12 months)	0.433	0.328
Day 394 (13 months)	0.433	0.328
Hazard ratio of ISIS 396443 to control (b)		0.90

- **Proportion of compound muscle action potential (CMAP) responders**.

The applicant defined a CMAP responder as a subject for whom the peroneal amplitude increased to, or was maintained at, 1 mV or more compared to baseline. Response was based on the later of the Day 183, Day 302, or Day 394 measurements. Subjects who died or were withdrawn from the study were considered non-responders. The results are shown in the following tables and figures, copied from the applicant.

Reviewer Comment: There appears to be a numerical improvement in CMAP amplitudes in both the peroneal and ulnar nerves for the nusinersen group, compared to a decline in CMAP amplitudes of both the peroneal and ulnar nerves for the sham-procedure control group. Note that a declining CMAP amplitude has been described as characteristic of type 1 SMA (Swoboda et al., 2005). The numerical improvement shown here is not normally seen in the natural history of type 1 SMA and is consistent with the positive efficacy result found for the primary endpoint described above.

Table 16: CMAP Peroneal Amplitude (mV): Change from Baseline by Visit - Interim Efficacy set

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
Peroneal Amplitude (mV)				
Baseline				
n	24		48	
Mean	0.368		0.375	
SD	0.3311		0.3229	
Median	0.205		0.300	
25th,75th percentiles	0.13, 0.64		0.16, 0.50	
Min, Max	0.00, 1.30		0.00, 1.50	
Day 64				
n	20	19	44	41
Baseline mean	0.428		0.406	
Baseline median	0.320		0.300	
Mean	0.264	-0.176	0.432	0.039
SD	0.1749	0.3543	0.3045	0.3651
Median	0.240	-0.100	0.375	0.000
25th,75th percentiles	0.15, 0.36	-0.31, 0.00	0.25, 0.66	-0.10, 0.20
Min, Max	0.00, 0.70	-1.10, 0.50	0.00, 1.30	-1.40, 0.90
Day 183				
n	18	16	38	36
Baseline mean	0.441		0.400	
Baseline median	0.325		0.300	
Mean	0.335	-0.171	0.772	0.398
SD	0.3087	0.3310	0.6137	0.5967
Median	0.315	-0.150	0.600	0.300
25th,75th percentiles	0.10, 0.50	-0.30, 0.00	0.30, 1.20	0.00, 0.72
Min, Max	0.00, 1.20	-1.20, 0.27	0.00, 2.40	-1.20, 2.00

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
Peroneal Amplitude (mV) (continued)				
Day 302				
n	12	10	24	21
Baseline mean	0.522		0.460	
Baseline median	0.500		0.400	
Mean	0.412	-0.248	1.063	0.536
SD	0.4642	0.4171	0.6831	0.6770
Median	0.310	-0.250	0.950	0.500
25th,75th percentiles	0.19, 0.40	-0.33, -0.01	0.55, 1.60	0.10, 0.90
Min, Max	0.00, 1.80	-1.20, 0.40	0.04, 2.60	-1.00, 1.80
Day 394				
n	7	5	16	13
Baseline mean	0.446		0.451	
Baseline median	0.330		0.300	
Mean	0.337	-0.294	1.399	0.964
SD	0.4401	0.5274	0.8423	0.7547
Median	0.260	-0.070	1.500	1.000
25th,75th percentiles	0.10, 0.30	-0.30, 0.00	0.69, 1.95	0.26, 1.40
Min, Max	0.00, 1.30	-1.20, 0.10	0.14, 3.20	0.00, 2.40

Table 17: CMAP Ulnar Amplitude (mV): Change from Baseline by Visit - Interim Efficacy set. Source: CS3B CSR, p. 319

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
Ulnar Amplitude (mV)				
Baseline				
n	24		49	
Mean	0.239		0.219	
SD	0.1135		0.1954	
Median	0.200		0.200	
25th,75th percentiles	0.19, 0.30		0.10, 0.30	
Min, Max	0.10, 0.60		0.00, 0.80	
Day 64				
n	20	18	44	42
Baseline mean	0.269		0.239	
Baseline median	0.240		0.200	
Mean	0.192	-0.061	0.253	0.014
SD	0.1446	0.1408	0.1824	0.2099
Median	0.195	-0.090	0.200	0.000
25th,75th percentiles	0.10, 0.29	-0.20, 0.07	0.10, 0.38	-0.04, 0.10
Min, Max	0.00, 0.53	-0.30, 0.23	0.00, 0.81	-0.60, 0.68
Day 183				
n	18	16	40	38
Baseline mean	0.263		0.222	
Baseline median	0.205		0.200	
Mean	0.142	-0.122	0.325	0.117
SD	0.1224	0.1770	0.2316	0.2585
Median	0.100	-0.100	0.300	0.100
25th,75th percentiles	0.05, 0.20	-0.20, -0.10	0.12, 0.50	0.00, 0.30
Min, Max	0.00, 0.48	-0.50, 0.36	0.00, 0.89	-0.80, 0.50

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
Ulnar Amplitude (mV) (continued)				
Day 302				
n	12	10	24	22
Baseline mean	0.281		0.233	
Baseline median	0.205		0.200	
Mean	0.183	-0.122	0.461	0.252
SD	0.1632	0.2167	0.3825	0.3282
Median	0.145	-0.100	0.300	0.200
25th,75th percentiles	0.10, 0.20	-0.30, -0.05	0.20, 0.70	0.02, 0.40
Min, Max	0.00, 0.50	-0.40, 0.30	0.03, 1.60	-0.23, 1.30
Day 394				
n	7	6	16	14
Baseline mean	0.247		0.289	
Baseline median	0.200		0.250	
Mean	0.103	-0.127	0.533	0.284
SD	0.1157	0.1657	0.5016	0.4714
Median	0.100	-0.100	0.310	0.270
25th,75th percentiles	0.00, 0.20	-0.20, -0.06	0.15, 0.78	0.00, 0.50
Min, Max	0.00, 0.30	-0.40, 0.10	0.08, 1.80	-0.40, 1.50

Figure 14: Peroneal nerve CMAP Amplitude Over Time: Mean Change from Baseline - Interim Efficacy Set. Source: CS3B CSR, p. 120

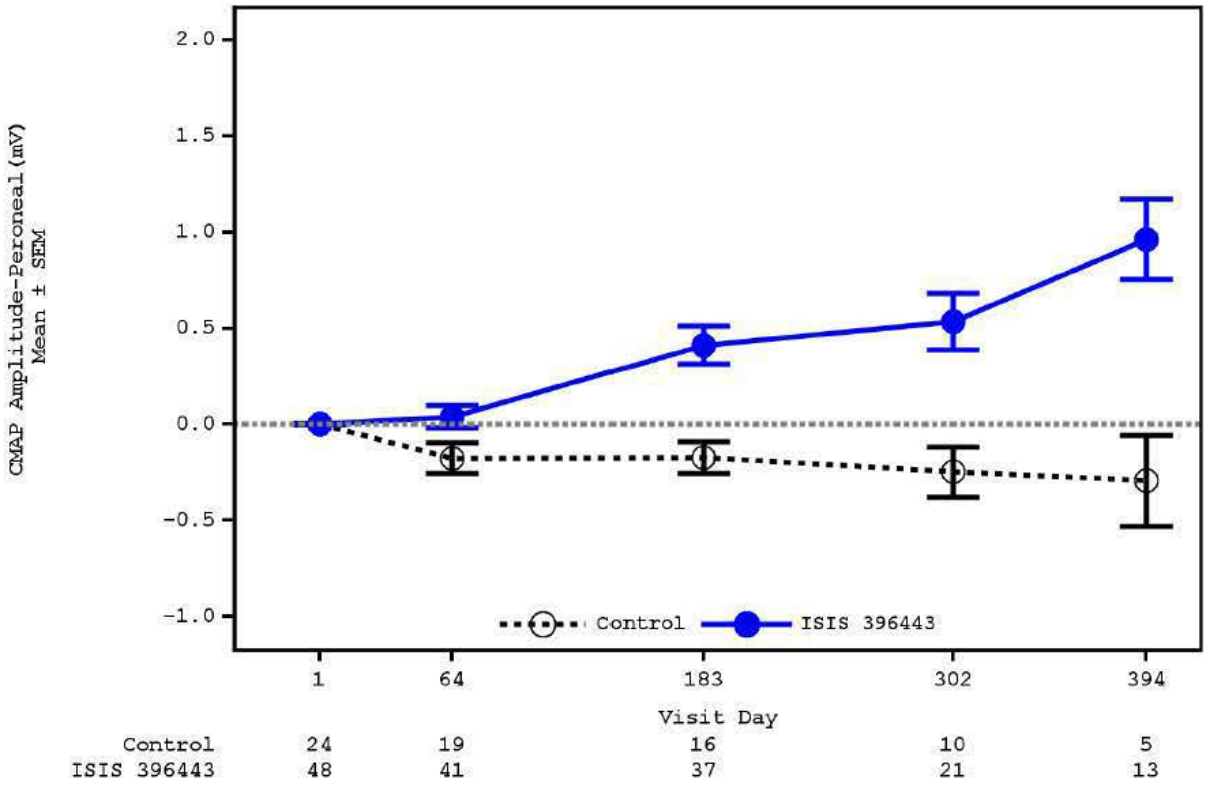
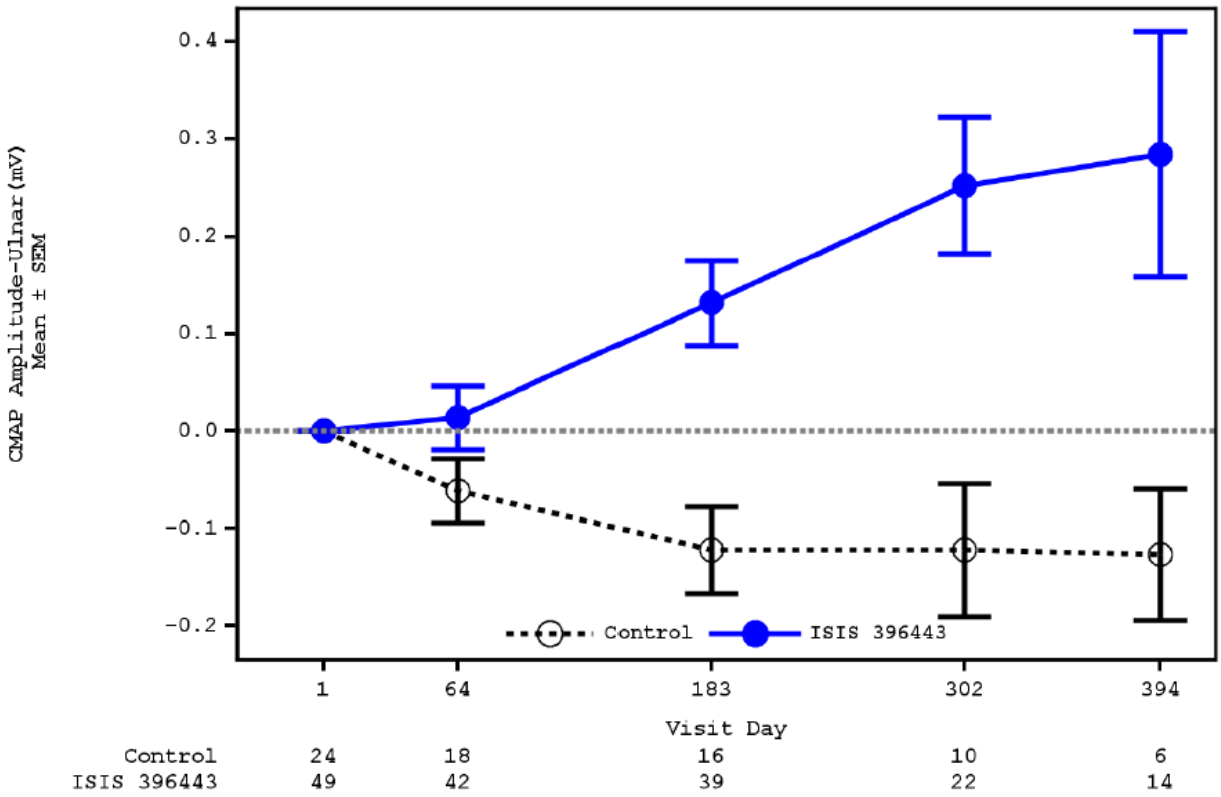


Figure 15: Ulnar nerve CMAP Amplitude Over Time: Mean Change from Baseline - Interim Efficacy Set. Source: CS3B CSR, p. 121



- **Time to death or permanent ventilation in the subgroups of subjects below the study median disease duration.**

  The results are summarized descriptively in the following table copied from the applicant, showing a numerical difference favoring the nusinersen group.

Table 18: Summary of Time to Death or Permanent Ventilation in the Subgroups of Subjects Below the Study Median Disease Duration - Descriptive Analysis, ITT Set. Source: CS3B CSR, p. 106.

	Control	ISIS 396443
Number of subjects Dosed	21 (100)	39 (100)
Number of subjects who died or required permanent ventilation	10 (48)	6 (15)
Time (weeks) to death or permanent ventilation (a)		
10th percentile	4.4	30.6
25th percentile	10.0	39.1
50th percentile - median (95% CI)	31.3 (10.0, NA)	NA (39.1, NA)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects who died or required permanent ventilation by		
Day 91 (13 weeks/3 months)	0.263	0.083
Day 182 (26 weeks/6 months)	0.493	0.083
Day 273 (39 weeks/9 months)	0.696	0.190
Day 364 (52 weeks/12 months)	0.696	0.264
Day 394 (13 months)	0.696	0.264
Hazard ratio of ISIS 396443 to control (b)		0.21

NOTE: Results are based on all available data.
(a) Based on the Kaplan-Meier product-limit method.
(b) Based on Cox regression adjusting for each subject's disease duration at screening.
(b) An HR < 1 indicates lower risk of event for the ISIS 396443 group.
Abbreviation: CI=confidence interval.

- **Time to death or permanent ventilation in the subgroups of subjects above the study median disease duration.**

  The results are summarized descriptively in the following table copied from the applicant, showing a numerical trend favoring the sham-procedure control group. As described in the results of "Percent of subjects not requiring permanent ventilation**"** above, the applicant attributes this negative finding to death or permanent ventilation events occurring prior to completion of the loading dose in the nusinersen group.

  Reviewer Comment: An alternative interpretation might be that nusinersen was less effective or even harmful in patients with a longer disease duration at the time of treatment. However, the proportion (55%) of subjects above the study median disease duration who died or required permanent ventilation matches the control group by study day 182, suggesting that the baseline imbalance (discussed above in "Other Baseline Characteristics") in the age of onset and severity of SMA associated symptoms might account for the early difference in times to death or permanent ventilation. Note that this is the only secondary endpoint result that is not consistent with the positive efficacy result of the primary endpoint.

Table 19: Summary of Time to Death or Permanent Ventilation in the Subgroups of Subjects Above the Study Median Disease Duration - Descriptive Analysis, ITT Set. Source: CS3B CSR, p. 107.

	Control	ISIS 396443
Number of subjects Dosed	20 (100)	41 (100)
Number of subjects who died or required permanent ventilation	10 (50)	21 (51)
Time (weeks) to death or permanent ventilation (a)		
10th percentile	5.1	7.9
25th percentile	12.1	8.6
50th percentile - median (95% CI)	22.6 (12.1, NA)	17.4 (11.0, 40.3)
75th percentile	NA	NA
90th percentile	NA	NA
Estimated proportion (a) of subjects who died or required permanent ventilation by		
Day 91 (13 weeks/3 months)	0.276	0.411
Day 182 (26 weeks/6 months)	0.548	0.550
Day 273 (39 weeks/9 months)	0.623	0.642
Day 364 (52 weeks/12 months)	0.623	0.702
Day 394 (13 months)	0.623	0.702
Hazard ratio of ISIS 396443 to control (b)		1.32

NOTE: Results are based on all available data.
(a) Based on the Kaplan-Meier product-limit method.
(b) Based on Cox regression adjusting for each subject's disease duration at screening.
(b) An HR < 1 indicates lower risk of event for the ISIS 396443 group.
Abbreviation: CI=confidence interval.

Results of Tertiary Efficacy Endpoints

- **Change from baseline in growth parameters (weight for age/length, chest circumference, head to chest circumference ratio, and arm circumference).**

Change from baseline in growth parameters was similar between the control and nusinersen groups. There was a numerical difference at day 394 with a greater increase in weight (3.1 vs. 3.9kg control), body length (13.5 vs. 20.6cm control), and arm circumference (1.4 vs. 1.7cm control) in the control group. See Appendix 13.5 for the data tables.

Reviewer comment: This numerical difference does not appear to be clinically significant.

- **Number of serious respiratory events.**
  The results for this endpoint are shown in the table below, copied from the applicant. A greater percentage of subjects in the ISIS 396443 group experienced serious respiratory events (ISIS 396443 vs. control: 73% vs. 67%). Note that the nusinersen group was followed for a longer period of time, potentially allowing more serious respiratory events to be observed.

  Reviewer comment: This numerical difference is difficult to interpret given the difference in baseline respiratory symptom history between the nusinersen and control groups described in Section 6.1.1 above.

Table 20: Number of Serious Respiratory Events - Interim Efficacy Set

	Control	ISIS 396443
Number of subjects dosed	27 (100)	51 (100)
Number of subjects with		
no serious respiratory events	9 (33)	14 (27)
1 serious respiratory event	5 (19)	14 (27)
2 serious respiratory events	4 (15)	6 (12)
3 serious respiratory events	3 (11)	5 (10)
4 serious respiratory events	3 (11)	5 (10)
>=5 serious respiratory events	3 (11)	7 (14)
Total number of serious respiratory events	55	107
Total number of subject-years followed	17.9	37.7
Unadjusted annualized rate of serious respiratory events (a)	3.065	2.836

Numbers in parentheses are percentages.
(a) The unadjusted annualized rate is the total number of events that occurred during the study for all subjects divided by the total number of subject-years of follow-up.

- **Number of hours of ventilation support.**

  Patients in the nusinersen group spent numerically less time with ventilation support than patients in the control group, as shown in the table below copied from the applicant.

  Reviewer comment: This numerical difference appears to be consistent with the primary efficacy endpoint results.

Table 21: Percentage of Time on Ventilator Support - Interim Efficacy Set. Source: CS3B CSR, p. 125

	Control	ISIS 396443
Number of subjects dosed	27	51
Percentage of Time of Ventilatory Support		
<10%	6 (22)	17 (33)
>=10% to <20%	3 (11)	3 (6)
>=20% to <30%	0	6 (12)
>=30% to <40%	4 (15)	2 (4)
>=40% to <50%	2 (7)	7 (14)
>=50% to <60%	5 (19)	5 (10)
>=60% to <70%	2 (7)	2 (4)
>=70% to <80%	2 (7)	2 (4)
>=80% to <90%	2 (7)	4 (8)
>=90%	1 (4)	3 (6)
n	27	51
Mean	40.5	34.9
SD	29.82	31.22
Median	43.0	27.1
Min, Max	0.0, 91.5	0.0, 95.2

- **Number and length of hospitalizations.**
  Patients in the nusinersen group had more hospitalizations than the control group but spent a smaller proportion of time in the hospital as described in the following tables copied from the applicant.

  Reviewer comment: This descriptive result is difficult to interpret given the potential for lumbar puncture-related adverse events to increase the number of hospital visits in the nusinersen group. The numerical difference in hospitalization time, greater in the control group, does not contradict the positive primary endpoint result.

Table 22: Number of Hospitalizations - Interim Efficacy Set. Source: CS3B CSR, p. 127

	Control	ISIS 396443
Number of subjects dosed	27 (100)	51 (100)
Number of subjects with		
0 hospitalizations	3 (11)	1 (2)
1 hospitalization	5 (19)	15 (29)
2 hospitalizations	6 (22)	12 (24)
3 hospitalizations	4 (15)	5 (10)
4 hospitalizations	3 (11)	1 (2)
>=5 hospitalizations	6 (22)	17 (33)
Total number of hospitalizations	78	170
Number of hospitalizations for		
General observation	3	4
Observation after dosing	10	21
Serious adverse event	57	135
Ancillary procedure	8	10
Unknown	0	0
Total number of subject-years followed	17.9	37.7
Unadjusted annualized rate of hospitalization (a)	4.346	4.505

Numbers in parentheses are percentages.
(a) The unadjusted annualized rate is the total number of events that occurred during the study for all subjects divided by the total number of subject-years of follow-up.

Table 23: Proportion of Time of Hospitalization - Interim Efficacy Set. Source: CS3B CSR, p. 128

	Control	ISIS 396443
Number of subjects dosed	27 (100)	51 (100)
Proportion of Time in Hospital		
<10%	11 (41)	30 (59)
>=10% to <20%	6 (22)	12 (24)
>=20% to <30%	5 (19)	6 (12)
>=30% to <40%	2 (7)	1 (2)
>=40% to <50%	1 (4)	1 (2)
>=50% to <60%	0	1 (2)
>=60%	2 (7)	0
n	27	51
Mean	18.53	11.37
SD	19.094	10.939
Median	13.87	8.86
Min, Max	0.0, 75.0	0.0, 50.0

Dose/Dose Response

See section 7.1.4.

Durability of Response

In study CS3B, separation from the control group in motor milestone measurements did not clearly occur until after Day 64, likely reflecting the need for completion of the loading dose period before maximal benefit was observed. Improvements in motor milestones over time continued to be seen at up to 1 year (Day 394).

Persistence of Effect

This analysis is not permitted by the available data. Persistence of effect is expected for at least 4 months, which is nusinersen's half-life in spinal cord tissue and CSF.

Additional Analyses Conducted on the Individual Trial

The reader is referred to the separate statistical review for sensitivity analyses.

6.2. Uncontrolled Open-label studies

The applicant provided data from six uncontrolled open-label studies of nusinersen both in the above-discussed infantile-onset SMA patients, as well as in other types/age ranges of SMA patients (pre-symptomatic infants with genetically diagnosed SMA from ages 8-42 days; later-onset patients from ages 2-17 years; SMN2 copy numbers ranging from 2-5 corresponding to SMA types 2 and 3) listed in the table below provided by the applicant. The studies are described briefly below. Study CS10 was an extension study for patients who completed CS1. Study CS12 was an extension study for patients who completed studies CS2 and CS10.

Reviewer Comment: These open-label studies are difficult to interpret due to the intrinsic limitations of the study design, such as the lack of placebo control groups and the potential for observer bias in some endpoints. The results are reported descriptively. The results may lend supportive efficacy evidence if there is a consistent positive trend across studies and endpoints.

Figure 16: Uncontrolled Open-Label Studies of Nusinersen. Source: Summary of Clinical Efficacy-iii, pp. 35-37

Study ID	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Study Type/Design	Phase 2, Open-label, multiple-dose	Phase 2, Open-label, multiple-dose, single-arm	Phase 1, Open-label, escalating dose	Phase 1, Open-label, single dose	Phase 1, open-label, dose-escalation, multiple dose	Phase 1, Open-label, multiple-dose, single-arm
Study population	Subjects with symptomatic infantile-onset SMA	Presymptomatic subjects with genetically diagnosed SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA	Subjects with symptomatic later-onset SMA
Number of Study Centers that enrolled subjects Number of Subjects Enrolled by Location	4 centers US: 18 Canada: 3	10 centers Australia: 1 Germany: 1 Italy: 2 Taiwan: 1 US: 12	4 centers US: 28	4 centers US: 18	4 centers US: 34	4 centers US: 47
Study Start Enrollment Status Total Enrolled as of Data Cutoff Date[a] (Planned)	May 2013 Completed 21 subjects (20 subjects)	20 May 2015 Ongoing 11 subjects (25)	05 Dec 2011 Completed 28 subjects (NA)	10 Jan 2013 Completed 18 subjects (NA)	12 Oct 2012 Completed 34 subjects (NA)	30 January 2014 Completed 47 subjects (NA)
Study Status	Ongoing	Ongoing	Completed	Completed	Completed	Ongoing

Study ID	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Study Objectives	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, dose finding, efficacy	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy and PK
Primary efficacy endpoint	Motor milestones (HINE Section 2)	Time to death or respiratory intervention	HFMSE	HFMSE	HFMSE	HFMSE
Secondary efficacy endpoints	CHOP INTEND, CMAP, overall and event-free survival, growth	Development of clinically manifested SMA, motor milestones, CHOP INTEND, CMAP, overall and event-free survival, growth	PedsQL™, CMAP, MUNE	PedsQL™, CMAP, MUNE	PedsQL™, CMAP, MUNE, ULM, myometry, 6MWT, ACEND	6MWT, ULM, CMAP
Test Product, Route of Administration **Dosage Regimen** Duration of Treatment	ISIS 396443 IT injection by LP: Cohort 1: • 6 mg scaled equivalent loading dose and 12 mg maintenance dose Cohort 2: • 12 mg scaled equivalent loading dose and 12 mg maintenance dose Loading dose: Days 1, 15, and 85 Maintenance dose: Day 253 and every 4 months thereafter.	ISIS 396443: 12 mg (scaled equivalent) IT injection by LP Loading dose: Days 1, 15, 29, and 64 Maintenance dose: Days 183, 302, 421, 540, 659, and 778 Total duration: approximately 2.4 yrs	ISIS 396443 1, 3, 6, and 9 mg single dose IT injection by LP	ISIS 396443 IT injection by LP Cohort 1: 6 mg on Day 1 Cohort 2: 9 mg on Day 1	ISIS 396443 IT injection by LP: Cohort 1: 3 mg on Days 1, 29, 85 Cohort 2: 6 mg on Days 1, 29, 85 Cohort 3: 9 mg on Days 1, 85 Cohort 4: 12 mg on Days 1, 29, 85 Total Duration: approximately 8 months	ISIS 396443: 12 mg IT injection by LP Doses on Days 1, 169, 351, and 533 Total duration: approximately 1.5 yrs

Study ID	Study CS3A	Study SM201	Study CS1	Study CS10	Study CS2	Study CS12
Number of Subjects by Arm Dosed	Cohort 1: 4 Cohort 2: 16 1 subject withdrew before dosing	12 mg: 17	1 mg cohort: 6 3 mg cohort: 6 6 mg cohort: 6 9 mg cohort: 10	Cohort 1: 4 Cohort 2: 14	Cohort 1: 8 Cohort 2: 8 Cohort 3: 9 Cohort 4: 9	12 mg: 47
Sex	60% male 40% female	65% male 35% female	39% male 61% female	28% male 72% female	59% male 41% female	49% male 51% female
Mean (median) Age at baseline	155 days (36 to 210 days)	21.9 (19) days (8 to 42 days)	Mean 6.1 yrs (2-14 yrs)	Mean 6.6 yrs (2-11 yrs)	Mean 7.4 yrs (2-15 yrs)	8 years (3-17 yrs)
Mean (median) Age at symptom onset	Median 56 days	NA (presymptomatic)	Not summarized	Not summarized	Not summarized	Not summarized
Number *SMN2* Copies	2 (n=17) 3 (n=2) Unknown (n=1)	2 (n=12) 3 (n=5)	3 (n=25) 4 (n=2) 5 (n=1)	3 (n=17) 4 (n=1)	2 (n=1) 3 (n=25) 4 (n=8)	3 (n=39) 4 (n=8)

[a] As of 26 January 2016 for Study CS3A, 15 June 2016 for Study CS3B, 08 June 2016 for Study SM201, and 07 April 2016 for CS12.
6MWT = six-minute walk test; ACEND = Assessment of Caregiver Experience with Neuromuscular Disease; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; CSR = clinical study report; IT = intrathecal; LP = lumbar puncture; MUNE = motor unit number estimation; NA = not applicable; PedsQL™ = Pediatric Quality of Life Inventory; PK = pharmacokinetic; SMA = spinal muscular atrophy; ULM = Upper Limb Module; UK = United Kingdom; US = United States; yrs = years.

6.2.1. Study 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

Study CS3A was an unblinded, open-label, historical control trial in 20 infants with infantile-onset SMA in which patients received 6mg or 12mg of nusinersen loading dose followed by 12mg maintenance dose for up to 163 weeks (~3 years). Patients had genetic documentation of 5q SMA homozygous gene deletion or mutation and onset of clinical signs and symptoms consistent with SMA at ≥21 days and ≤6 months (180 days) of age.

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) discussed previously. Improvement was defined as achievement of at least one of the following:

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

The secondary efficacy endpoints were the following:

- Event-free survival determined by the proportion of subjects who are alive and do 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 muscle strength 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 (Study CS3A CSR, p. 26

6.2.1.1 Study CS3A Results

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

There was improvement in motor milestone scores as shown in the following tables copied from the applicant. Cohort 1 (n=4) had a 6mg loading dose on Days 1, 15, and 85, while cohort 2 (n=16) had a 12mg loading dose on Days 1, 15, and 85.

Reviewer Comment: This result is consistent with the results of the sham-procedure control study, CS3B, reported in Section 6.1 above.

Table 24: Summary of Motor Milestones Total Score at Last Visit, Safety Population (N=20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 92

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Baseline[1]			
N	4	16	20
Mean (SD, SEM)	2.00 (0.82, 0.41)	2.31 (2.70, 0.68)	2.25 (2.43, 0.54)
Median (P25, P75)	2.00 (1.50, 2.50)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)
Min, Max	1.00, 3.00	1.00, 12.00	1.00, 12.00
Last Visit			
N	2	13	15
Mean (SD, SEM)	7.50 (9.19, 6.50)	12.92 (7.95, 2.21)	12.20 (7.99, 2.06)
Median (P25, P75)	7.50 (1.00, 14.00)	14.00 (7.00, 19.00)	14.00 (4.00, 19.00)
Min, Max	1.00, 14.00	3.00, 26.00	1.00, 26.00
Change from Baseline			
N	2	13	15
Mean (SD, SEM)	6.00 (8.49, 6.00)	10.46 (6.89, 1.91)	9.87 (6.95, 1.79)
Median (P25, P75)	6.00 (0.00, 12.00)	12.00 (5.00, 17.00)	12.00 (2.00, 17.00)
Min, Max	0.00, 12.00	1.00, 20.00	0.00, 20.00
Percent Change from Baseline			
N	2	13	15
Mean (SD, SEM)	300.0 (424.3, 300.0)	732.1 (688.1, 190.8)	674.4 (664.7, 171.6)
Median (P25, P75)	300.0 (0.0, 600.0)	500.0 (200.0, 1400.0)	500.0 (116.7, 1400.0)
Min, Max	0.0, 600.0	50.0, 1800.0	0.0, 1800.0

Note: If subjects who died or withdrew, their last values were set to missing.
[1]Baseline is defined as the last non-missing value prior to the first dose.

Table 25: Summary of Proportion of Subjects who Achieve Full Head Control, Independent Sitting, Rolling, Crawling, Standing, or Walking at Last Visit, Safety Population (N=20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 263

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Number of subjects (Last Visit)	4	16	20
Number (%) of Subjects who Achieve Full Head Control, Independent Sitting, Rolling, Crawling, Standing or Walking[1]:	1(25.0%)	9(56.3%)	10(50.0%)
Full head control: (All the Time Upright)	0(0.0%)	9(56.3%)	9(45.0%)
Independent sitting: (Either Prop, Stable Sit or Pivot)	1(25.0%)	7(43.8%)	8(40.0%)
Rolling: (Prone to Supine or Supine to Prone)	1(25.0%)	6(37.5%)	7(35.0%)
Crawling: (Crawling On outstretched hand, flat on abdomen, or On hands and knees)	0(0.0%)	2(12.5%)	2(10.0%)
Standing: (Stands with support or Stands unaided)	0(0.0%)	5(31.3%)	5(25.0%)
Walking: (Cruising (holding on) or Walking independently)	0(0.0%)	2(12.5%)	2(10.0%)
Number of subjects who died	1(25.0%)	3(18.8%)	4(20.0%)
Number of subjects withdrew for reasons other than death	1(25.0%)	0(0.0%)	1(5.0%)

Note: (1) Motor milestone results at 3, 6 hours and 1 day after dosing are excluded.
(2) The denominator is the number of subjects within each group.
[1]Subjects who died or withdrew are considered non-responders.

Secondary efficacy endpoints:

- **Event-free survival** determined by the proportion of subjects who are alive and do 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)

  The results for event-free survival are described in the following table, copied from the applicant. Note that cohort 2 of study CS3A, with the same 12mg loading dose used in study CS3B, had a higher percentage of event-free survival compared to the lower dose (6mg) of cohort 1 (69% cohort 2 vs. 50% cohort 1 at day 910).

  Reviewer Comment: This result is consistent with the results of the sham-procedure control study, CS3B, reported in Section 6.1 above.

Table 26: Summary of Event-Free Survival, Safety Population (N=20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 103

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Number of Patients	4	16	20
Number of Events	2	5	7
Number of Censored	2	11	13
Percent of Censoring (%)	50.0%	68.8%	65.0%
Median (Month)			
95% CI of Median (Month)	(8.75,)	(11.21,)	(11.21,)
Estimated proportion of subjects who are alive and do not require permanent ventilatory support by			
Day 91 (13 weeks/3 months)	100.0%	100.0%	100.0%
Day 182 (26 weeks/6 months)	100.0%	93.8%	95.0%
Day 273 (39 weeks/9 months)	75.0%	81.3%	80.0%
Day 364 (52 weeks/12 months)	75.0%	75.0%	75.0%
Day 455 (65 weeks/15 months)	50.0%	75.0%	70.0%
Day 546 (78 weeks/18 months)	50.0%	68.8%	65.0%
Day 637 (91 weeks/21 months)	50.0%	68.8%	65.0%
Day 728 (104 weeks/24 months)	50.0%	68.8%	65.0%
Day 819 (117 weeks/27 months)	50.0%	68.8%	65.0%
Day 910 (130 weeks/30 months)	50.0%	68.8%	65.0%

- **Improvement in muscle strength** as measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND)

  The results for change in CHOP INTEND scores are described in the following table and figure, copied from the applicant.

  Reviewer Comment: This result is consistent with the results of the sham-procedure control study, CS3B, reported in Section 6.1 above. The initial drop in CHOP INTEND score of the lower dose cohort 1 at day 29 contrasts with the initial increase of the higher dose cohort 2, although following completion of the loading doses (day 85) the CHOP INTEND scores began to increase at day 92 for the lower dose cohort 1 also. Given the long half-life of nusinersen, this finding may suggest that a sufficient concentration was not present following the second loading dose and that the third loading dose was needed in order to reach an effective concentration in the CSF.

Table 27: Summary of CHOP INTEND Infant Motor Function Scale Total Score to Day 92, Safety Population (N = 20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 402

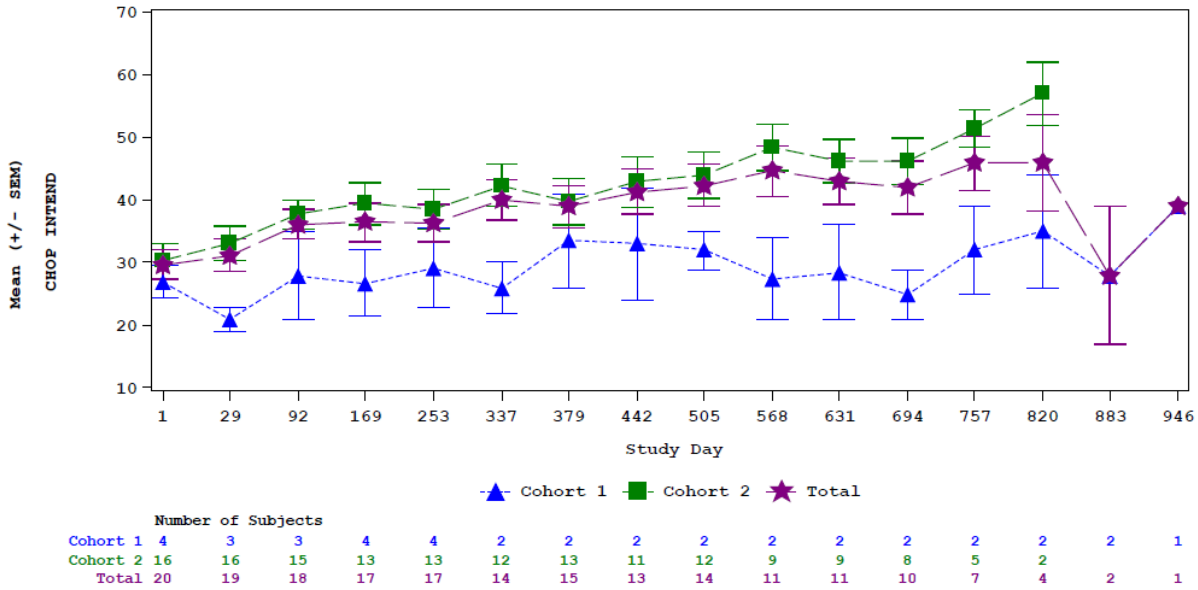
	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Baseline [1]			
N	4	16	20
Mean (SD, SEM)	27.00 (5.10, 2.55)	30.31 (11.52, 2.88)	29.65 (10.52, 2.35)
Median (P25, P75)	26.00 (23.50, 30.50)	28.00 (22.00, 35.00)	26.50 (22.50, 34.00)
Min, Max	22.00, 34.00	17.00, 64.00	17.00, 64.00
Day 29			
N	3	16	19
Mean (SD, SEM)	21.00 (3.46, 2.00)	33.13 (10.96, 2.74)	31.21 (11.05, 2.53)
Median (P25, P75)	19.00 (19.00, 25.00)	30.50 (27.00, 35.50)	29.00 (25.00, 33.00)
Min, Max	19.00, 25.00	21.00, 64.00	19.00, 64.00
Change from Baseline			
N	3	16	19
Mean (SD, SEM)	-6.00 (7.94, 4.58)	2.81 (6.95, 1.74)	1.42 (7.63, 1.75)
Median (P25, P75)	-3.00 (-15.00, 0.00)	2.50 (-2.50, 7.50)	1.00 (-3.00, 7.00)
Min, Max	-15.00, 0.00	-11.00, 14.00	-15.00, 14.00
Percent Change from Baseline			
N	3	16	19
Mean (SD, SEM)	-19.3 (22.6, 13.0)	14.6 (30.9, 7.7)	9.3 (31.8, 7.3)
Median (P25, P75)	-13.6 (-44.1, 0.0)	10.3 (-7.5, 27.0)	3.8 (-13.2, 23.5)
Min, Max	-44.1, 0.0	-34.4, 82.4	-44.1, 82.4

[1]Baseline is defined as the last non-missing value prior to the first dose.

	Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Day 92			
N	3	15	18
Mean (SD, SEM)	28.00 (12.12, 7.00)	37.73 (9.08, 2.35)	36.11 (9.96, 2.35)
Median (P25, P75)	35.00 (14.00, 35.00)	37.00 (31.00, 41.00)	35.00 (31.00, 40.00)
Min, Max	14.00, 35.00	26.00, 61.00	14.00, 61.00
Change from Baseline			
N	3	15	18
Mean (SD, SEM)	3.33 (14.22, 8.21)	7.40 (7.57, 1.95)	6.72 (8.57, 2.02)
Median (P25, P75)	10.00 (-13.00, 13.00)	7.00 (2.00, 13.00)	8.50 (2.00, 13.00)
Min, Max	-13.00, 13.00	-5.00, 23.00	-13.00, 23.00
Percent Change from Baseline			
N	3	15	18
Mean (SD, SEM)	17.0 (57.2, 33.0)	33.6 (38.6, 10.0)	30.8 (40.6, 9.6)
Median (P25, P75)	40.0 (-48.1, 59.1)	23.8 (7.7, 52.2)	31.9 (7.7, 52.2)
Min, Max	-48.1, 59.1	-15.6, 135.3	-48.1, 135.3

[1]Baseline is defined as the last non-missing value prior to the first dose.

Figure 17: Summary of CHOP INTEND Infant Motor Function Scale Total Score Over Time, Safety Population (N=20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 110



- **Improvement in neuromuscular electrophysiology** measured by the compound muscle action potential (CMAP) of the ulnar and peroneal nerves (Study CS3A CSR, p. 26

The result for change in CMAP amplitudes is described in the following tables and figures, copied from the applicant.

Reviewer Comment: This result is consistent with the results of the sham-procedure control study, CS3B, reported in Section 6.1 above.

Table 28: Summary of CMAP amplitude to Day 92, Safety Population (N = 20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 468

Parameter		Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Peroneal: CMAP Amplitude (mV)	Baseline[1]			
	N	4	16	20
	Mean (SD, SEM)	0.67 (0.50, 0.25)	0.52 (0.66, 0.17)	0.55 (0.63, 0.14)
	Median (P25, P75)	0.50 (0.35, 1.00)	0.33 (0.20, 0.50)	0.35 (0.22, 0.55)
	Min, Max	0.30, 1.40	0.00, 2.70	0.00, 2.70
	Day 29			
	N	3	16	19
	Mean (SD, SEM)	0.74 (0.57, 0.33)	0.55 (0.59, 0.15)	0.58 (0.58, 0.13)
	Median (P25, P75)	0.41 (0.40, 1.40)	0.32 (0.20, 0.75)	0.33 (0.20, 0.90)
	Min, Max	0.40, 1.40	0.00, 2.30	0.00, 2.30
	Change from Baseline			
	N	3	16	19
	Mean (SD, SEM)	-0.06 (0.12, 0.07)	0.03 (0.25, 0.06)	0.02 (0.23, 0.05)
	Median (P25, P75)	0.00 (-0.20, 0.02)	-0.03 (-0.08, 0.07)	-0.01 (-0.10, 0.02)
	Min, Max	-0.20, 0.02	-0.40, 0.60	-0.40, 0.60
	Percent Change from Baseline			
	N	3	14	17
	Mean (SD, SEM)	-9.4 (20.9, 12.1)	23.7 (73.1, 19.5)	17.9 (67.6, 16.4)
	Median (P25, P75)	0.0 (-33.3, 5.1)	-7.8 (-15.6, 65.0)	-7.7 (-15.6, 5.1)
	Min, Max	-33.3, 5.1	-40.0, 200.0	-40.0, 200.0

[1]Baseline is defined as the last non-missing value prior to the first dose.

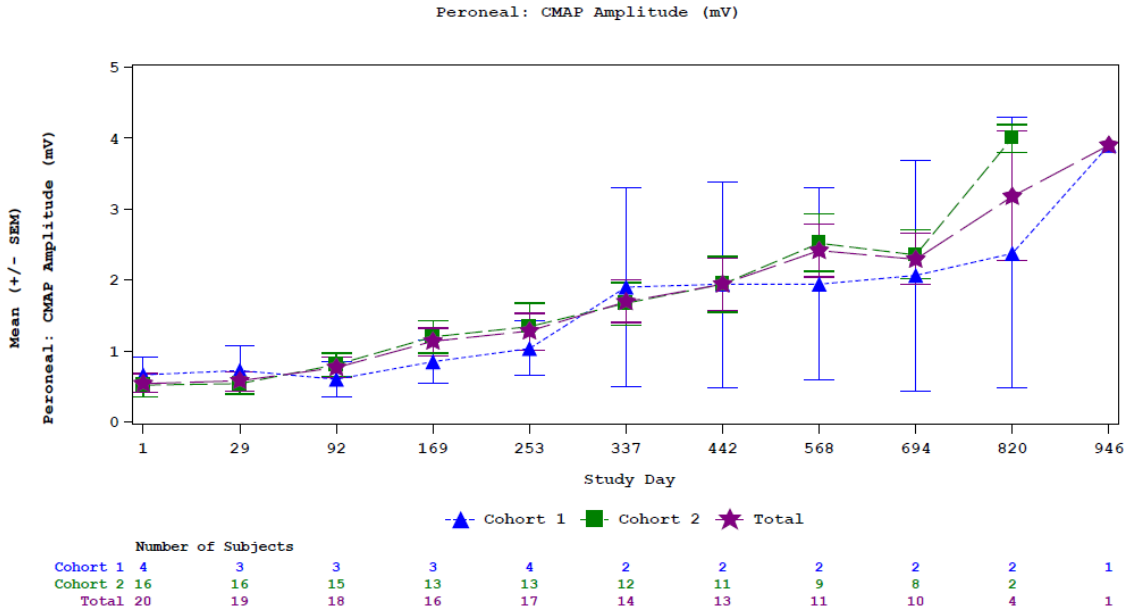
Parameter		Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Peroneal: CMAP Amplitude (mV)	Day 92			
	N	3	15	18
	Mean (SD, SEM)	0.61 (0.43, 0.25)	0.81 (0.65, 0.17)	0.78 (0.62, 0.15)
	Median (P25, P75)	0.82 (0.12, 0.90)	0.71 (0.40, 0.90)	0.76 (0.40, 0.90)
	Min, Max	0.12, 0.90	0.00, 2.70	0.00, 2.70
	Change from Baseline			
	N	3	15	18
	Mean (SD, SEM)	-0.08 (0.47, 0.27)	0.30 (0.37, 0.09)	0.24 (0.40, 0.09)
	Median (P25, P75)	-0.18 (-0.50, 0.43)	0.24 (-0.03, 0.60)	0.15 (-0.03, 0.50)
	Min, Max	-0.50, 0.43	-0.10, 1.10	-0.50, 1.10
	Percent Change from Baseline			
	N	3	13	16
	Mean (SD, SEM)	4.8 (92.1, 53.2)	123.6 (145.0, 40.2)	101.3 (142.3, 35.6)
	Median (P25, P75)	-35.7 (-60.0, 110.3)	100.0 (-2.2, 275.0)	56.9 (-14.5, 220.8)
	Min, Max	-60.0, 110.3	-20.0, 350.0	-60.0, 350.0

[1]Baseline is defined as the last non-missing value prior to the first dose.

Parameter		Cohort 1 (N=4)	Cohort 2 (N=16)	Total (N=20)
Ulnar: CMAP Amplitude (mV)	Day 169			
	N	3	13	16
	Mean (SD, SEM)	0.270 (0.128, 0.074)	0.856 (0.910, 0.252)	0.746 (0.849, 0.212)
	Median (P25, P75)	0.300 (0.130, 0.380)	0.500 (0.380, 0.600)	0.400 (0.325, 0.600)
	Min, Max	0.130, 0.380	0.100, 3.000	0.100, 3.000
	Change from Baseline			
	N	3	13	16
	Mean (SD, SEM)	-0.160 (0.131, 0.076)	0.271 (0.314, 0.087)	0.190 (0.333, 0.083)
	Median (P25, P75)	-0.140 (-0.300, -0.040)	0.270 (0.200, 0.400)	0.235 (-0.090, 0.400)
	Min, Max	-0.300, -0.040	-0.220, 1.000	-0.300, 1.000
	Percent Change from Baseline			
	N	3	12	15
	Mean (SD, SEM)	-37.1 (23.9, 13.8)	167.5 (176.4, 50.9)	126.6 (178.1, 46.0)
	Median (P25, P75)	-50.0 (-51.9, -9.5)	150.0 (9.1, 289.4)	50.0 (-9.5, 245.5)
	Min, Max	-51.9, -9.5	-38.6, 500.0	-51.9, 500.0

[1]Baseline is defined as the last non-missing value prior to the first dose.

Figure 18: CMAP Over Time: Mean Results, Safety Population (N = 20). Cohort 1 had 6mg loading dose. Cohort 2 had 12mg loading dose. Source: CS3A CSR, p. 114



6.2.2. Study SM201: An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

Study SM201 was a multicenter, open-label study in up to 25 infants with genetically diagnosed, presymptomatic SMA who were ≤6 weeks of age at the time of enrollment. Eligible subjects had a genetic diagnosis of 5q SMA and 2 or 3 copies of SMN2 (corresponding to types 1, 2, or 3 SMA) but no signs or symptoms of SMA. The study examined 12 mg equivalent loading and maintenance doses of ISIS 396443 in an identical regimen to the sham-procedure controlled study CS3B, described in Section 6.1 above. Study SM201 evaluated both motor function and survival along with safety and PK of ISIS 396443. Preliminary efficacy data for thirteen subjects evaluated at up to 64 days were available. (Clinical Overview, p. 12; Summary of Clinical Efficacy iii, p. 53).

The primary endpoint of the study was the time to death or respiratory intervention (invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 days OR tracheostomy).

The secondary efficacy endpoints of this study were as follows (all were assessed at approximately 13 and 24 months of age unless otherwise noted):

- Proportion of subjects who developed clinically manifested SMA as defined by any of the following:
  - Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support
  - Failure to achieve the ability to sit without support
  - Failure to achieve standing with assistance
  - Failure to achieve hands and knees crawling
  - Failure to achieve walking with assistance by 24 months of age
  - Failure to achieve standing alone by 24 months of age
  - Failure to achieve walking alone by 24 months of age

- Proportion of subjects alive at 13 and 24 months of age
- Attainment of motor milestones assessed as part of the HINE, Section 2, at 13 and 24 months of age
- Attainment of motor milestones as assessed by WHO criteria at 13 and 24 months of
- age
- Change from Baseline in the CHOP INTEND motor function scale
- Change from Baseline in growth parameters: weight for age/length, head circumference, chest circumference, head-to-chest circumference ratio, and arm circumference (Study SM201 CSR, pp. 21-22)

6.2.2.1 Study SM201 Results

Primary Endpoint: Time to Death or Respiratory Intervention
No subject has met the primary endpoint of death or respiratory intervention, defined as either invasive or noninvasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days or tracheostomy.

Secondary endpoints

- **Proportion of subjects who developed clinically manifested SMA**

  Four out of 10 subjects who had an opportunity to have Days 183 assessments had manifestations of SMA symptoms, as illustrated in the following table provided by the applicant.

  Reviewer Comment: Note that no subjects lost motor milestones that had been attained, consistent with both the HINE motor milestone results of this study and the primary efficacy study CS3B.

Table 29: Summary of SMA Symptoms in Subjects Observed up to 6 Months of Age (Efficacy Set With Opportunity to Attend Day 183) . Source: SM201 CSR, p. 83

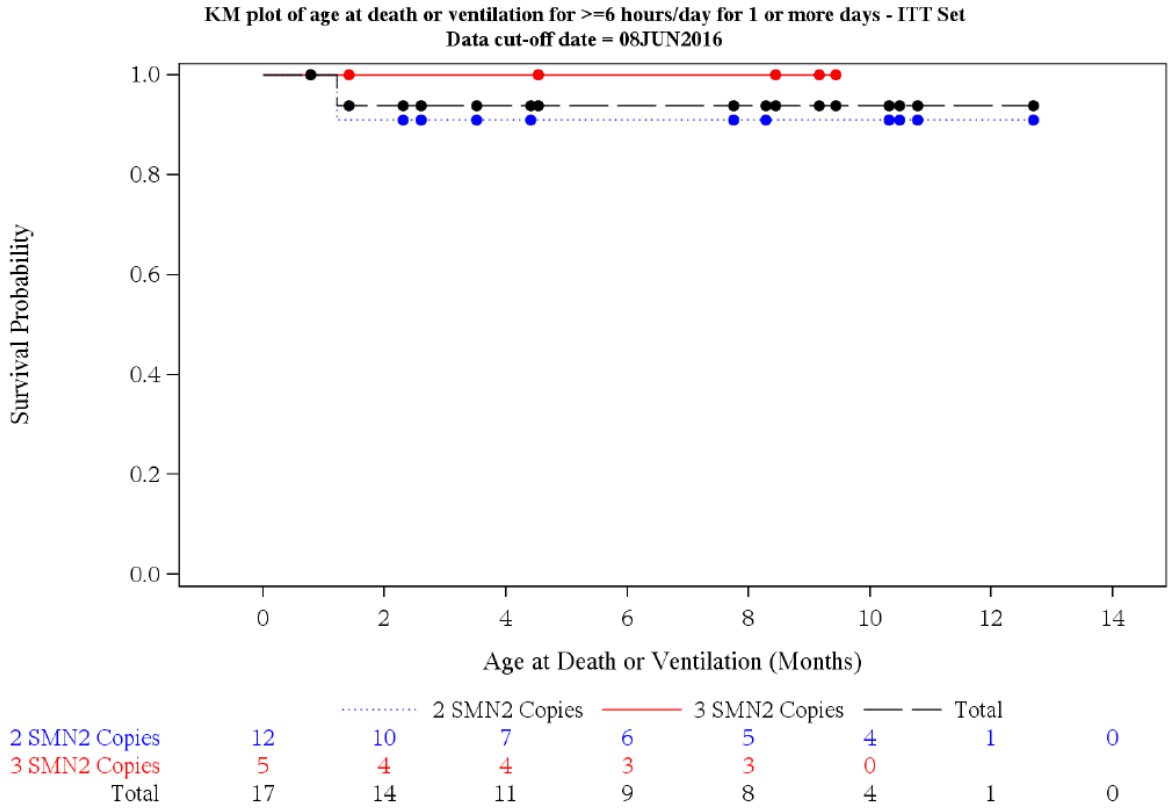
	ISIS 396443 2 SMN2 copies	ISIS 396443 3 SMN2 copies	Total
Number of subjects in Efficacy Set with an opportunity to attend Day 183	7 (100)	3 (100)	10 (100)
Number of subjects who have discontinued treatment	0	0	0
Number of subjects who have died	0	0	0
Number of subjects with percutaneous gastric tube inserted	1 (14)	0	1 (10)
Number of subjects with weight below the 5th percentile at Day 183	2 (29)	0	2 (20)
Number of subjects with weight dropping >2 major percentiles in 6 months to Day 183 (a)	3 (43)	1 (33)	4 (40)
Number of subjects who lose a WHO milestone (b)	0	0	0
Number of subjects with manifestation of SMA symptoms (c)	3	1	4
Proportion (95% CI) (d)	0.43 (0.12-0.80)	0.33 (0.02-0.87)	0.40 (0.14-0.73)

NOTE: Visit data up to Day 183 visit date used to assess each symptom, except where stated.
(a) Major WHO percentiles considered are 3rd, 5th, 10th, 25th and 50th.
(b) Any subject who having been judged by the investigator to have achieved a WHO milestone but at a subsequent assessment is judged to have 'No, inability'.
(c) Criteria considered here to indicate manifestation of SMA symptoms: Discontinuation, Death, Gastric tube inserted, weight below 5th WHO percentile, weight dropping >2 major percentiles, lose the ability to perform a WHO milestone.
(d) Wilson Score CI with continuity correction.

- **Proportion of subjects alive at 13 and 24 months of age**

  The applicant reports that no subjects had died by the time of data reporting. One subject had reached 13 months of age, as shown in the figure below. No subjects had yet reached 24 months of age at the time of data reporting for this application.

Figure 19: Kaplan-Meier Plot of Age at Death or Ventilation for ≥6 Hours/Day for 1 or More Days - ITT Set. Source: SM201 CSR, p. 394



Reviewer Comment: Most type 1 SMA patients do not survive to 24 months of age, and less than 25% would be expected to survive to 13 months of age without treatment. Intensive ventilatory support can extend life beyond 24 months. The applicant reports that 6/10 patients with efficacy data for day 183 had not yet manifested any SMA symptoms. Note, however, that 3 of the 10 subjects had 3 copies of SMN2, which corresponds to type 2 or 3 SMA, in which patients typically survive into adulthood.

- **Attainment of motor milestones assessed as part of the HINE, Section 2, at 13 and 24 months of age**

  Reviewer comment: As seen in the following table copied from the applicant, there appears to be a positive trend of increasing motor milestone scores that is consistent with the results of the primary efficacy study CS3B, described above in Section 6.1.

Table 30: HINE Total Motor Milestones: Change From Baseline by Visit - Efficacy Set. Source: SM201 CSR, pp. 244-245

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
n	9		4		13	
Mean	2.3		4.8		3.1	
SD	1.41		1.71		1.85	
Median	3.0		4.5		3.0	
Min, Max	0, 4		3, 7		0, 7	
Day 64						
n	9	9	4	4	13	13
Mean	4.4	2.1	7.8	3.0	5.5	2.4
Baseline mean	2.3		4.8		3.1	
Baseline median	3.0		4.5		3.0	
SD	1.74	1.17	2.22	2.94	2.40	1.80
Median	4.0	2.0	7.0	2.5	6.0	2.0
Min, Max	2, 7	1, 4	6, 11	0, 7	2, 11	0, 7
Day 183						
n	7	7	3	3	10	10
Mean	11.3	9.1	17.3	12.0	13.1	10.0
Baseline mean	2.1		5.3		3.1	
Baseline median	3.0		5.0		3.0	
SD	4.03	3.72	1.15	1.73	4.43	3.43
Median	10.0	9.0	18.0	11.0	15.0	10.5
Min, Max	6, 16	3, 14	16, 18	11, 14	6, 18	3, 14
Day 302						
n	5	5			5	5
Mean	16.0	14.4			16.0	14.4
Baseline mean	1.6				1.6	
Baseline median	2.0				2.0	
SD	4.80	4.77			4.80	4.77
Median	17.0	14.0			17.0	14.0
Min, Max	11, 23	9, 21			11, 23	9, 21

Subject 504-003 attended the Day 64 assessment on study day 98.
Where at least one milestone is assessed at a visit and the remainder are missing, an imputation is performed to allow a total score to be evaluated.

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 365						
n	1	1			1	1
Mean	25.0	23.0			25.0	23.0
Baseline mean	2.0				2.0	
Baseline median	2.0				2.0	
SD						
Median	25.0	23.0			25.0	23.0
Min, Max	25, 25	23, 23			25, 25	23, 23

Subject 504-003 attended the Day 64 assessment on study day 98.
Where at least one milestone is assessed at a visit and the remainder are missing, an imputation is performed to allow a total score to be evaluated.

- **Attainment of motor milestones as assessed by WHO criteria at 13 and 24 months of age**

  The applicant reports that "at Day 302, 5 subjects with 2 SMN2 copies had a WHO motor milestone assessment, and 1 subject achieved the WHO motor milestone of sitting without support, while 1 subject, who was able to sit without support at Day 183, achieved the WHO motor milestones of crawling on hands and knees, standing with assistance, and walking with assistance. This subject achieved the WHO motor milestone of standing alone at Day 365" (SM201 CSR, p. 74).

  Reviewer Comment: The reported motor milestone development is inconsistent with the natural history of SMA and is consistent with the results of the primary efficacy study CS3B, described above in Section 6.1. Note that no subjects in study CS3B became able to walk, whereas one of five subjects (20%) with 2 SMN2 copies corresponding to type 1 SMA in study SM201 became able to walk with assistance and stand alone. This result suggests that earlier treatment may yield a greater benefit.

Table 31: WHO motor milestones by visit - Efficacy Set. Source: SM201 CSR, pp. 428-435

	Baseline		
	ISIS 396443 2 SMN2 copies	ISIS 396443 3 SMN2 copies	Total
Sitting without Support			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0
Hands-and-knees Crawling			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0
Standing with Assistance			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0

NOTE: Numbers in parentheses are percentages. Subject 504-003 attended the Day 64 assessment on study day 98.

	Baseline		
	ISIS 396443 2 SMN2 copies	ISIS 396443 3 SMN2 copies	Total
Walking with Assistance			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0
Standing Alone			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0
Walking Alone			
n	7 (100)	3 (100)	10 (100)
No (inability)	7 (100)	3 (100)	10 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0

NOTE: Numbers in parentheses are percentages. Subject 504-003 attended the Day 64 assessment on study day 98.

Day 302

	ISIS 396443 2 SMN2 copies	ISIS 396443 3 SMN2 copies	Total
Sitting without Support			
n	5 (100)	0	5 (100)
No (inability)	1 (20)	0	1 (20)
No (refusal)	0	0	0
Yes	4 (80)	0	4 (80)
Unable to test	0	0	0
Hands-and-knees Crawling			
n	5 (100)	0	5 (100)
No (inability)	4 (80)	0	4 (80)
No (refusal)	0	0	0
Yes	1 (20)	0	1 (20)
Unable to test	0	0	0
Standing with Assistance			
n	5 (100)	0	5 (100)
No (inability)	3 (60)	0	3 (60)
No (refusal)	0	0	0
Yes	2 (40)	0	2 (40)
Unable to test	0	0	0

NOTE: Numbers in parentheses are percentages. Subject 504-003 attended the Day 64 assessment on study day 98.

Day 302

	ISIS 396443 2 SMN2 copies	ISIS 396443 3 SMN2 copies	Total
Walking with Assistance			
n	5 (100)	0	5 (100)
No (inability)	4 (80)	0	4 (80)
No (refusal)	0	0	0
Yes	1 (20)	0	1 (20)
Unable to test	0	0	0
Standing Alone			
n	5 (100)	0	5 (100)
No (inability)	5 (100)	0	5 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0
Walking Alone			
n	5 (100)	0	5 (100)
No (inability)	5 (100)	0	5 (100)
No (refusal)	0	0	0
Yes	0	0	0
Unable to test	0	0	0

NOTE: Numbers in parentheses are percentages. Subject 504-003 attended the Day 64 assessment on study day 98.

- **Change from Baseline in the CHOP INTEND motor function scale.**

  Reviewer comment: As seen in the table below copied from the applicant, there appears to be a positive trend of increasing CHOP INTEND scores that is consistent with the results of the primary efficacy study CS3B, described above in Section 6.1.

Table 32: Total CHOP INTEND: Change From Baseline by Visit - Efficacy Set. Source: Study SM201 CSR, p. 143

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Baseline						
n	9		4		13	
Mean	48.9		53.5		50.3	
SD	8.71		9.15		8.74	
Median	45.0		57.0		55.0	
Min, Max	39, 60		40, 60		39, 60	
Day 64						
n	9	9	4	4	13	13
Mean	51.0	2.1	61.8	8.3	54.3	4.0
Baseline mean	48.9		53.5		50.3	
Baseline median	45.0		57.0		55.0	
SD	7.30	6.21	2.63	6.95	7.99	6.82
Median	53.0	2.0	62.5	6.5	57.0	4.0
Min, Max	41, 60	-6, 15	58, 64	2, 18	41, 64	-6, 18

Subject 504-003 attended the Day 64 assessment on study day 98.

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 183						
n	7	7	3	3	10	10
Mean	58.6	9.9	62.7	10.7	59.8	10.1
Baseline mean	48.7		52.0		49.7	
Baseline median	45.0		56.0		50.5	
SD	4.58	7.93	2.31	8.33	4.37	7.58
Median	60.0	11.0	64.0	8.0	60.0	9.5
Min, Max	50, 64	-1, 20	60, 64	4, 20	50, 64	-1, 20
Day 302						
n	5	5			5	5
Mean	56.2	5.2			56.2	5.2
Baseline mean	51.0				51.0	
Baseline median	57.0				57.0	
SD	7.85	8.64			7.85	8.64
Median	58.0	4.0			58.0	4.0
Min, Max	43, 64	-2, 19			43, 64	-2, 19

Subject 504-003 attended the Day 64 assessment on study day 98.

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 365						
n	1	1			1	1
Mean	64.0	7.0			64.0	7.0
Baseline mean	57.0				57.0	
Baseline median	57.0				57.0	
SD						
Median	64.0	7.0			64.0	7.0
Min, Max	64, 64	7, 7			64, 64	7, 7

Subject 504-003 attended the Day 64 assessment on study day 98.

- **Change from Baseline in growth parameters:**
  weight for age/length, head circumference, chest circumference, head-to-chest circumference ratio, and arm circumference (Study SM201 CSR, pp. 21-22)

  The applicant reports that at Day 183, 4 subjects (3 subjects with 2 SMN2 copies and 1 subject with 3 SMN2 copies) were determined to have growth failure because their weight for age decreased by ≥2 major percentiles. Individual length for age percentiles increased over time for all subjects. At Day 183, 4 subjects were within the 10th and 75th percentile for length for age, 3 subjects were ≤3rd percentile for length for age, and 2 subjects were above the 95th percentile for length for age.

  Reviewer Comment: These open-label and uncontrolled results for a small study population are of unclear clinical significance.

Table 33: A subset of growth parameters at day 302 of Study SM201. Source: SM201 CSR, pp. 342-353

Parameter: Weight (kg)

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 302						
n	5	5			5	5
Mean	7.600	4.156			7.600	4.156
Baseline mean	3.444				3.444	
Baseline median	3.310				3.310	
SD	1.3168	1.6506			1.3168	1.6506
Median	7.250	3.920			7.250	3.920
Min, Max	6.05, 9.42	2.57, 6.11			6.05, 9.42	2.57, 6.11
Day 303						
n	5	5			5	5
Mean	7.606	4.162			7.606	4.162
Baseline mean	3.444				3.444	
Baseline median	3.310				3.310	
SD	1.4130	1.7163			1.4130	1.7163
Median	7.280	3.920			7.280	3.920
Min, Max	5.94, 9.65	2.48, 6.34			5.94, 9.65	2.48, 6.34

Parameter: Body Length (cm)

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 183						
n	7	7	3	3	10	10
Mean	65.59	13.80	68.17	14.47	66.36	14.00
Baseline mean	51.79		53.70		52.36	
Baseline median	51.00		55.00		52.65	
SD	3.795	4.243	6.110	3.782	4.411	3.909
Median	65.90	12.10	69.50	13.90	66.00	13.00
Min, Max	61.0, 71.6	10.1, 22.6	61.5, 73.5	11.0, 18.5	61.0, 73.5	10.1, 22.6
Day 302						
n	5	5			5	5
Mean	69.96	19.18			69.96	19.18
Baseline mean	50.78				50.78	
Baseline median	49.00				49.00	
SD	5.600	5.229			5.600	5.229
Median	69.50	18.50			69.50	18.50
Min, Max	62.5, 76.3	13.6, 27.3			62.5, 76.3	13.6, 27.3

Parameter: Head Circumference (cm)

	ISIS 396443 2 SMN2 copies		ISIS 396443 3 SMN2 copies		Total	
	Actual result	Change from baseline	Actual result	Change from baseline	Actual result	Change from baseline
Day 183						
n	7	7	3	3	10	10
Mean	43.87	7.69	44.37	6.37	44.02	7.29
Baseline mean	36.19		38.00		36.73	
Baseline median	35.50		38.40		36.15	
SD	1.715	1.110	2.359	0.208	1.804	1.112
Median	43.30	8.00	44.60	6.30	43.80	7.05
Min, Max	42.0, 47.3	6.2, 9.1	41.9, 46.6	6.2, 6.6	41.9, 47.3	6.2, 9.1
Day 302						
n	5	5			5	5
Mean	45.00	9.40			45.00	9.40
Baseline mean	35.60				35.60	
Baseline median	35.30				35.30	
SD	1.395	1.229			1.395	1.229
Median	45.00	9.50			45.00	9.50
Min, Max	43.0, 46.7	7.7, 10.6			43.0, 46.7	7.7, 10.6

6.2.3. **Study CS1: An Open-label, Escalating Dose Study to Assess the Safety, Tolerability and Dose-range Finding of a Single Intrathecal Dose of ISIS 396443 in Patients with Spinal Muscular Atrophy**

Study CS1 was a Phase 1, open-label, single-dose, dose-escalation study to evaluate the safety, tolerability, and PK of a single dose of ISIS 396443 administered IT in subjects with SMA who were 2 to 14 years of age. The study consisted of 4 dose cohorts (Cohort 1 = 1 mg ISIS 396443, [n = 6]; Cohort 2 = 3 mg ISIS 396443, [n = 6]; Cohort 3 = 6 mg ISIS 396443, [n = 6]; and Cohort 4 = 9 mg ISIS 396443, [n = 10]).

Exploratory Efficacy Variables

As described by the applicant (CS1 CSR, pp. 31-32), the following exploratory efficacy variables were assessed.

At Baseline, Day 29, and Day 85 (Cohorts 3 and 4 only), subjects were evaluated using the
Hammersmith Functional Motor Scale – Expanded (HFMSE). The HFMSE is a tool used to assess motor function in children that has been validated for use in SMA (Glanzman 2011). The maximum score for this test is 66; higher scores indicate better motor function.

Health-related quality of life was assessed using the Pediatric Quality of Life Inventory™ (Generic Core Scales and Neuromuscular Module).

In Cohort 4 only, plasma samples were collected at Baseline, Day 29, and Day 85 for evaluation using the Spinal Muscular Atrophy-Multi Analyte Profiling (SMA-MAP) plasma biomarker panel, an exploratory method for identifying potential biomarkers of SMA disease.

In Cohort 4 only, measurements of Compound Muscle Action Potential (CMAP) and quantitative multipoint Motor Unit Number Estimation (MUNE) were assessed in subjects at Baseline and End-of Study (Day 85). CMAP and MUNE are electrophysiological techniques that used to assess motor neurons in a muscle or group of muscles.

6.2.3.1 Study CS1 Results

The HFMSE results are shown in the following table, copied from the applicant. There is an increase in HFMSE scores that was largest in the 9mg dose cohort at the Day 85 assessment.

Reviewer Comment: This result could suggest a nusinersen dose-dependent improvement in motor function as measured by the HFMSE, although the performance at the 6mg dose was worse than at the 3mg or 1mg doses at day 29.

Table 34: Hammersmith Test of Motor Function – Expanded Version Data for all Subjects Enrolled in ISIS 396443-CS1. Source: CS1 CSR, p. 53

	Cohort 1 (1 mg) N = 6	Cohort 2 (3 mg) N = 6	Cohort 3 (6 mg) N = 6	Cohort 4 (9 mg) N = 7[a]/10
Day 29				
Baseline Mean Score	34.5	34.2	26.0	25.5
Mean Change from Baseline	+1.0	+1.0	-0.3	+2.4*
Median Change from Baseline	+0.5	0.0	0.0	+3.0
Minimum, Maximum	-1, 4	0, 4	-3, 1	0, 4
Mean % Change From Baseline	+0.3%	+2.2%	-3.5%	+12.4%*
Minimum, Maximum	-12.5, 8.9	0.0, 9.3	-25.0, 6.7	0.0, 36.4
Subjects with ≥ 3 Point Increase	1/6 (16.7%)	1/6 (16.7%)	0/6 (0%)	4/7 (57.0%)
Day 85				
Baseline Mean Score	NA[b]	NA[b]	26.0	25.5
Mean Change From Baseline			+0.7	+3.1‡
Median Change from Baseline			-0.5	+4.0
Minimum, Maximum			-3.0, 5.0	-1.0, 7.0
Mean % Change From Baseline			+5.4%	+17.6%‡
Minimum, Maximum			-20.0, 41.7	-1.9, 45.5
Subjects with ≥ 3 Point Increase			2/6 (33.3%)	7/10 (70.0%)

NA = Not available; N = number of subjects
a Seven of the 10 subjects in Cohort 4 were evaluated at Day 29, as allowed in the protocol
b Subjects in Cohorts 1 and 2 were followed through Day 29 only
* P value = 0.03;
‡ P value = 0.02

The Pediatric Quality of Life Inventory showed higher health-related quality of life assessments over time with increasing dose, as seen in the following table copied from the applicant.

Reviewer Comment: Note that although the quality of life results appear favorable towards nusinersen, such subjective measurements are susceptible to bias given the open-label nature of the study.

Table 35: Summary of PedsQL Generic Core Scales - Patient: Total Score Safety Population (N=28)

	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Baseline					
N	4	4	3	7	18
Mean (SD)	64.7 (14.7)	66.0 (12.7)	55.8 (10.7)	67.2 (17.1)	64.5 (14.2)
Median (P25, P75)	59.8 (54.9, 74.5)	60.9 (58.1, 73.9)	62.0 (43.5, 62.0)	68.5 (57.6, 81.5)	62.5 (57.5, 73.9)
Min - Max	53.3 - 85.9	57.5 - 84.8	43.5 - 62.0	37.0 - 89.1	37.0 - 89.1

	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 29					
N	4	4	3	6	17
Mean (SD)	61.4 (18.0)	66.6 (12.6)	57.6 (9.3)	77.0 (12.1)	67.5 (14.4)
Median (P25, P75)	57.1 (50.5, 72.3)	62.6 (58.3, 75.0)	58.7 (47.8, 66.3)	75.5 (67.4, 84.8)	65.2 (57.6, 79.3)
Min - Max	44.6 - 87.0	56.5 - 84.8	47.8 - 66.3	63.0 - 95.7	44.6 - 95.7
Day 29 - Change from Baseline					
N	4	4	3	6	17
Mean (SD)	-3.3 (5.1)	0.6 (2.2)	1.8 (4.4)	4.7 (11.6)	1.4 (7.7)
Median (P25, P75)	-2.7 (-7.6, 1.1)	1.1 (-1.1, 2.3)	4.3 (-3.3, 4.3)	6.0 (-6.5, 10.9)	1.1 (-3.3, 4.3)
Min - Max	-8.7 - 1.1	-2.2 - 2.5	-3.3 - 4.3	-9.8 - 21.7	-9.8 - 21.7

	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 29 - Percent Change from Baseline					
N	4	4	3	6	17
Mean (SD)	-5.9 (9.0)	1.0 (3.7)	3.9 (8.1)	7.7 (17.0)	2.3 (12.0)
Median (P25, P75)	-4.5 (-13.3, 1.6)	1.7 (-1.9, 3.9)	7.0 (-5.3, 10.0)	8.4 (-8.8, 15.9)	1.9 (-5.3, 7.3)
Min - Max	-16.3 - 1.9	-3.7 - 4.3	-5.3 - 10.0	-12.0 - 34.5	-16.3 - 34.5

	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 85					
N	0	0	4	7	11
Mean (SD)			62.0 (10.9)	71.4 (12.4)	68.0 (12.3)
Median (P25, P75)			63.0 (54.3, 69.6)	76.1 (65.2, 79.3)	73.9 (60.9, 77.2)
Min - Max			47.8 - 73.9	45.7 - 80.4	45.7 - 80.4
Day 85 - Change from Baseline					
N	0	0	3	7	10
Mean (SD)			2.2 (2.9)	4.2 (13.4)	3.6 (11.1)
Median (P25, P75)			3.3 (-1.1, 4.3)	8.7 (-8.7, 17.4)	3.8 (-5.4, 8.7)
Min - Max			-1.1 - 4.3	-13.0 - 21.7	-13.0 - 21.7

	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 85 - Percent Change from Baseline					
N	0	0	3	7	10
Mean (SD)			4.5 (5.9)	9.8 (20.9)	8.2 (17.5)
Median (P25, P75)			5.3 (-1.8, 10.0)	12.7 (-11.8, 27.6)	7.6 (-6.7, 23.5)
Min - Max			-1.8 - 10.0	-14.6 - 37.7	-14.6 - 37.7

The applicant reports that no clinically significant changes from baseline were noted from the assessment of the exploratory SMA-MAP plasma biomarker panel in the Cohort 4 subjects studied. Data tables from the applicant are presented in Appendix 13.7.

In Cohort 4 only, measurements of Compound Muscle Action Potential (CMAP) and quantitative multipoint Motor Unit Number Estimation (MUNE) were assessed in subjects at Baseline and End-of Study (Day 85). As seen in the tables below, there was a small (6%) drop in CMAP amplitude at the day 85 assessment compared to baseline and a 37% increase in MUNE.

Reviewer Comment: This observed increase in the number of motor units in the studied muscle is difficult to interpret. Kang et al. (2014) reported a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in SMA2 patients.

Table 36: Summary of CMAP Amplitude, Safety Population (N=28). Source: CS1 CSR, p. 195

CMAP Amplitude (mV)	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Baseline					
N	0	0	0	10	10
Mean (SD)				3.1 (2.9)	3.1 (2.9)
Median (P25, P75)				1.2 (0.9, 5.9)	1.2 (0.9, 5.9)
Min - Max				0.4 - 8.1	0.4 - 8.1

CMAP Amplitude (mV)	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 85					
N	0	0	0	9	9
Mean (SD)				3.2 (2.8)	3.2 (2.8)
Median (P25, P75)				1.5 (1.2, 4.8)	1.5 (1.2, 4.8)
Min - Max				0.5 - 7.5	0.5 - 7.5
Day 85 - Change from Baseline					
N	0	0	0	9	9
Mean (SD)				-0.2 (1.0)	-0.2 (1.0)
Median (P25, P75)				-0.1 (-0.7, 0.3)	-0.1 (-0.7, 0.3)
Min - Max				-2.1 - 1.5	-2.1 - 1.5

CMAP Amplitude (mV)	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Day 85 - Percent Change from Baseline					
N	0	0	0	9	9
Mean (SD)				1.9 (33.1)	1.9 (33.1)
Median (P25, P75)				-7.7 (-12.7, 25.0)	-7.7 (-12.7, 25.0)
Min - Max				-37.5 - 66.7	-37.5 - 66.7

Table 37: Summary of MUNE, Safety Population (N=28). Source: CS1 CSR, p. 202

MUNE	ISIS-396443 1 mg	ISIS-396443 3 mg	ISIS-396443 6 mg	ISIS-396443 9 mg	Total
	(N=6)	(N=6)	(N=6)	(N=10)	(N=28)
Baseline					
N	0	0	0	10	10
Mean (SD)				46.8 (45.0)	46.8 (45.0)
Median (P25, P75)				25.0 (12.3, 61.2)	25.0 (12.3, 61.2)
Min - Max				8.4 - 137.4	8.4 - 137.4
Day 85					
N	0	0	0	9	9
Mean (SD)				68.1 (57.8)	68.1 (57.8)
Median (P25, P75)				38.9 (27.4,101.7)	38.9 (27.4,101.7)
Min - Max				6.8 - 177.2	6.8 - 177.2
Day 85 - Change from Baseline					
N	0	0	0	9	9
Mean (SD)				16.9 (15.1)	16.9 (15.1)
Median (P25, P75)				14.1 (10.6, 21.7)	14.1 (10.6, 21.7)
Min - Max				-5.5 - 40.5	-5.5 - 40.5
Day 85 - Percent Change from Baseline					
N	0	0	0	9	9
Mean (SD)				37.4 (43.8)	37.4 (43.8)
Median (P25, P75)				28.9 (22.0, 56.5)	28.9 (22.0, 56.5)
Min - Max				-44.7 - 119.1	-44.7 - 119.1

6.2.4. Study CS10: An Open-label Study to Assess the Safety and Tolerability of a Single Intrathecal Dose of ISIS 396443 in Patients with Spinal Muscular Atrophy Who Previously Participated in ISIS 396443-CS1

Study CS10 was an open-label study to evaluate the safety, tolerability, and PK of a single dose of ISIS 396443 (6 or 9 mg) administered IT by lumbar puncture (LP) in subjects with SMA who previously participated in ISIS 396443-CS1. This study was initiated using a single dose of 6 mg ISIS 396443 (4 subjects enrolled); however, emerging data indicated that 9 mg ISIS 396443 was well-tolerated and thus the study was amended to a single dose of 9 mg ISIS 396443 (14 subjects enrolled). (CS10 CSR, p. 2)

The same exploratory efficacy variables described above for study CS1 (HFMSE, Pediatric Quality of Life Inventory™, CMAP and MUNE, but without the Spinal Muscular Atrophy-Multi Analyte Profiling (SMA-MAP) plasma biomarker panel) were used for study CS10.

6.2.4.1 Study CS10 Results

HFMSE was measured at Screening, Day 85, and Day 169 or early termination. The results are summarized in the following figure and table copied from the applicant, which shows the largest changes from baseline in the cohort that received the highest dose, 9mg, in both studies CS1 and CS10.

Reviewer Comment: This result provides further support to the interpretation that there is a nusinersen dose-dependent improvement in motor function.

Figure 20: Long-Term Progression of HFMSE Scores from ISIS 396443-CS1 Baseline to ISIS 396443-CS10 Day 169 as Presented by their ISIS 396443-CS1 Dose Cohort. Bars represent Mean ± SD. Source: CS10 CSR, p. 44

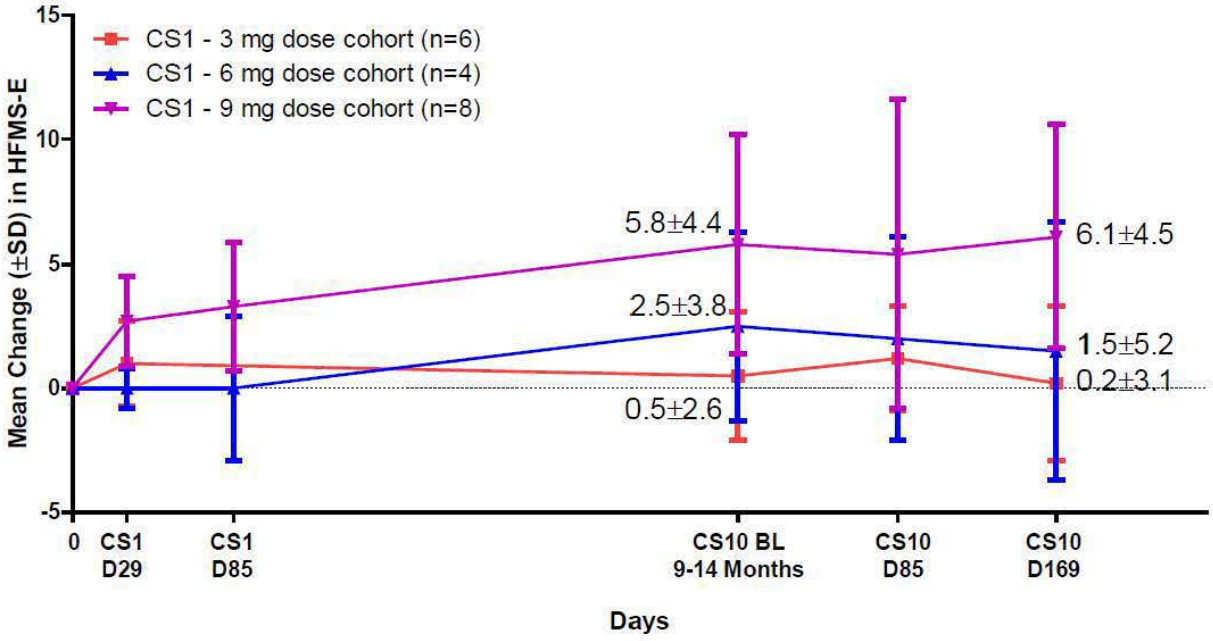


Table 38: Hammersmith Test of Motor Function - Expanded Version Data - ISIS 396443-CS1 and ISIS 396443-CS10. Source: CS10 CSR, p. 45

	3 mg ISIS 396443-CS1 dose cohort N = 6	6 mg ISIS 396443-CS1 dose cohort N = 4	9 mg ISIS 396443-CS1 dose cohort N = 8
CS1 Baseline			
Mean Score	34.2	25.5	29.5
CS10 Baseline			
Mean Score	34.7	28.0	35.3
Mean Change from CS1 Baseline	0.5	2.5	5.8
Median Change from CS1 Baseline	0.5	1.0	4.5
Minimum, Maximum	-2.0, 5.0	0.0, 8.0	1.0, 14.0
Mean % Change From CS1 Baseline	-0.7%	13.3%	32.8%
Minimum, Maximum	-15.4, 9.4	0.0, 40.0	1.9, 81.8
Subjects with ≥ 3 point Increase	1/6 (17%)	1/4 (25%)	6/8 (75%)
CS10 Day 85			
Mean Score	35.3	27.5	34.9
Mean Change From CS1 Baseline	1.2	2.0	5.4
Median Change from CS1 Baseline	0.5	0.5	5.5
Minimum, Maximum	-1.0, 5.0	-1.0, 8.0	-6.0, 15.0
Mean % Change From CS1 Baseline	2.6%	8.8%	35.8%
Minimum, Maximum	-2.0, 9.4	-6.7, 40.0	-11.5, 90.9
Subjects with ≥ 3 point Increase	1/6 (17%)	1/4 (25%)	6/8 (75%)
CS10 Day 169			
Mean Score	34.3	27.0	35.6
Mean Change From CS1 Baseline	0.2	1.5	6.1
Median Change from CS1 Baseline	-1.0	0.0	5.5
Minimum, Maximum	-2.0, 6.0	-3.0, 9.0	0.0, 14.0
Mean % Change From CS1 Baseline	-1.4%	6.3%	36.6%
Minimum, Maximum	-15.4, 11.3	-20.0, 45.0	0.0, 100.0
Subjects with ≥ 3 point Increase	1/6 (17%)	1/4 (25%)	7/8 (88%)

Abbreviations: CS1 = ISIS 396443-CS1; CS10 = ISIS 396443-CS10; N = number of subjects.

The applicant reports that the patient-reported Pediatric Quality of Life Inventory™ was incomplete because some patients were too young to complete the questionnaire. The patient and parental results are summarized in the following tables, copied from the applicant.

Reviewer Comment: Parents appear to favor the higher two nusinersen doses (6mg, 9mg) in the parental quality of life responses, while patients favor the two lower doses (3mg, 6mg).

However, these subjective results are difficult to interpret given the open-label nature of the study.

Table 39: Summary of PedsQL Generic Core Scales Compared to CS1 Baseline; Evaluable Population (N=18). Source: CS10 CSR, p. 252

	ISIS-396443 CS01 3 mg	ISIS-396443 CS01 6 mg	ISIS-396443 CS01 9 mg	Total
	(N=6)	(N=4)	(N=8)	(N=18)
CS10 Day 169				
N	6	3	5	14
Mean (SD)	61.8 (20.0)	50.7 (17.9)	69.3 (2.7)	62.1 (16.0)
Median (P25, P75)	59.2 (47.8, 69.6)	57.6 (30.4, 64.1)	69.6 (69.6, 69.6)	65.2 (53.3, 69.6)
Min - Max	39.1 - 95.7	30.4 - 64.1	65.2 - 72.8	30.4 - 95.7
CS10 Day 169 - Change from CS01 Baseline				
N	4	2	5	11
Mean (SD)	-2.7 (12.4)	8.2 (8.5)	-4.8 (10.8)	-1.7 (11.2)
Median (P25, P75)	-1.6 (-11.9, 6.5)	8.2 (2.2, 14.1)	-4.3 (-12.0, -3.3)	-3.3 (-12.0, 10.9)
Min - Max	-18.4 - 10.9	2.2 - 14.1	-16.3 - 12.0	-18.4 - 14.1

	ISIS-396443 CS01 3 mg	ISIS-396443 CS01 6 mg	ISIS-396443 CS01 9 mg	Total
	(N=6)	(N=4)	(N=8)	(N=18)
CS10 Day 169 - Percent Change from CS01 Baseline				
N	4	2	5	11
Mean (SD)	-6.2 (19.4)	18.0 (20.5)	-4.6 (15.3)	-1.1 (18.4)
Median (P25, P75)	-2.9 (-20.6, 8.1)	18.0 (3.5, 32.5)	-5.9 (-14.7, -4.8)	-4.8 (-14.7, 12.8)
Min - Max	-31.9 - 12.8	3.5 - 32.5	-18.3 - 20.8	-31.9 - 32.5

Table 40: Summary of PedsQL Generic Core Scales Compared to CS10 Baseline; Evaluable Population (N=18). Source: CS10 CSR, p. 254

	ISIS-396443 CS01 3 mg	ISIS-396443 CS01 6 mg	ISIS-396443 CS01 9 mg	Total
	(N=6)	(N=4)	(N=8)	(N=18)
CS10 Day 169				
N	6	3	5	14
Mean (SD)	61.8 (20.0)	50.7 (17.9)	69.3 (2.7)	62.1 (16.0)
Median (P25, P75)	59.2 (47.8, 69.6)	57.6 (30.4, 64.1)	69.6 (69.6, 69.6)	65.2 (53.3, 69.6)
Min - Max	39.1 - 95.7	30.4 - 64.1	65.2 - 72.8	30.4 - 95.7
CS10 Day 169 - Change from CS10 Baseline				
N	6	3	5	14
Mean (SD)	-0.2 (11.6)	4.3 (11.5)	-2.6 (4.4)	-0.1 (9.2)
Median (P25, P75)	3.3 (-10.9, 9.8)	3.3 (-6.5, 16.3)	-2.2 (-6.5, 1.1)	0.6 (-6.5, 6.5)
Min - Max	-17.4 - 10.9	-6.5 - 16.3	-7.6 - 2.2	-17.4 - 16.3

	ISIS-396443 CS01 3 mg	ISIS-396443 CS01 6 mg	ISIS-396443 CS01 9 mg	Total
	(N=6)	(N=4)	(N=8)	(N=18)
CS10 Day 169 - Percent Change from CS10 Baseline				
N	6	3	5	14
Mean (SD)	0.1 (21.2)	9.1 (28.7)	-3.4 (5.8)	0.8 (18.3)
Median (P25, P75)	3.7 (-18.5, 20.0)	5.4 (-17.6, 39.5)	-3.2 (-8.6, 1.5)	0.8 (-9.9, 7.3)
Min - Max	-30.8 - 22.5	-17.6 - 39.5	-9.9 - 3.2	-30.8 - 39.5

Table 41: PedsQLTM Generic Core Scales and Neuromuscular Module – Parent Assessments. Source: CS10 CSR, p. 47

	PedsQL™ Generic Core Scales Total Scores (Parent)		
	3 mg ISIS 396443-CS1 dose cohort N = 6	6 mg ISIS 396443-CS1 dose cohort N = 4	9 mg ISIS 396443-CS1 dose cohort N = 8
CS1 Baseline			
Mean	66.5	48.7	55.7
CS10 Baseline			
Mean	58.0	45.1	64.5
Mean Change From CS1 Baseline	-8.5	-3.7	8.8
Mean % Change From CS1 Baseline	-3.7%	-3.5%	17.0%
CS10 Day 169			
Mean	57.0	50.8	64.9
Mean Change From CS1 Baseline	-16.5	8.6	9.1
Mean % Change From CS1 Baseline	-20.2%	25.1%	16.2%
Mean Change From CS10 Baseline	-2.2	7.7	0.3
Mean % Cahnge Form CS10 Baseline	-4.3%	19.1%	0.2%
	PedsQL™ Neuromuscular Module Total Scores (Parent)		
CS1 Baseline			
Mean	74.8	58.8	73.1
CS10 Baseline			
Mean	72.8	54.3	76.5
Mean Change From CS1 Baseline	-2.0	-4.5	3.4
Mean % Change From CS1 Baseline	1.5%	-6.6%	5.7%
CS10 Day 169			
Mean	71.4	55.0	77.3
Mean Change From CS1 Baseline	-9.2	-0.3	4.1
Mean % Change From CS1 Baseline	-12.6%	1.2%	7.0%
Mean Change From CS10 Baseline	-3.8	2.3	0.7
Mean % Cahnge Form CS10 Baseline	-6.4%	5.1%	0.8%

Abbreviations: CS1 = ISIS 396443-CS1; CS10 = ISIS 396443-CS10; N = number of subjects; PedsQLTM = Pediatric Quality of Life Inventory.

CMAP and quantitative multipoint MUNE were assessed only in subjects who were previously enrolled in the 9-mg ISIS 396443-CS1 dose cohort (N = 8); assessments were performed at Screening, Day 85, and Day 169. The results are shown in the following tables copied from the applicant.

Reviewer Comment: These results are consistent with the results of study CS1, with a relatively stable CMAP amplitude and an increase in MUNE. This observed increase in the number of

motor units in the studied muscle is difficult to interpret. Kang et al. (2014) reported a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in SMA2 patients.

Table 42: CMAP and MUNE Results

	CMAP Amplitude (mV) N = 8	MUNE N = 8
CS1 Baseline		
Mean	3.7	56.3
Minimum – Maximum	0.8 - 8.1	12.3 - 137.4
CS10 Baseline		
Mean	3.3	70.5
Minimum – Maximum	0.4 – 9.4	7.4 - 167.9
Mean Change from CS1 Baseline	-0.4	14.3
Mean % Change from CS1 Baseline	-3.6%	29.3%
CS10 Day 169		
Mean	3.1	67.7
Median	2.3	46.0
Minimum – Maximum	0.4 – 8.6	5.7 – 161.6
Mean Change from CS1 Baseline	-0.6	11.4
Mean % Change from CS1 Baseline	-2.2%	24.7%
Mean Change from CS10 Baseline	-0.2	-2.9
Mean % Change from CS10 Baseline	0.9%	-0.3%

Abbreviations: CS1 = ISIS 396443-CS1; CS10 = ISIS 396443-CS10; CMAP = compound muscle action potential; MUNE = motor unit number estimation; N = number of subjects.

6.2.5. Study CS2: An Open-label, Dose Escalation Study to Assess the Safety, Tolerability and Dose-range Finding of Multiple Doses of ISIS 396443 Delivered Intrathecally to Patients with Spinal Muscular Atrophy

Study CS2 was a multiple-dose, dose-escalation study to test the safety, tolerability, and dose-range of ISIS 396443 administered as IT injections by lumbar puncture (LP) to SMA patients aged 2 to 15 years. Four (4) dose levels (3, 6, 9, and 12 mg) of ISIS 396443 were evaluated sequentially in 4 separate cohorts as follows:

- Cohort 1: 3 mg ISIS 396443 administered on Days 1, 29, and 85, IT injection
- Cohort 2: 6 mg ISIS 396443 administered on Days 1, 29, and 85, IT injection

• Cohort 3: 9 mg ISIS 396443 administered on Days 1 and 85, IT injection
• Cohort 4: 12 mg ISIS 396443 administered on Days 1, 29, and 85, IT injection (CS2 CSR, p. 22).

Exploratory efficacy variables included HFMSE, Pediatric Quality of Life Inventory™, CMAP and MUNE, the Upper Limb Module test, muscle strength using hand-held dynamyometry, the 6-minute Walk Test (6MWT), and the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) questionnaire. (CS2 CSR p. 38)

The Upper Limb Module Test assesses upper limb function in patients with SMA. It consists of 9 upper limb performance items (e.g., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container).

The 6MWT evaluates functional exercise capability by measuring the distance a person can walk in 6 minutes.

The ACEND questionnaire is intended to quantify the caregiver impact experienced by parents of children, including domains assessing physical impact (feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (time, emotion, and finance).

6.2.5.1 Study CS2 Results

Hammersmith Test of Motor Function Expanded Version (HFMSE) (CS2 CSR, p. 65)
Subjects were evaluated using the HFMSE at Baseline and on Days 92, 169, and 253. The results are shown in the following table and figure, copied from the applicant.

Reviewer Comment: There appears to be a consistent trend of increasing HFMSE over time with nusinersen treatment in the 6mg, 9mg, and 12mg cohorts.

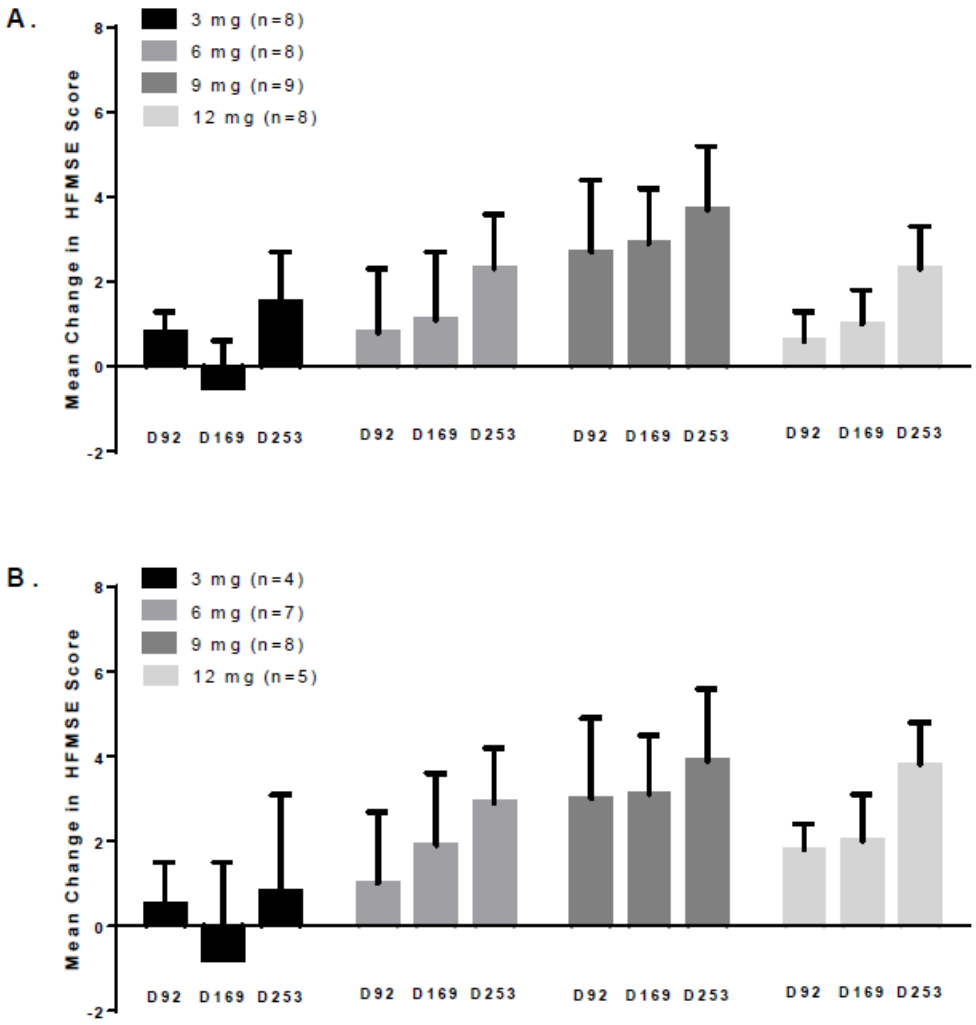
Table 43: Hammersmith Test of Motor Function Expanded Version Data for Efficacy Evaluable Subjects. Source: CS2 CSR, p. 72

	ISIS 396443 3 mg		ISIS 396443 6 mg		ISIS 396443 9 mg		ISIS 396443 12 mg	
BL HFMSE score (n)	All n = 8	> 10 and ≤ 54 n = 4	All n = 8	> 10 and ≤ 54 n = 7	All n = 9	> 10 and ≤ 54 n = 8	All n = 8	> 10 and ≤ 54 n = 5
Baseline								
Mean (SD)	31.9 20.7)	20.0 (7.7)	29.6 (15.3)	33.0 (12.9)	40.0 (16.4)	37.8 (15.9)	44.5 (18.0)	34.4 (15.0)
Minimum, Maximum	8.0, 57.0	14, 30	6.0, 50.0	17, 50.0	16.0, 58.0	16.0, 54.0	15.0, 63.0	15.0, 54.0
Day 92								
Mean (SD)	32.6 (20.9)	20.5 (7.7)	30.4 (16.5)	34.0 (14.0)	42.7 (14.4)	40.8 (14.1)	45.1 (16.7)	36.2 (14.7)
Mean Change from Baseline (SD)	0.8 (1.4)	0.5 (1.9)	0.8 (4.2)	1.0 (4.5)	2.7 (5.1)	3.0 (5.3)	0.6 (2.0)	1.8 (1.3)
Median Change from Baseline	1.0	0	-0.5	0	1.0	1.5	0.5	2.0
Minimum, Maximum	-1.0, 3.0	-1.0, 3.0	-4.0, 9.0	-4.0, 9.0	-3.0, 4.0	-3.0, 14.0	-2.0, 3.0	0.0, 3.0
Mean % Change from Baseline (SD)	3.5 (7.3)	2.6 (9.5)	0.3 (16.8)	2.7 (16.5)	11.6 (26.3)	13.1 (27.7)	3.7 (7.7)	7.2 (7.8)
Minimum, Maximum	-7.1, 13.6	-7.1, 13.6	-16.7, 36.0	-11.8, 36.0	-6.3, 77.8	-6.3, 77.8	-3.4, 20.0	0.0, 20.0

	ISIS 396443 3 mg		ISIS 396443 6 mg		ISIS 396443 9 mg		ISIS 396443 12 mg	
BL HFMSE score (n)	All n = 8	> 10 and ≤ 54 n = 4	All n = 8	> 10 and ≤ 54 n = 7	All n = 9	> 10 and ≤ 54 n = 8	All n = 8	> 10 and ≤ 54 n = 5
Day 169								
Mean (SD)	31.4 (21.1)	19.3 (9.3)	30.8 (17.3)	34.9 (13.9)	42.9 (15.1)	40.9 (14.8)	45.5 (16.4)	36.4 (13.7)
Mean Change from Baseline (SD)	-0.5 (3.1)	-0.8 (4.6)	1.1 (4.6)	1.9 (4.5)	2.9 (3.8)	3.1 (4.0)	1.0 (2.4)	2.0 (2.5)
Median Change from Baseline	0.0	0.0	-0.5	0.0	2.0	2.5	0.5	3.0
Minimum, Maximum	-7.0, 4.0	-7.0, 4.0	-4.0, 9.0	-3.0, 9.0	-1.0, 10.0	-1.0, 10.0	-2.0, 4.0	-2.0, 4.0
Mean % Change from Baseline (SD)	-2.8 (21.7)	-5.1 (32.9)	-3.5 (29.8)	5.5 (16.6)	10.7 (19.2)	11.9 (20.2)	4.9 (8.7)	8.6 (9.3)
Minimum, Maximum	-50.0, 28.6	-50.0, 28.6	-66.7, 36.0	-15, 36.0	-6.3, 55.6	-6.3, 55.6	-3.7, 20.0	-3.7, 20.0
Day 253								
Mean (SD)	33.4 (20.5)	20.8 (10.2)	31.9 (16.7)	35.9 (13.3)	43.7 (14.8)	41.6 (14.4)	46.8 (15.5)	38.2 (13.3)
Mean Change from Baseline (SD)	1.5 (3.5)	0.8 (4.6)	2.3 (3.7)	2.9 (3.5)	3.7 (4.4)	3.9 (4.7)	2.3 (2.8)	3.8 (2.3)
Median Change from Baseline	2.0	2.5	1.5	2	2.0	2.5	2.0	4.0
Minimum, Maximum	-6.0, 6.0	-6.0, 4.0	-2.0, 8.0	-1.0, 8.0	0.0, 12.0	0.0, 12.0	-1.0, 6.0	0.0, 6.0
Mean % Change from Baseline (SD)	10.8 (32.9)	1.5 (31.0)	4.1 (19.0)	9.5 (12.5)	13.4 (20.2)	14.7 (21.2)	9.4 (12.6)	15.4 (12.7)
Minimum, Maximum	-42.9, 75.0	-42.9, 28.6	-33.3, 32.0	-5.0, 32.0	0.0, 55.6	0.0, 55.6	-1.6, 33.3	0.0, 33.3

Abbreviations: N = number of subjects; SD = standard deviation

Figure 21: Mean (SEM) Change in HFMSE Score. Source: CS2 CSR, p. 71



Abbreviations: HFMSE = Hammersmith Functional Motor Scale - Expanded; SEM = standard error of the mean
A. For all efficacy evaluable subjects. B. For efficacy evaluable subjects with HFMSE BL ≥ 10 and ≤ 54.

Pediatric Quality of Life Inventory™

The patient results are summarized in the following table, copied from the applicant.

Reviewer Comment: The results appear similar across doses, but these subjective results are difficult to interpret given the open-label nature of the study.

Table 44: Summary of PedsQL™ Generic Core Scales - Patient: Total Score for Efficacy Evaluable Population. Source: CS2 CSR, p. 76

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)
Baseline, n	6	6	3	5
Mean (SD)	71.7 (12.7)	64.1 (14.4)	69.2 (13.4)	63.9 (6.6)
Minimum, Maximum	54.3, 91.3	46.7, 83.7	54.3, 80.4	55.4, 72.8
Day 169, n	6	6	3	5
Mean (SD)	73.7 (15.0)	59.8 (18.2)	71.7 (5.4)	72.0 (11.4)
Mean (SD) % Change from Baseline	2.7 (7.5)	-5.3 (24.7)	5.4 (14.4)	13.5 (21.5)
Minimum, Maximum	-12.5, 7.1	-39.4, 29.5	-4.1, 22.0	-6.9, 47.1
Day 253, n	6	6	3	5
Mean (SD)	72.8 (10.7)	69.4 (18.6)	75.0 (11.5)	67.6 (9.0)
Mean (SD) % Change from Baseline	3.0 (16.5)	7.5 (11.8)	9.5 (12.9)	5.7 (7.9)
Minimum, Maximum	-17.2, 30.0	-7.0, 27.3	-5.4, 17.9	-7.1, 11.8

Abbreviations: N = number of subjects; n = number of subjects in subgroup; PedsQL™ = Pediatric Quality of Life Inventory™; SD = standard deviation

Table 45: Summary of PedsQL™ Generic Core Scales - Parent: Total Score for Efficacy Evaluable Population. Source: CS2 CSR, p. 75

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)
Baseline, n	8	8	9	8
Mean (SD)	52.9 (10.5)	57.6 (16.8)	61.7 (17.5)	52.9 (21.4)
Minimum, Maximum	33.3, 65.2	29.3, 83.7	38.9, 90.5	30.4, 91.3
Day 169, n	8	8	9	8
Mean (SD)	57.3 (15.1)	58.4 (18.3)	68.2 (8.8)	55.9 (18.4)
Mean (SD) % Change from Baseline	8.8 (21.5)	1.5 (10.8)	17.4 (31.5)	10.9 (25.0)
Minimum, Maximum	-16.1, 45.2	-14.3, 19.0	-26.3, 71.4	-17.1, 58.1
Day 253, n	8	8	9	8
Mean (SD)	55.8 (14.5)	59.1 (18.9)	66.3 (7.5)	54.9 (16.2)
Mean (SD) % Change from Baseline	6.3 (25.3)	2.4 (10.3)	13.3 (25.4)	8.4 (16.7)
Minimum, Maximum	-18.2, 57.1	-10.8, 15.5	-26.3, 62.2	-9.4, 31.0

Abbreviations: N = number of subjects; n = number of subjects in subgroup; PedsQL™ = Pediatric Quality of Life Inventory™; SD = standard deviation

CMAP and MUNE

CMAP and quantitative multipoint MUNE were assessed at Baseline and on Days 92, 169, and 253. Mean change and mean percent change results for CMAP amplitude, CMAP area, single motor unit action potential (SMUP) amplitude, and MUNE are shown in the following table, copied from the applicant.

Reviewer Comment: These results are consistent with the results of studies CS1 and CS10, with a relatively stable CMAP amplitude and an increase in MUNE. This observed increase in the number of motor units in the studied muscle is difficult to interpret. Kang et al. (2014) reported a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in SMA2 patients.

Table 46: Mean Change and Mean Percent Change of CMAP Amplitude, CMAP Area, SMUP Amplitude, and MUNE Results for Efficacy Evaluable Population. Source: CS2 CSR, p. 79

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)
CMAP Amplitude (mV)				
Baseline				
Mean (SD)	3.4 (2.4)	3.8 (3.0)	3.9 (1.5)	4.9 (3.7)
Minimum, Maximum	0.6, 7.6	0.7, 9.5	2.1, 6.2	0.6, 9.5
Day 92				
Mean Change from Baseline (SD)	0.3 (1.3)	-0.5 (1.2)	0.5 (1.3)	-0.3 (0.7)
Mean % Change from Baseline (SD)	1.5 (25.7)	-9.2 (29.5)	10.9 (28.9)	-11.8 (17.0)
Day 169				
Mean Change from Baseline (SD)	0.4 (0.9)	-0.4 (1.2)	0.5 (0.9)	-0.0 (0.7)
Mean % Change from Baseline (SD)	6.1 (25.2)	-11.7 (15.4)	15.9 (25.8)	-7.2 (22.2)
Day 253				
Mean Change from Baseline (SD)	0.6 (1.3)	-0.2 (1.3)	0.4 (0.9)	-0.0 (1.0)
Mean % Change from Baseline (SD)	17.1 (42.6)	6.1 (29.7)	10.5 (17.8)	3.9 (14.4)
CMAP Area (mVms)				
Baseline				
Mean (SD)	10.8 (11.2)	9.0 (8.5)	9.9 (6.1)	10.7 (9.4)
Minimum, Maximum	0.7, 33.4	1.1, 27.6	2.7, 21.3	1.0, 24.3
Day 92				
Mean Change from Baseline (SD)	-0.8 (2.7)	-0.1 (2.8)	1.4 (2.4)	1.0 (2.1)
Mean % Change from Baseline (SD)	-7.9 (22.1)	3.1 (32.9)	23.0 (37.3)	26.2 (61.6)
Day 169				
Mean Change from Baseline (SD)	-0.4 (4.0)	-0.5 (3.7)	1.3 (3.3)	0.4 (3.8)
Mean % Change from Baseline (SD)	-0.9 (30.9)	5.1 (20.8)	20.1 (39.0)	20.3 (50.7)
Day 253				
Mean Change from Baseline (SD)	-0.3 (3.1)	-0.4 (4.2)	1.4 (2.9)	7.3 (19.8)
Mean % Change from Baseline (SD)	-5.1 (31.5)	6.0 (26.2)	21.9 (35.1)	66.0 (118.1)

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)
SMUP Amplitude (uV)				
Baseline				
Mean (SD)	60.1 (17.2)	48.2 (13.5)	51.3 (16.4)	48.6 (9.1)
Minimum, Maximum	40.4, 93.4	28.1, 73.9	37.8, 88.4	34.7, 62.6
Day 92				
Mean Change from Baseline (SD)	3.1 (16.0)	10.8 (18.1)	-5.4 (13.2)	0.0 (14.3)
Mean % Change from Baseline (SD)	5.1 (27.5)	22.4 (35.7)	-7.3 (24.0)	2.0 (29.6)
Day 169				
Mean Change from Baseline (SD)	4.6 (45.8)	-0.7 (10.5)	6.5 (20.8)	2.4 (18.5)
Mean % Change from Baseline (SD)	12.6 (75.7)	0.3 (22.0)	16.3 (43.1)	9.0 (40.7)
Day 253				
Mean Change from Baseline (SD)	-7.5 (18.7)	-1.0 (17.4)	8.9 (24.4)	-3.4 (11.3)
Mean % Change from Baseline (SD)	-9.3 (21.3)	-1.2 (32.6)	17.2 (48.5)	-5.9 (12.5)
MUNE				
Baseline				
Mean (SD)	56.7 (40.2)	75.1 (56.1)	82.7 (39.7)	102.9 (80.5)
Minimum, Maximum	14.8, 123.7	20.7, 190.0	28.3, 141.3	12.2, 206.5
Day 92				
Mean Change from Baseline (SD)	1.0 (24.8)	-14.9 (22.1)	23.9 (31.2)	0.8 (48.3)
Mean % Change from Baseline (SD)	-1.2 (25.4)	-20.9 (34.9)	25.4 (35.2)	-5.2 (38.5)
Day 169				
Mean Change from Baseline (SD)	2.0 (30.8)	0.4 (12.7)	7.5 (19.8)	9.5 (23.3)
Mean % Change from Baseline (SD)	17.0 (50.5)	-9.3 (18.5)	6.0 (24.4)	-1.1 (45.0)
Day 253				
Mean Change from Baseline (SD)	6.0 (16.3)	8.9 (23.4)	6.1 (17.6)	21.5 (20.5)
Mean % Change from Baseline (SD)	29.5 (55.9)	13.2 (39.3)	1.5 (24.3)	16.7 (24.8)

Abbreviations: CMAP = Compound Muscle Action Potential; MUNE = Motor Unit Number Estimation; N = number of subjects; SD = standard deviation; SMUP = single motor unit action potential

Upper Limb Module Test

At Baseline and on Days 92, 169, and 253, 22 subjects who were non-ambulant were evaluated using the Upper Limb Module Test. The results are shown in the following table, copied from the applicant.

Reviewer Comment: The small mean overall improvement (1.6) at day 253 with the largest change in the lowest dose cohort (3mg), a negative change at twice that dose (6mg), and the open-label nature of the study make this result difficult to interpret.

Table 47: Mean Change and Mean Percent Change of Upper Limb Module Test Results in the Non-Ambulant Efficacy Evaluable Subjects. Source: CS2 CSR, p. 82

	ISIS 396443 3 mg (N = 8)		ISIS 396443 6 mg (N = 8)		ISIS 396443 9 mg (N = 9)		ISIS 396443 12 mg (N = 8)		ISIS 396443 Total	
	All Subjects	Subjects w/ BL ≤ 14	All subjects	Subjects w/BL ≤ 14	All Subjects	Subjects w/BL ≤ 14	All Subjects	Subjects w/BL ≤ 14	All subjects	Subjects w/BL ≤ 14
Baseline, n	7	4	6	3	5	3	4	3	22	13
Mean (SD)	12.6 (5.2)	9.0 (3.6)	14.7 (2.8)	12.7 (2.3)	13.6 (4.3)	10.7 (2.1)	13.3 (3.3)	11.7 (1.2)	13.5 (3.9)	10.8 (2.7)
Minimum, Maximum	6.0, 18.0	6.0, 14.0	10.0, 18.0	10.0, 14.0	9.0, 18.0	11.0, 13.0	11.0, 18.0	11.0, 13.0	6.0-18.0	6.0- 14.0
Day 92, n	4	3	6	3	5	3	4	3	19	12
Mean Change from Baseline (SD)	1.0 (1.4)	1.0 (1.7)	0.2 (0.8)	0.0 (1.0)	1.4 (1.9)	2.3 (2.1)	0.5 (1.0)	0.7 (1.2)	0.7 (1.3)	1.0 (1.6)
Mean % Change from Baseline (SD)	10.7 (18.4)	12.2 (22.3)	1.0 (5.1)	0.0 (7.1)	14.9 (21.0)	24.8 (22.7)	4.5 (9.1)	6.1 (10.5)	7.4 (14.5)	10.8 (17.5)
Day 169, n	5	4	6	3	5	3	4	3	20	13
Mean Change from Baseline (SD)	1.6 (2.8)	2.3 (2.8)	-1.7 (2.7)	-3.3 (3.1)	2.0 (3.4)	3.3 (4.0)	1.3 (1.5)	1.7 (1.5)	0.7 (3.0)	1.1 (3.6)
Mean % Change from Baseline (SD)	26.1 (41.9)	34.1 (434.7)	-13.9 (21.7)	-27.6 (24.0)	21.4 (34.1)	35.6 (39.6)	10.7 (13.2)	14.2 (13.7)	9.8 (32.4)	15.6 (39.3)
Day 253, n	5	4	6	3	5	3	4	3	20	13
Mean Change from Baseline (SD)	3.2 (1.8)	3.5 (1.9)	-0.3 (1.4)	-1.0 (1.7)	2.2 (3.0)	3.7 (3.2)	1.5 (1.7)	2.0 (1.7)	1.6 (2.4)	2.2 (2.7)
Mean % Change from Baseline (SD)	40.0 (34.6)	46.8 (35.9)	-4.0 (12.9)	-10.0 (17.3)	23.1 (31.7)	38.5 (33.4)	13.3 (15.9)	17.7 (16.2)	17.2 (29.0)	25.1 (33.5)

Abbreviations: N = number of subjects; n = number of subjects in subgroup; SD = standard deviation

Muscle strength using hand-held dynamometry

At Baseline and on Days 92, 169, and 253, hand-held dynamometry was used to measure muscle strength (elbow flexion and extension; knee flexion and extension) in 20 subjects who were ≥ 5 years of age at Screening. The results are described in the following table, copied from the applicant. Overall, mean increases (0.5 to 1.5 lbs; or 5.9-16.9% change) were noted in each of the myometry parameters measured on Day 253. The largest increases were noted in the 12-mg dose cohort for all parameters with the exception of left knee extension (highest in the 6-mg dose cohort on Day 253).

Reviewer Comment: This result appears to indicate a nusinersen dose-dependent improvement in strength. There is the potential for effort-dependent bias, i.e., patients who know they are on the largest dose exerting maximal effort, given the open-label nature of the study.

Table 48: Mean Change and Mean Percent Change of Myometry Results at Each Measured Timepoint for 20 Efficacy Evaluable Subjects with Measurements. Source: CS2 CSR, p. 84

	ISIS 396443 3 mg (N = 6)	ISIS 396443 6 mg (N = 6)	ISIS 396443 9 mg (N = 3)	ISIS 396443 12 mg (N = 5)	ISIS 396443 Total (N = 20)
Right Knee Extension (lbs)					
Baseline					
Mean (SD)	5.4 (5.9)	3.9 (2.6)	5.2 (0.8)	6.4 (4.9)	5.2 (4.1)
Day 92					
Mean Change from Baseline (SD)	1.5 (1.9)	0.0 (0.8)	-1.5 (1.8)	0.3 (1.6)	0.3 (1.7)
Mean % Change from Baseline (SD)	39.5 (120.2)	-10.0 (45.0)	-26.0 (29.0)	-2.0 (19.3)	2.6 (67.2)
Day 169					
Mean Change from Baseline (SD)	1.3 (1.7)	0.2 (1.2)	-1.7 (1.7)	1.5 (2.1)	0.6 (1.9)
Mean % Change from Baseline (SD)	63.3 (112.6)	-3.6 (60.2)	-30.4 (28.2)	42.4 (62.0)	21.9 (77.7)
Day 253					
Mean Change from Baseline (SD)	0.8 (3.2)	0.6 (1.5)	0.2 (0.4)	1.3 (2.4)	0.8 (2.2)
Mean % Change from Baseline (SD)	6.5 (85.7)	-0.1 (56.9)	3.3 (7.2)	19.9 (32.1)	7.4 (53.2)
Left Knee Extension (lbs)					
Baseline					
Mean (SD)	4.7 (4.5)	3.3 (2.9)	6.1 (1.3)	5.8 (3.6)	4.8 (3.4)
Day 92					
Mean Change from Baseline (SD)	0.9 (1.3)	0.9 (1.0)	-1.6 (1.4)	0.6 (1.9)	0.4 (1.6)
Mean % Change from Baseline (SD)	36.3 (82.5)	27.1 (33.7)	-25.6 (19.3)	16.0 (27.6)	18.8 (53.0)
Day 169					
Mean Change from Baseline (SD)	1.0 (2.2)	1.2 (1.1)	-2.1 (1.2)	1.4 (1.7)	0.7 (2.0)
Mean % Change from Baseline (SD)	52.5 (80.1)	69.1 (115.5)	-35.0 (16.1)	32.0 (38.8)	37.7 (79.7)

	ISIS 396443 3 mg (N = 6)	ISIS 396443 6 mg (N = 6)	ISIS 396443 9 mg (N = 3)	ISIS 396443 12 mg (N = 5)	ISIS 396443 Total (N = 20)
Left Knee Extension (lbs) ***Continued***					
Day 253					
Mean Change from Baseline (SD)	0.9 (3.9)	1.2 (1.3)	-1.3 (1.3)	0.5 (1.3)	0.6 (2.4)
Mean % Change from Baseline (SD)	0.8 (61.9)	36.2 (28.8)	-19.2 (18.8)	11.8 (25.7)	9.9 (42.4)
Right Knee Flexion (lbs)					
Baseline					
Mean (SD)	7.1 (5.2)	4.6 (3.5)	8.6 (1.6)	15.3 (8.7)	8.6 (6.6)
Day 92					
Mean Change from Baseline (SD)	0.9 (1.0)	0.1 (0.6)	-0.8 (2.8)	2.0 (5.3)	0.7 (2.8)
Mean % Change from Baseline (SD)	23.9 (36.0)	5.8 (14.2)	-10.2 (32.4)	5.4 (29.4)	8.9 (29.2)
Day 169					
Mean Change from Baseline (SD)	2.7 (2.0)	0.4 (0.4)	-1.2 (1.5)	1.0 (1.7)	1.0 (1.9)
Mean % Change from Baseline (SD)	41.3 (32.2)	8.0 (4.6)	-14.2 (16.4)	8.7 (11.2)	15.2 (27.4)
Day 253					
Mean Change from Baseline (SD)	0.6 (1.0)	0.7 (0.8)	-0.0 (3.7)	3.9 (4.2)	1.4 (2.8)
Mean % Change from Baseline (SD)	16.2 (28.3)	11.8 (17.6)	-2.2 (44.7)	21.2 (17.9)	13.4 (25.4)
Left Knee Flexion (lbs)					
Baseline					
Mean (SD)	8.0 (6.7)	4.5 (2.5)	10.1 (1.2)	13.3 (7.9)	8.6 (6.2)
Day 92					
Mean Change from Baseline (SD)	-0.7 (3.3)	0.4 (1.1)	-0.5 (2.0)	3.2 (5.0)	0.6 (3.4)
Mean % Change from Baseline (SD)	7.3 (37.5)	-9.7 (46.5)	-6.3 (21.5)	10.8 (34.9)	1.0 (36.4)

	ISIS 396443 3 mg (N = 6)	ISIS 396443 6 mg (N = 6)	ISIS 396443 9 mg (N = 3)	ISIS 396443 12 mg (N = 5)	ISIS 396443 Total (N = 20)
Left Knee Flexion (lbs) *Continued*					
Day 169					
Mean Change from Baseline (SD)	0.0 (2.9)	0.5 (1.2)	-1.0 (1.6)	1.7 (1.9)	0.4 (2.1)
Mean % Change from Baseline (SD)	15.2 (38.5)	-4.3 (50.2)	-10.8 (16.5)	10.6 (14.7)	4.3 (35.1)
Day 253					
Mean Change from Baseline (SD)	-1.2 (3.0)	1.1 (1.7)	-0.3 (2.8)	3.9 (3.7)	0.9 (3.3)
Mean % Change from Baseline (SD)	-2.0 (27.7)	3.4 (54.9)	-5.1 (29.2)	24.9 (20.3)	5.9 (36.2)
Right Elbow Extension (lbs)					
Baseline					
Mean (SD)	4.1 (3.9)	2.7 (2.5)	3.9 (2.6)	14.7 (9.3)	6.3 (7.1)
Day 92					
Mean Change from Baseline (SD)	0.7 (0.6)	-0.0 (0.7)	0.2 (0.5)	2.5 (3.2)	0.9 (1.8)
Mean % Change from Baseline (SD)	32.2 (42.5)	-5.8 (11.8)	9.8 (13.9)	18.5 (23.3)	15.3 (29.1)
Day 169					
Mean Change from Baseline (SD)	0.5 (1.0)	-0.6 (1.0)	1.1 (1.3)	0.7 (1.7)	0.3 (1.3)
Mean % Change from Baseline (SD)	5.1 (17.7)	-35.0 (47.8)	28.2 (32.6)	8.9 (20.2)	0.9 (35.1)
Day 253					
Mean Change from Baseline (SD)	0.1 (0.6)	-0.2 (1.1)	1.6 (1.0)	2.3 (2.7)	0.8 (1.8)
Mean % Change from Baseline (SD)	13.1 (18.2)	-7.7 (31.7)	44.6 (16.9)	19.5 (18.4)	15.6 (26.3)
Left Elbow Extension (lbs)					
Baseline					
Mean (SD)	3.5 (3.0)	2.5 (2.3)	5.0 (4.8)	14.7 (9.2)	6.2 (7.0)

	ISIS 396443 3 mg (N = 6)	ISIS 396443 6 mg (N = 6)	ISIS 396443 9 mg (N = 3)	ISIS 396443 12 mg (N = 5)	ISIS 396443 Total (N = 20)
Left Elbow Extension (lbs) ***Continued***					
Day 92					
Mean Change from Baseline (SD)	0.4 (0.5)	-0.4 (0.6)	0.5 (0.1)	0.6 (0.5)	0.2 (0.6)
Mean % Change from Baseline (SD)	21.7 (36.0)	-30.5 (41.4)	16.3 (11.4)	4.0 (4.0)	1.4 (34.5)
Day 169					
Mean Change from Baseline (SD)	0.2 (0.6)	-0.9 (0.8)	0.2 (0.8)	0.7 (1.7)	-0.0 (1.1)
Mean % Change from Baseline (SD)	10.2 (25.6)	-45.5 (35.4)	16.7 (24.5)	2.8 (7.8)	-6.2 (34.4)
Day 253					
Mean Change from Baseline (SD)	0.4 (0.6)	-0.2 (0.9)	1.5 (1.1)	1.7 (3.6)	0.7 (2.0)
Mean % Change from Baseline (SD)	17.4 (21.3)	-28.8 (43.1)	36.1 (8.6)	15.0 (26.9)	7.0 (36.1)
Right Elbow Flexion (lbs)					
Baseline					
Mean (SD)	11.9 (9.2)	9.3 (7.6)	16.0 (10.7)	16.1 (6.0)	12.8 (8.1)
Day 92					
Mean Change from Baseline (SD)	0.1 (1.6)	0.2 (2.0)	0.9 (0.6)	1.6 (1.2)	0.6 (1.6)
Mean % Change from Baseline (SD)	10.2 (24.0)	1.3 (12.1)	9.0 (9.4)	11.0 (8.0)	7.5 (15.2)
Day 169					
Mean Change from Baseline (SD)	0.3 (1.8)	-0.3 (0.7)	0.0 (1.2)	2.3 (2.1)	0.6 (1.8)
Mean % Change from Baseline (SD)	0.0 (15.2)	-4.9 (10.6)	7.1 (18.4)	14.3 (11.8)	3.2 (14.6)

	ISIS 396443 3 mg (N = 6)	ISIS 396443 6 mg (N = 6)	ISIS 396443 9 mg (N = 3)	ISIS 396443 12 mg (N = 5)	ISIS 396443 Total (N = 20)
Right Elbow Flexion (lbs) *Continued*					
Day 253					
Mean Change from Baseline (SD)	-0.8 (1.8)	-0.3 (1.4)	0.6 (0.9)	3.1 (3.4)	0.5 (2.6)
Mean % Change from Baseline (SD)	4.7 (23.3)	-3.6 (20.5)	8.3 (10.6)	24.2 (22.7)	7.6 (22.1)
Left Elbow Flexion (lbs)					
Baseline					
Mean (SD)	10.5 (7.9)	8.6 (7.4)	16.7 (12.5)	16.3 (6.3)	12.3 (8.3)
Day 92					
Mean Change from Baseline (SD)	0.9 (2.1)	1.1 (1.3)	1.0 (2.3)	1.6 (2.9)	1.1 (2.0)
Mean % Change from Baseline (SD)	6.3 (16.7)	11.3 (12.0)	21.7 (32.2)	13.8 (28.8)	12.0 (20.5)
Day 169					
Mean Change from Baseline (SD)	1.0 (3.2)	0.3 (1.1)	0.0 (1.3)	2.4 (3.6)	1.0 (2.6)
Mean % Change from Baseline (SD)	2.0 (19.3)	-0.3 (14.5)	-0.1 (7.4)	18.7 (30.4)	5.1 (20.5)
Day 253					
Mean Change from Baseline (SD)	1.1 (1.2)	0.8 (1.2)	-0.3 (3.1)	4.1 (3.6)	1.5 (2.6)
Mean % Change from Baseline (SD)	12.7 (20.8)	10.6 (24.9)	9.7 (23.4)	34.0 (38.8)	16.9 (27.5)

Abbreviations: N = number of subjects; SD = standard deviation
Note: The best (highest) response of the 3 trials was used in this summary.

The 6-minute Walk Test (6MWT)

The 6MWT was assessed at Baseline and on Days 92, 169, and 253 in 13 subjects who were ambulant. The results are summarized in the following table, copied from the applicant.

Reviewer Comment: The result indicates an increase in the distance patients were able to walk during the course of the study across all dose cohorts. There is no clear dose dependence, with the largest percent change in the lowest dose cohort.

Table 49: Mean Change and Mean Percent Change of 6-Minute Walk Test Results for Efficacy Evaluable Population. Source: CS2 CSR, p. 89

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)	ISIS 396443 Total (N = 33)
Baseline, n	3	2	4	5	14
Mean (SD)	226.3 (162.8)	203.0 (32.5)	248.0 (68.3)	320.2 (246.8)	262.7 (161.7)
Minimum, Maximum	45.0, 360.0	180.0, 226.0	174.0, 308.0	0.0, 563.0	0.0, 563.0
Day 92, n	2	2	4	5	13
Mean Change from Baseline (SD)	3.5 (0.7)	15.5 (14.8)	10.0 (32.3)	33.8 (24.4)	19.0 (25.2)
Mean % Change from Baseline (SD)	3.9 (3.9)	8.3 (8.6)	6.7 (14.5)	9.2 (6.2)	7.3 (8.9)
Day 169, n	2	2	4	5	13
Mean Change from Baseline (SD)	38.5 (29.0)	5.5 (33.2)	19.0 (36.2)	22.8 (62.9)	21.4 (43.6)
Mean % Change from Baseline (SD)	68.1 (89.2)	4.1 (17.0)	11.4 (18.3)	-4.7 (28.5)	14.2 (41.7)
Day 253, n	3	2	4	4	13
Mean Change from Baseline (SD)	43.7 (47.9)	30.0 (15.6)	3.3 (32.4)	62.0 (23.0)	34.8 (37.4)
Mean % Change from Baseline (SD)	76.8 (124.0)	15.6 (10.2)	4.1 (14.5)	14.1 (3.9)	26.7 (61.7)

Abbreviations: N = number of subjects; n = number of subjects in subgroup; SD = standard deviation; 6MWT = 6-Minute Walk Test

Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) questionnaire.

The ACEND questionnaire was administered at Baseline and on Days 92, 169, and 253. The ACEND is scored on a scale of 0-100 and higher scores are indicative of less intense caregiver impact. The results are summarized in the following table, copied from the applicant. At Day 253 there appear to be small improvements in total score across all dose cohorts.

Reviewer Comment: It is difficult to interpret the small ACEND score changes given the open-label study design and the subjective nature of the result.

Table 50: Mean Change and Mean Percent Change for ACEND at Day 253 – Efficacy Evaluable Population. Source: CS2 CSR, p. 92

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)	ISIS 396443 Total (N = 33)
Total Score – Feeding/Grooming/Dressing					
Baseline, n	8	8	9	8	33
Mean (SD)	76.0 (19.2)	77.9 (20.5)	80.4 (18.1)	79.2 (26.3)	78.4 (20.2)
Minimum, Maximum	50.0, 100.0	40.0, 100.0	53.3, 100.0	33.3, 100.0	33.3, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	2.8 (4.4)	3.8 (9.3)	6.3 (16.1)	2.9 (7.0)	4.0 (10.1)
Mean % Change from Baseline (SD)	4.5 (7.3)	7.7 (18.3)	11.4 (29.3)	7.3 (18.5)	7.8 (19.5)
Total Score – Sitting/Play					
Baseline, n	8	8	9	8	33
Mean (SD)	96.0 (6.0)	96.0 (11.3)	95.1 (10.9)	94.5 (10.7)	95.4 (9.5)
Minimum, Maximum	84.0, 100.0	68.0, 100.0	68.0, 100.0	72.0, 100.0	68.0, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	3.5 (6.6)	-0.5 (1.4)	0.9 (4.4)	4.5 (8.9)	2.1 (6.0)
Mean % Change from Baseline (SD)	4.1 (7.5)	-0.7 (2.1)	0.9 (5.2)	6.0 (12.1)	2.5 (7.7)
Total Score – Transfer					
Baseline, n	8	8	9	8	33
Mean (SD)	36.3 (34.0)	42.6 (34.8)	62.7 (32.7)	67.5 (40.7)	52.6 (36.4)
Minimum, Maximum	0.0, 90.0	5.0, 100.0	20.0, 100.0	12.0, 100.0	0.0, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	4.7 (4.5)	1.4 (9.9)	2.2 (13.1)	4.5 (6.6)	3.2 (9.0)
Mean % Change from Baseline (SD)	19.0 (26.3)	-10.5 (53.6)	-2.8 (32.7)	15.8 (28.5)	4.7 (37.3)

	ISIS 396443 3 mg (N = 8)	ISIS 396443 6 mg (N = 8)	ISIS 396443 9 mg (N = 9)	ISIS 396443 12 mg (N = 8)	ISIS 396443 Total (N = 33)
Total Score – Mobility					
Baseline, n	8	8	9	8	33
Mean (SD)	40.7 (37.2)	58.2 (29.3)	69.2 (31.4)	71.8 (35.9)	60.3 (34.2)
Minimum, Maximum	0.0, 100.0	2.9, 91.4	11.4, 97.1	2.9, 100.0	0.0, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	7.5 (20.5)	-10.0 (17.0)	-4.4 (18.7)	2.5 (6.4)	-1.2 (17.2)
Mean % Change from Baseline (SD)	3.0 (37.8)	-34.8 (47.0)	-3.8 (36.6)	15.5 (35.3)	-5.5 (42.0)
Total Score – Time					
Baseline, n	8	8	9	8	33
Mean (SD)	64.1 (17.0)	68.0 (29.4)	84.0 (14.0)	74.2 (26.2)	72.9 (22.6)
Minimum, Maximum	43.8, 93.8	18.8, 100.0	56.3, 100.0	31.3, 100.0	18.8, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	13.3 (20.2)	3.9 (16.7)	-7.6 (24.8)	-0.8 (9.1)	1.9 (19.5)
Mean % Change from Baseline (SD)	27.1 (37.1)	10.1 (37.5)	-7.2 (31.2)	-2.6 (17.1)	6.4 (33.2)
Total Score – Emotion					
Baseline, n	8	8	9	8	33
Mean (SD)	65.6 (18.4)	67.0 (24.4)	70.4 (25.8)	59.4 (27.0)	65.7 (23.4)
Minimum, Maximum	41.7, 94.4	30.6, 94.4	25.0, 94.4	22.2, 97.2	22.2, 97.2
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	8.3 (15.8)	1.4 (8.1)	0.3 (14.6)	5.6 (16.9)	3.8 (14.0)
Mean % Change from Baseline (SD)	18.3 (27.5)	2.3 (11.8)	9.9 (39.9)	25.6 (64.6)	13.9 (39.8)
Total Score – Finance					
Baseline, n	8	8	9	8	33
Mean (SD)	75.6 (17.6)	73.1 (25.2)	73.3 (14.4)	73.1 (23.6)	73.8 (19.5)
Minimum, Maximum	55.0, 100.0	30.0, 100.0	50.0, 90.0	35.0, 100.0	30.0, 100.0
Day 253, n	8	8	9	8	33
Mean Change from Baseline (SD)	5.6 (15.9)	1.2 (10.3)	3.3 (7.9)	2.5 (13.4)	3.2 (11.6)
Mean % Change from Baseline (SD)	11.6 (23.3)	6.6 (19.7)	5.7 (12.5)	9.9 (29.1)	8.4 (20.9)

6.2.6. **Study CS12: An Open-Label Study to Assess the Safety and Tolerability of ISIS 396443 in Patients With Spinal Muscular Atrophy Who Previously Participated in ISIS 396443-CS2 or ISIS 396443-CS10**

Study CS12 was a Phase 1, open-label study to test the safety, tolerability, efficacy, and PK of ISIS 396443 (4 doses of 12 mg at 6-month intervals) administered as IT injections by lumbar puncture in subjects with later-onset (type II and type III) SMA who previously participated in studies CS2 or CS10, summarized in the table above. Subjects were expected to participate in CS12 for up to approximately 2 years (final follow up study visit on Day 715).

The Hammersmith Functional Motor Scale – Expanded (HFMSE), a tool used to assess motor function in children that has been validated for use in SMA (Glanzman 2011) was used to evaluate motor function in all subjects. The maximum score for this test is 66; higher scores indicate better motor function. Subjects were evaluated using the HFMSE at Baseline (i.e., during the Screening Period of the CS12 study) and on Days 85, 169, 260, 351, 442, 533, 624, and 715.

The 6MWT was used to evaluate the walking ability and endurance of ambulatory subjects. Subjects were considered ambulatory at Screening if they had ever walked at least 15 feet independently without support or braces (based on reported medical and SMA history) AND maintained that ability at Screening of Study CS12. Consistent with the natural history of type II SMA, none of the subjects with type II SMA had achieved independent ambulation at baseline (Table 37); 21 of 25 subjects with type III SMA were considered ambulatory (Table 38). (CS12 CSR, p. 60)

The Upped Limb Module Test (ULMT) was used to measure motor function in non-ambulatory subjects. The ULMT was conducted at Baseline (during the Screening Period of the study) and on Days 85, 169, 260, 351, 442, 533, 624, and 715. The total score ranges from 0 to 18, with higher scores indicating greater functional ability.

6.2.4.1 Study CS12 Results

HFMSE results are described in the tables copied from the applicant below. Mean HFMSE, 6MWT distance, and ULT are above baseline at day 624. There is a decrease in both mean HFMSE and 6MWT distance at day 715 which the applicant attributes to an outlier (a patient with a femur fracture at the time of evaluation).

Reviewer Comment: There appear to be small positive trends across the evaluated parameters. The clinical significance of these small changes in efficacy measurements is unclear. Note that HFMSE scores are generally stable over 12 month intervals in the natural history of type 2 SMA. Kaufman (2012) reported a mean HFMSE decline of -0.54 (95% CI -1.45 to 0.36) over 2 years in type 2 SMA.

Table 51: Summary of Expanded Hammersmith Functional Motor Scale Total Score - Evaluable Set, Source: CS12 CSR, pp. 41-49

	ISIS 396443 12 mg (N=47)
Baseline[1]	
N	47
Mean (SD, SEM)	38.40 (17.21, 2.51)
Median (P25, P75)	40.00 (22.00, 53.00)
Min, Max	5.00, 63.00

	ISIS 396443 12 mg (N=47)
Day 624	
N	34
Mean (SD, SEM)	39.18 (17.65, 3.03)
Median (P25, P75)	42.50 (23.00, 54.00)
Min, Max	5.00, 62.00
Change from Baseline	
N	34
Mean (SD, SEM)	0.47 (3.86, 0.66)
Median (P25, P75)	0.00 (-1.00, 2.00)
Min, Max	-6.00, 9.00
Percent Change from Baseline	
N	34
Mean (SD, SEM)	-0.2 (12.0, 2.1)
Median (P25, P75)	0.0 (-5.9, 5.7)
Min, Max	-27.3, 34.6

	ISIS 396443 12 mg (N=47)
Day 715	
N	23
Mean (SD, SEM)	36.09 (17.04, 3.55)
Median (P25, P75)	38.00 (19.00, 54.00)
Min, Max	4.00, 58.00
Change from Baseline	
N	23
Mean (SD, SEM)	-0.65 (8.49, 1.77)
Median (P25, P75)	0.00 (-1.00, 3.00)
Min, Max	-36.00, 8.00
Percent Change from Baseline	
N	23
Mean (SD, SEM)	-0.5 (19.3, 4.0)
Median (P25, P75)	0.0 (-5.0, 11.1)
Min, Max	-73.5, 30.8

Table 52: Summary of 6 Minute Walk Test - Evaluable Set. Source: CS12 CSR, p. 277

Evaluable Set

Parameter		ISIS 396443 12 mg (N=47)
Total Distance (m)	Baseline[1]	
	N	22
	Mean (SD, SEM)	252.14 (182.39, 38.89)
	Median (P25, P75)	229.00 (103.00, 362.00)
	Min, Max	0.00, 650.00

Note: For patients who are non-ambulant at baseline and able to walk at a post baseline visit, their walk distances at baseline and all visits prior to the visit that patients start to walk are assigned to 0 meter.
[1]Baseline is defined as the last non-missing value prior to the first dose.

Parameter		ISIS 396443 12 mg (N=47)
Total Distance (m)	Day 533	
	N	17
	Mean (SD, SEM)	251.35 (129.52, 31.41)
	Median (P25, P75)	266.00 (167.00, 341.00)
	Min, Max	45.00, 464.00
	Change from Baseline	
	N	17
	Mean (SD, SEM)	35.00 (71.96, 17.45)
	Median (P25, P75)	42.00 (-23.00, 89.00)
	Min, Max	-121.00, 150.00
	Percent Change from Baseline	
	N	15
	Mean (SD, SEM)	23.9 (61.7, 15.9)
	Median (P25, P75)	10.9 (-13.1, 36.7)
	Min, Max	-36.6, 217.4

Parameter		ISIS 396443 12 mg (N=47)
Total Distance (m)	Day 624	
	N	16
	Mean (SD, SEM)	256.00 (126.33, 31.58)
	Median (P25, P75)	281.50 (146.50, 363.00)
	Min, Max	31.00, 422.00
	Change from Baseline	
	N	16
	Mean (SD, SEM)	26.13 (70.55, 17.64)
	Median (P25, P75)	22.50 (-18.50, 89.50)
	Min, Max	-88.00, 150.00
	Percent Change from Baseline	
	N	15
	Mean (SD, SEM)	8.9 (28.6, 7.4)
	Median (P25, P75)	9.6 (-10.8, 34.8)
	Min, Max	-39.5, 56.7

Parameter		ISIS 396443 12 mg (N=47)
Total Distance (m)	Day 715	
	N	8
	Mean (SD, SEM)	256.25 (100.91, 35.68)
	Median (P25, P75)	243.50 (172.00, 324.50)
	Min, Max	145.00, 425.00
	Change from Baseline	
	N	8
	Mean (SD, SEM)	-10.88 (82.55, 29.18)
	Median (P25, P75)	-18.50 (-47.50, 25.50)
	Min, Max	-146.00, 140.00
	Percent Change from Baseline	
	N	8
	Mean (SD, SEM)	-0.0 (36.6, 13.0)
	Median (P25, P75)	-5.4 (-21.2, 9.3)
	Min, Max	-44.1, 78.7

Table 53: Summary of Upper Limb Function Test - Evaluable Set. Source: CS12 CSR, p. 51

	ISIS 396443 12 mg (N=47)
Baseline[1]	
N	27
Mean (SD, SEM)	14.63 (2.82, 0.54)
Median (P25, P75)	15.00 (13.00, 17.00)
Min, Max	6.00, 18.00

	ISIS 396443 12 mg (N=47)
Day 624	
N	19
Mean (SD, SEM)	15.58 (2.80, 0.64)
Median (P25, P75)	16.00 (14.00, 18.00)
Min, Max	7.00, 18.00
Change from Baseline	
N	19
Mean (SD, SEM)	0.58 (1.26, 0.29)
Median (P25, P75)	0.00 (0.00, 1.00)
Min, Max	-2.00, 3.00
Percent Change from Baseline	
N	19
Mean (SD, SEM)	4.8 (9.5, 2.2)
Median (P25, P75)	0.0 (0.0, 12.5)
Min, Max	-13.3, 23.1

	ISIS 396443 12 mg (N=47)
Day 715	
N	14
Mean (SD, SEM)	15.14 (2.77, 0.74)
Median (P25, P75)	15.50 (15.00, 16.00)
Min, Max	7.00, 18.00
Change from Baseline	
N	14
Mean (SD, SEM)	1.00 (1.11, 0.30)
Median (P25, P75)	1.00 (0.00, 1.00)
Min, Max	-1.00, 3.00
Percent Change from Baseline	
N	14
Mean (SD, SEM)	8.1 (8.3, 2.2)
Median (P25, P75)	7.1 (0.0, 15.4)
Min, Max	-5.9, 23.1

6.3. Study CS4: A Phase 3 sham-procedure controlled study of nusinersen in patients with later-onset spinal muscular atrophy (SMA)

The following description of the interim analysis of a sham-procedure controlled study of nusinersen in later-onset (type 2 based on SMN2 number, age of onset, and lack of baseline ambulation) SMA was provided by the applicant following NDA submission.

Reviewer Comment: The results described by the applicant below appear to indicate a clinically meaningful benefit from nusinersen in type 2 SMA patients, although the data from this study were not submitted as part of this NDA and therefore could not be reviewed.

As of the August 31, 2016 data cut-off for the interim analysis, a total of 126 subjects received at least 1 dose of study treatment (ISIS 396443 (n= 84) or sham procedure control (n= 42)) and were included in the Intent-to-treat (ITT) Set. No subjects in either treatment group discontinued treatment. In total, 35 (42%) of subjects in the ISIS 396443 group and 19 (45%) of subjects in the sham control group have completed the study. The ITT population is the primary population for the analysis of efficacy endpoints, with the exception of WHO motor milestone endpoints.

An Interim Efficacy Set (IES) was defined for the analysis of WHO motor milestone endpoints, and was defined as all subjects who had the opportunity to be assessed at the Month 15 visit. The IES included 54 subjects (35 subjects randomized to ISIS 396443 and 19 subjects randomized to sham). Baseline disease characteristics were generally well-balanced between the two treatment groups. Consistent with a population most-likely to have type 2 SMA, the majority of subjects in the ITT had 3 copies of the SMN2

gene (range: 2-4 copies), no subject was able to walk independently at baseline, and the mean age at symptom onset was 11.2 months (range: 6-20).

The primary efficacy endpoint is the change from baseline in HFMSE score at 15 months. The HFMSE is a tool used to assess motor function in children with SMA [O'Hagen 2007]. Over 12 months, a decline of -0.56 and -0.57 points was observed in ambulant and non-ambulant patients with later-onset SMA [Mercuri 2016]. An improvement of ≥3 points in HFMSE is estimated to represent a clinically meaningful improvement [Swoboda 2010]. Since not all subjects have had the opportunity for assessment at Month 15, the multiple imputation method was used to account for missing month 15 values at the interim, as outlined in the Statistical Analysis Plan (SAP).

A statistically significant change from baseline in HFMSE score was observed in the ISIS 396443 group (4.0 (95% CI: 2.9-5.1)) compared to the sham control group (-1.9 (95% CI: -3.8-0.0)) (p=0.0000002). A consistent effect was observed across all sensitivity analyses conducted, including an analysis based on observed Month 15 values.

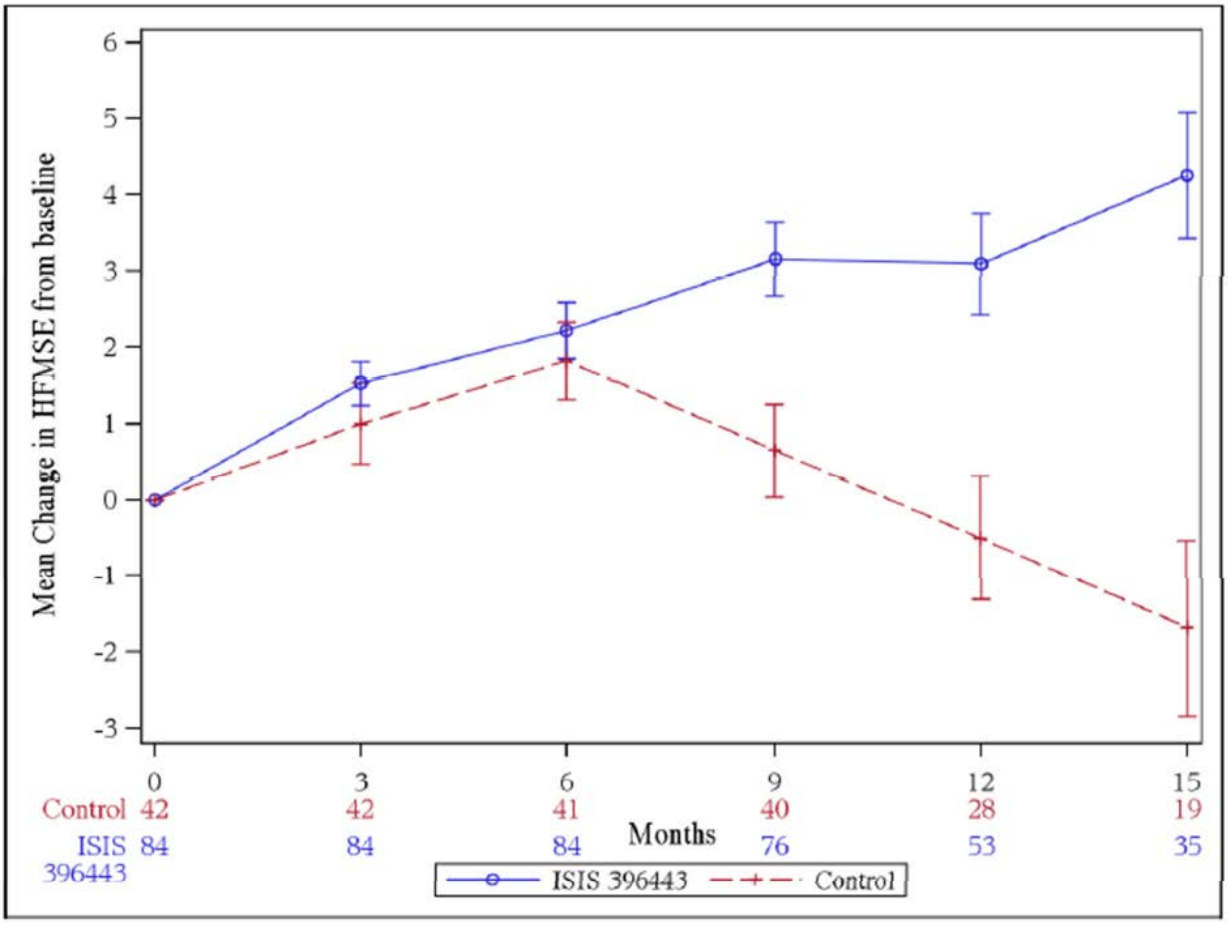
Secondary endpoints were descriptively reported as per the SAP and are described below. No formal statistical comparison was performed and no p-values were calculated for statistical inference for these endpoints.

HFMSE
A greater proportion of subjects in the ITT set achieved a 3-point or greater increase from baseline HFMSE score at 15 months in the ISIS 396443 group (57.3%) compared to the sham control group (20.5%).

WHO motor milestone achievement
A greater proportion of subjects in the IES achieved a new WHO motor milestone at 15 months in the ISIS 396443 group (17.1%) compared to the sham control group (10.5%). Similarly, the mean number of new motor milestones achieved at 15 months was greater in the ISIS 396443 group (0.2 (min, max: 0, 2) compared to the sham control group (-0.1, min, max: -1, 1).

In patients with type II SMA, the decline in muscle strength is reflected in a slowly progressive loss of upper limb function [Mercuri 2016]. The Upper Limb Module was designed specifically for assessing upper limb function in non-ambulatory patients with SMA [Mazzone 2016] and has been shown to correlate with the outcomes for HFMSE. In the ITT, the mean change from baseline in ULM score at 15 months was greater in the ISIS 396443 group (3.7) compared to the sham control group (0.3)" (CS4 Topline Data Summary).

Figure 22: Mean change from baseline (observed values) over time – ITT Set. Source: CS4 Topline Data Summary



NOTE: This figure is based upon subjects with an observed value. The error bars on this figure represent +/- standard error.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. **Primary Endpoints**

Motor milestone development was the primary endpoint used for infantile-onset SMA patients in both the main efficacy study, CS3B, and the open-label study CS3A. It was also a secondary endpoint in study SM201 of presymptomatic infants with genetically diagnosed SMA. Type 1

SMA infants have impaired development of motor milestones, which forms part of the phenotypic definition of SMA. As discussed in Section 6.1.1, The Hammersmith Infant Neurological Examination (HINE) appears to be an acceptable tool to assess motor milestone development in type 1 SMA patients based on a retrospective study of 33 type I SMA infants (De Sanctis et al., 2016).

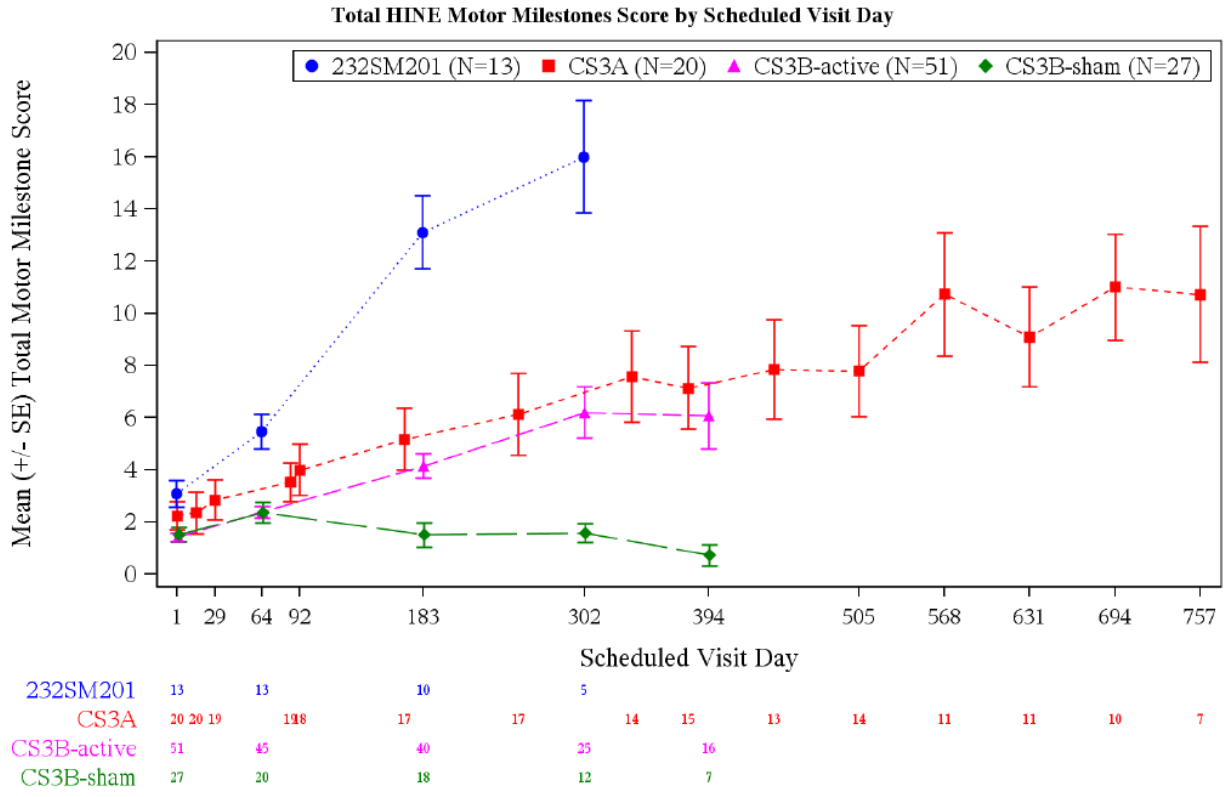
Study CS3B found that 40% (20/52) of the infants who received nusineren had an improvement in motor milestone development (milestone responder defined in Section 6.1.1) compared to 0% (0/30) of the sham-procedure control group, $p<0.0001$. This result is supported by the descriptive results of both studies CS3A and SM201. In study CS3A, there was a 732% mean increase from baseline HINE score (from 2.3 to 12.9) in infants who received the same dose, 12mg, of nusinersen used in study CS3B. Descriptions and rates of key motor milestone achievements in studies CS3A and CS3B are listed below (SCE, p. 66).

- Full head control: 9 subjects (18%) in CS3B and 9 subjects (45%) in CS3A
- Independent sitting (either prop, stable sit, or pivot): 5 subjects (10%) in CS3B and 8 subjects (40%) in CS3A
- Rolling (prone to supine or supine to prone): 18 subjects (35%) in CS3B and 7 subjects (35%) in CS3A
- Standing (with support or unaided): 1 subject (2%) in CS3B and 5 subjects (25%) in CS3A
- Walking (holding on or unaided): 2 subjects (10%) in CS3A

For study SM201, the mean HINE score increased from 3.1 at baseline to 25 after 1 year. Five subjects became able to sit independently, 1 became able to stand unaided, 2 other subjects became able to stand with support, and one subject became able to walk with support. Note that the genetically based diagnosis in these presymptomatic infants from study SM201 meant that some might actually be types 2 or 3 SMA, since final diagnosis is based on the timing of symptom development and phenotype.

A summary of HINE scores over time across these three studies is shown in the following figure, copied from the applicant.

Figure 23: Total HINE Motor Milestones Across Three Studies, CS3A, CS3B, and SM201.
Source: Summary of Clinical Efficacy, p. 65



Population used in figure: Nurture - interim efficacy set, CS3A - all dosed subjects, CS3B - interim efficacy set.
For each study, visits with n<5 are not plotted.

Reviewer Comment: Overall, these results show a clinically meaningful benefit, with motor milestone improvement that is inconsistent with the natural history of the disease for type 1 SMA infants.

7.1.2. Secondary and Other Endpoints

A descriptive summary of the secondary and other endpoints and results assessed across all studies, including the sham-procedure controlled study CS3B and all six open-label studies, is presented in the table of Appendix 13.8. Quality of life and care assessments (PedsQL and ACEND) are not further discussed here due to the high risk of bias in these subjective measures for open-label studies. Their results were previously discussed in Section 6. Note that only the primary endpoint for study CS3B, discussed above, was evaluated statistically for this

application. All other endpoints for study CS3B and the open-label studies are presented descriptively without correction for multiple comparisons.

As seen in the table of Appendix 13.8 and in the following figures copied from the applicant, all three studies which assessed nusinersen efficacy through CHOP INTEND scores, CMAP, and survival (through control-comparison in CS3B or in relation to the natural history of SMA for CS3A and SM201) showed positive results that appear to support the efficacy of nusinersen in infantile-onset SMA patients and presymptomatic infants with a genetic SMA diagnosis.

As shown in Appendix 13.8, there were mean CMAP amplitude decreases for CS1 and CS10 and a mean amplitude change of 0 for CS2. Motor Unit Number Estimation (MUNE) had mean increases in all three studies in which it was assessed (CS1, CS10, and CS2). However, CMAP and MUNE results in the later-onset (type 2 or 3) SMA patients of these open-label studies are difficult to interpret because Kang et al. (2014) found a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in type 2 SMA patients.

Motor function assessment through the Hammersmith Functional Motor Scale – Expanded (HFMSE) showed a trend of positive mean score changes, indicative of functional improvement, in studies CS1, CS10, and CS2. Study CS12 showed a trend of increasing HFSME mean scores through study day 624, but with a mean decrease in HFMSE at the final assessment of day 715 which the applicant attributes to an outlier.

Upper Limb Module testing of motor function in non-ambulatory later-onset SMA patients in both studies CS2 and CS12 showed a numerically positive mean change over time.

Growth changes were assessed in studies CS3B and SM201. The result for SM201 is difficult to interpret given the lack of a control group. For the sham-procedure controlled study CS3B, the numerical difference (greater weight, length, and arm circumference in the control group) is of unclear clinical significance. The reader is referred to the safety review of Dr. Evelyn Mentari for further discussion.

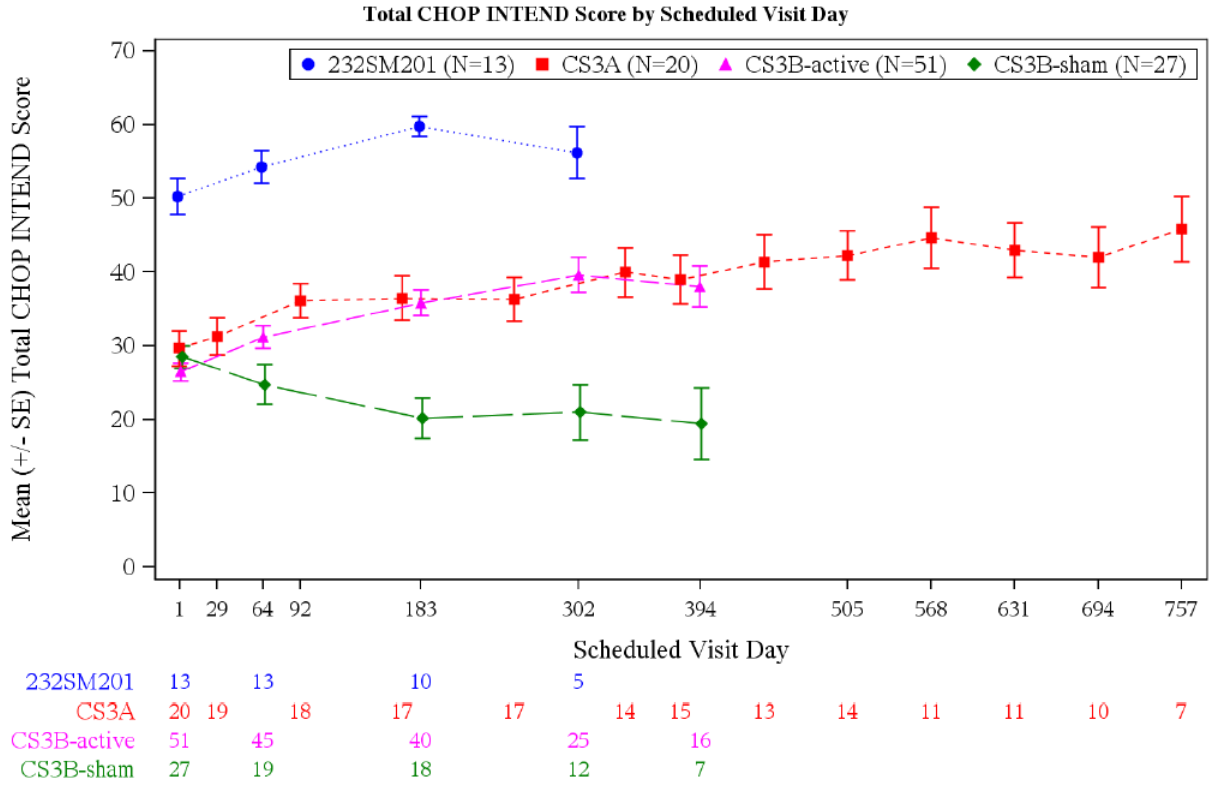
Myometry was only performed on later-onset SMA patients in study CS2 and showed a numerically positive increase in strength across all muscles tested.

The Six Minute Walk Test (6MWT) was assessed in later-onset SMA patients in studies CS2 and CS12. There were numerically positive changes in the distance walked for study CS2 and through day 624 of study CS12. There was a mean decrease in 6MWT at the final assessment of day 715 for study CS12 which the applicant attributes to an outlier.

Overall, the descriptive results of the secondary and other endpoints across all studies appear to lend support to the positive efficacy results of the primary endpoint (motor milestone response)

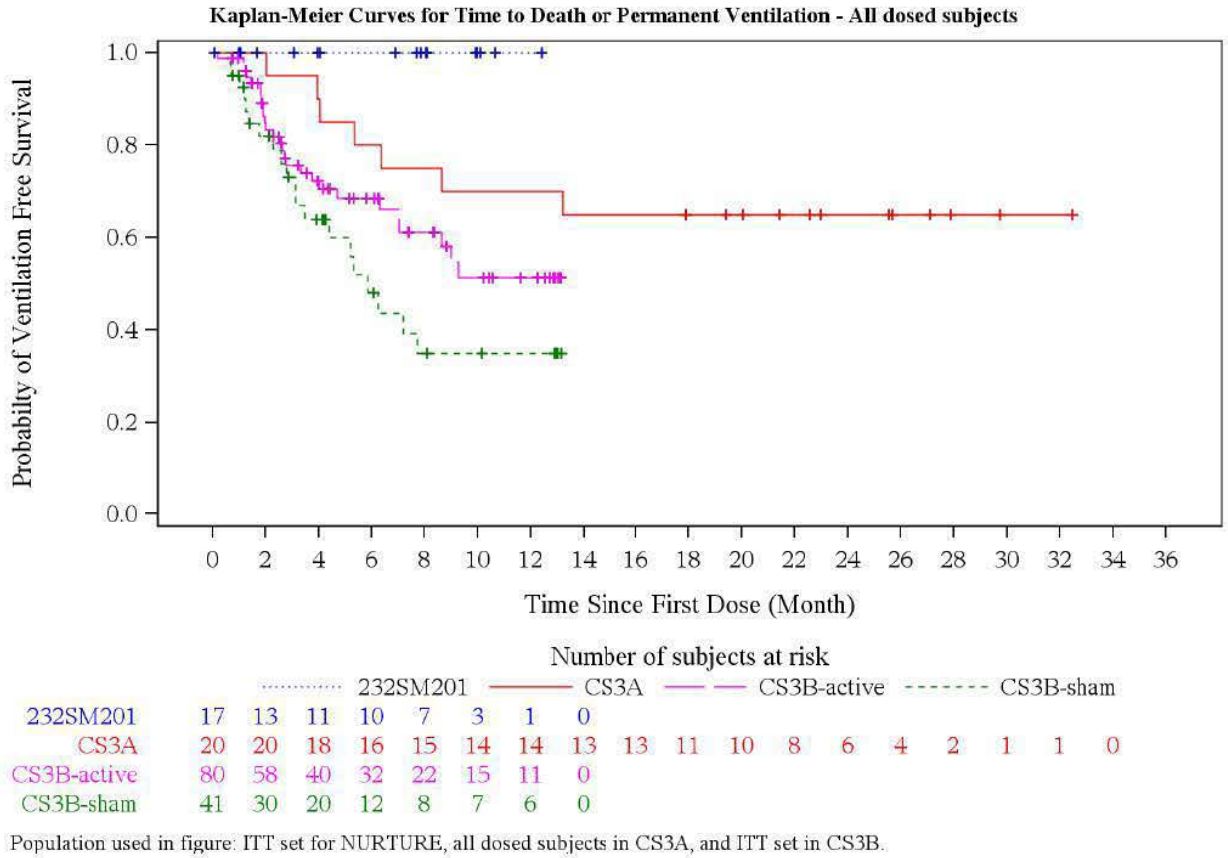
of sham-procedure controlled study CS3B.

Figure 24: Total CHOP INTEND Score Across Three Studies, CS3A, CS3B, and SM201. Source: Summary of Clinical Efficacy, p. 69



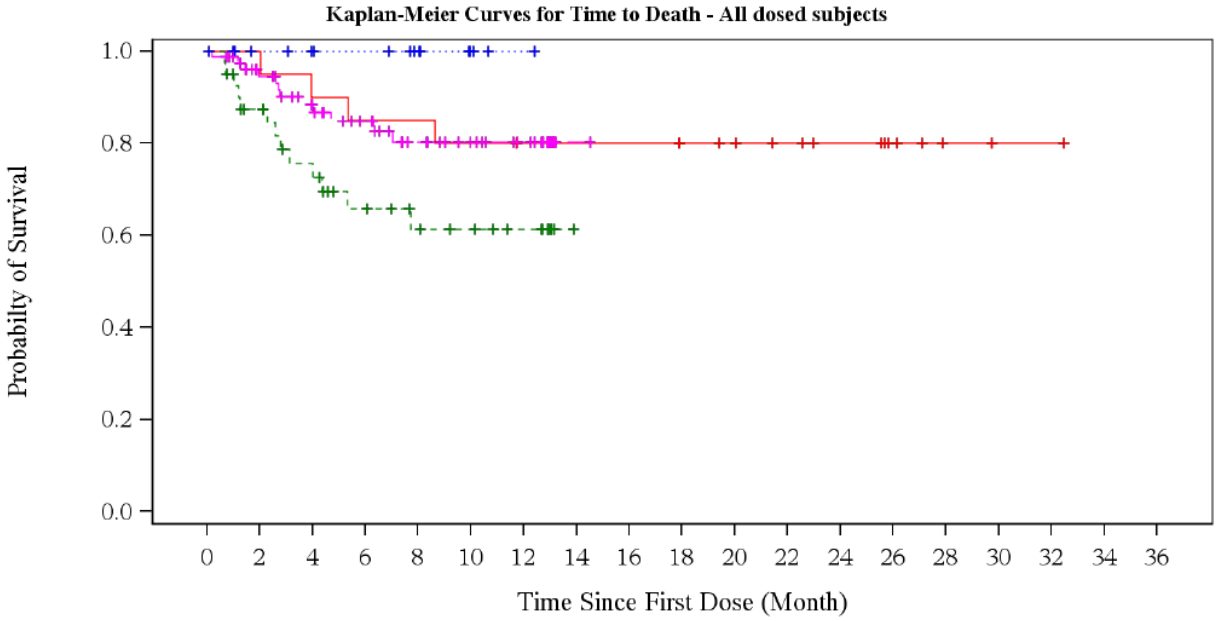
Population used in figure: Nurture - interim efficacy set, CS3A - all dosed subjects, CS3B - interim efficacy set.
For each study, visits with n<5 are not plotted.

Figure 25: Kaplan-Meier Curves for Time to Death or Permanent Ventilation - Study CS3B, CS3A, and SM201. Source: Summary of Clinical Efficacy, p. 81



Population used in figure: ITT set for NURTURE, all dosed subjects in CS3A, and ITT set in CS3B.

Figure 26: Kaplan-Meier Curves for Time to Death – Study CS3B, CS3A, and SM201. Source: Summary of Clinical Efficacy, p. 82

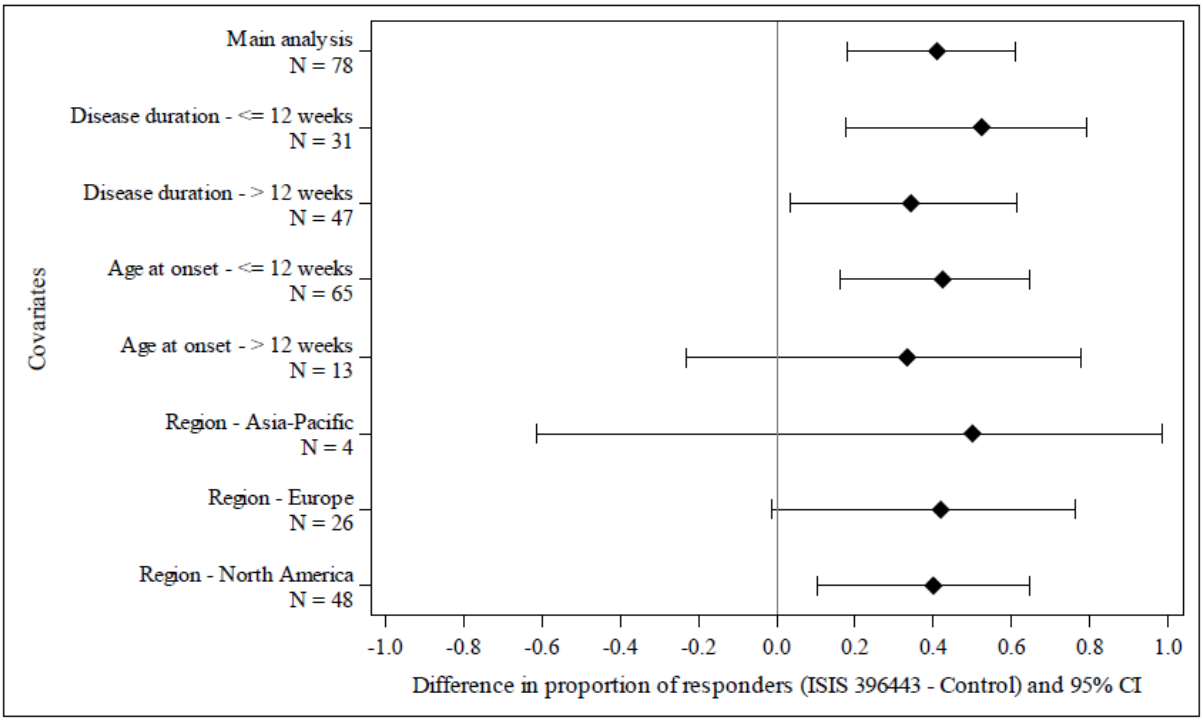


Population used in figure: ITT set for NURTURE, all dosed subjects in CS3A, and ITT set in CS3B.

7.1.3. Subpopulations

The effect of nusinersen relative to sham control on efficacy measures was evaluated in subgroups based on SMA history and geographic region in the pivotal study in infantile-onset SMA (Study CS3B), as summarized in the figure below copied from the applicant. The results are generally similar in the various subpopulations shown, although there appear to be insufficient data (N=4) to adequately assess response for the Asia-Pacific region. The response also appears to be better in subjects with an earlier age of symptom onset (<=12 weeks).

Figure 27: Difference in Proportion of Responders and 95% Confidence Intervals for Motor Milestones Subgroup Analyses - Interim Efficacy Set: Source: Summary of Clinical Efficacy, p. 86



NOTE 1: The diamond on the plot represents difference in proportion of responders.
NOTE 2: A difference in proportion of responders >0 represents ISIS 396443 is better and difference in proportion of responders <0 represents that sham is better.

7.1.4. Dose and Dose-Response

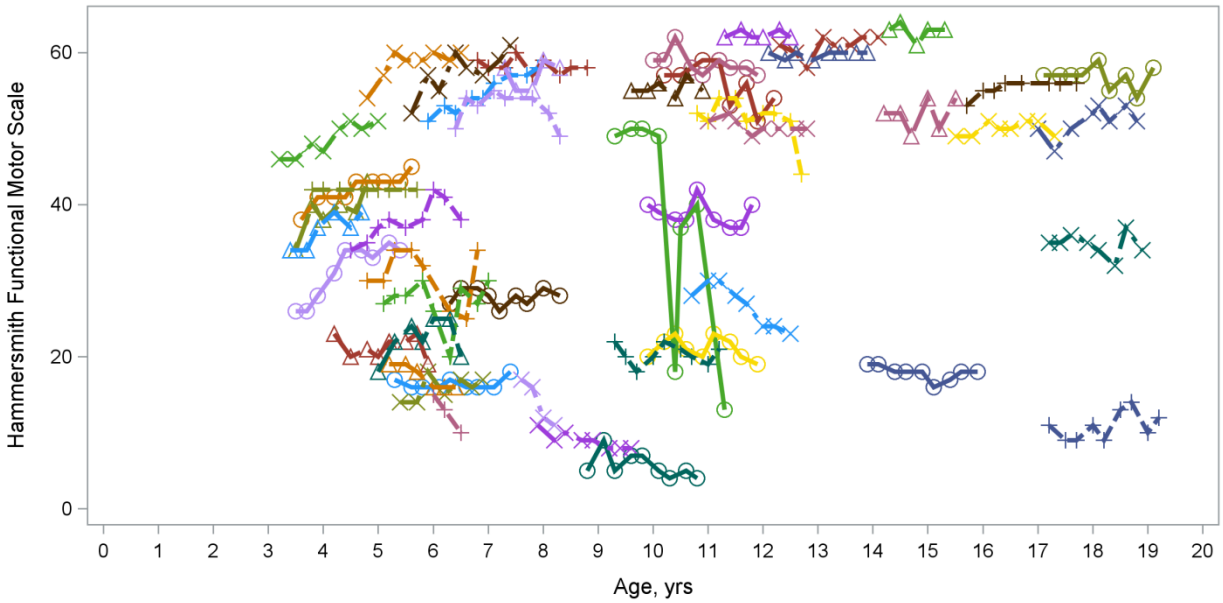
The applicant's recommended dose is 4 loading doses of 12 mg ISIS 396443 on Days (b) (4) followed by maintenance doses of 12 mg every 4 months. (b) (4) (Introduction, p. 2)

The applicant reports that the dose level selected for this multiple-dose clinical study (12 mg ISIS 396443) was predicted to achieve levels of approximately 10 µg/g lumbar spinal cord tissue and 3 µg/g cervical spinal cord tissue following the first dose based on nonclinical studies in juvenile monkeys. Pharmacology and PK results in SMA transgenic mice led to estimates that

the target tissue concentration needed to produce 50% to 90% SMN2 exon 7 inclusion is between 1 and 10 µg/g in spinal cord tissue. The loading dose interval (i.e., doses on Study Days 1, 15, 29, and 64) was selected based on nonclinical PK and pharmacology data to achieve and maintain ISIS 396443 spinal cord tissue levels within the upper end of the pharmacologically active range by Day 64 (approximately 30 µg/g lumbar and 10 µg/g cervical spinal cord tissue concentrations). The maintenance dose interval (once every 4 months on Study Days 183 and 302) was selected based on the estimated spinal tissue and CSF drug half-life (4 to 6 months) to maintain spinal cord tissue levels of ISIS 396443 at a steady-state level within the estimated pharmacologically active range (CS3B CSR, pp. 37-38).

Reviewer Comment: Doses of 1, 3, 6, 9, and 12 mg of nusinersen were studied by the applicant in prior open-label studies. 12mg was selected based on the positive efficacy results of those studies, which are discussed in more detail in Section 6. The applicant does not explicitly address the question of weight or age-based dosing of nusinersen for adult patients, who have a larger total CSF volume than children (125 to 150 ml in adults; 65 to 140ml in children ages 4-13; and 40ml in a term gestation neonate (Bonadio, 1992)). The applicant's argument for the current dose does not have a clear rationale for extrapolating the dose to adults, focusing instead on the spinal cord drug distribution models and the results of their trials in infants and children. (b) (4) *The applicant's argument is essentially that nusinersen is effective in children despite the lower concentration, justifying a single dose regimen for all. In order to evaluate this assertion, FDA staff analyzed the Hammersmith Functional Motor Scale-Expanded (HFMSE) scores from study CS12 stratified by age. The results, shown in the following figure, indicate relative stability of HFMSE scores in the teenage and young adult patients studied over approximately 2 years. This result is not inconsistent with a treatment benefit in patients with an adult CSF volume, although the potential for a greater effect with doses scaled as a function of weight or age cannot be excluded.*

Figure 28: Hammersmith Functional Motor Scale-Expanded (HFMSE) scores over time from study CS12 for individual subjects, showing subject age in the horizontal axis. Source: FDA staff analysis of study CS12 data



7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the sham-procedure controlled study CS3B, separation from the control group in motor milestone measurements did not clearly occur until after Day 64, likely reflecting the need for completion of the loading dose period before maximal benefit was observed.

Improvements in motor milestones over time continued to be seen at up to 1 year (Day 394) in study CS3B and up to study day 757 in study CS3A. See the figure in Section 7.1.1, "Total HINE Motor Milestones Across Three Studies." In study CS3A, there was an upward trend of CHOP INTEND scores through study day 820.

Table 54: Number of Doses and Time on Study: Studies in Symptomatic and Presymptomatic SMA. Source: Summary of Clinical Efficacy, p. 62

	Pre-symptomatic SMA (Study SM201): ISIS 396443	Infantile-onset SMA			Later-onset SMA (Studies CS2/CS12): ISIS 396443
		Open-label study (CS3A): ISIS 396443	Controlled study (CS3B)		
			ISIS 396443	Control	
Number of subjects [a]	17 (100)	20 (100)	80 (100)	41 (100)	28 (100)
Maximum number of doses or procedures allowed by protocol(s)	10	12	6	6	6/7 [b]
Number of doses or procedures administered					
1	1 (6)	0	2 (3)	2 (5)	1 (4) [d]
2	0	1 (5)	3 (4)	2 (5)	0
3	3 (18)	2 (10)	13 (16)	7 (17)	3 (11)
4	3 (18)	2 (10)	23 (29)	12 (29)	0
5	5 (29)	0	14 (18)	7 (17)	0
6	5 (29)	5 (25)	25 (31)	11 (27)	17 (61)
7	0	3 (15)	-	-	7 (25)
8	0	5 (25)	-	-	-
9	0	2 (10)	-	-	-
10	0	0	-	-	-
11	-	0	-	-	-
12	-	0	-	-	-
n	17	20	80	41	28
Median	5	7	4	4	6
Min., max.	1, 6	2, 9	1, 6	1, 6	1, 7
Time on study (days)					
n	17	20	80	41	28
Median	234	670	187.5	129	1051.5
Min., max.	2, 378	62, 988	6, 442	20, 423	31, 1219

NOTE: Numbers in parentheses are percentages.
[a] For Studies SM201 and CS3A, number of subjects represents those who received at least one dose; for Study CS3B, the number randomized and dosed; for CS2/CS12 the number who received their first-ever dose in CS2.
[b] Subjects could have received up to 2 or 3 doses in CS2 depending on the cohort to which they were recruited.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Given the invasive nature of nusinersen administration, requiring repeated lumbar punctures for an indefinite period of time, patients with milder forms of SMA (type 4) may need to weigh the potential benefits of treatment, the risk and discomfort of serial lumbar punctures, and the relative severity of their SMA symptoms in order to make individual treatment decisions.

7.2.2. Other Relevant Benefits

Although the primary sham-procedure control study CS3B was conducted in infantile-onset SMA patients, the applicant argues that nusinersen should be effective in treating all types of SMA. The underlying cause of SMA, a deficiency of survival motor neuron (SMN) protein, is common to patients with all types of SMA (with increasing amounts of SMN corresponding to less severe disease). It therefore may be reasonable to expect that nusinersen, which acts to increase the amount of full-length SMN2 mRNA for translation to SMN protein, should provide clinical benefit to all types of SMA patients. The open-label studies (CS1, CS2, CS10, and CS12) included patients (ages 2-17) with 2 to 5 copies of the SMN2 gene and later symptom onset that corresponded to types 2 and 3 SMA. The applicant subsequently submitted a summary (but no data, see Section 6.3) from study CS4, a sham-procedure controlled study of nusinersen in later-onset SMA (type 2 based on SMN2 number, age of onset, and lack of baseline ambulation). The reported results from the open-label studies in later-onset SMA (see Section 6.2, Appendix 13.8, and the figures below) combined with the results reported for study CS4 support the conclusion that nusinersen also provides clinical benefit to patients with types 2 and 3 SMA. Nusinersen has not been studied in any patients with type 4 SMA, who have adult onset of progressive weakness that can lead to eventual loss of ambulation after years. Nusinersen increases the amount of full-length SMN2 mRNA for translation to SMN protein, whose variably low levels in the different types of SMA patients cause the different SMA phenotypes, and would therefore be expected to provide clinical benefit to type 4 SMA patients also, although they might not tolerate indefinite serial lumbar punctures if their symptoms are mild at baseline.

The results available from study SM201 in presymptomatic genetically diagnosed SMA infants support early treatment with nusinersen in SMA patients. The finding of improved response to nusinersen in study CS3B for patients with shorter disease duration (see Section 7.1.3) also supports early treatment of SMA patients with nusinersen.

Figure 29: HFMSE Score Mean Change from Baseline Over Time- SMA Type II: Subjects with Later-onset Type II SMA, Longitudinal Analysis of Study CS2/CS12. Source: Summary of Clinical Efficacy, p. 72

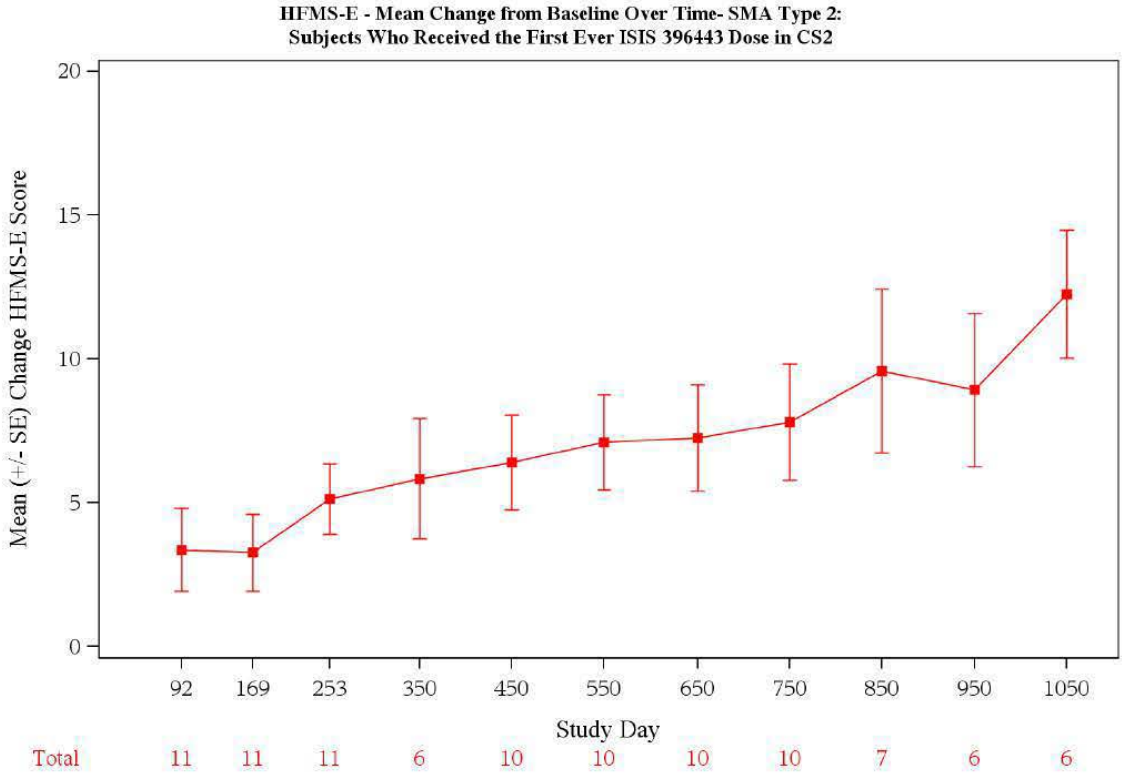


Figure 30: HFMSE Score Mean Change from Baseline Over Time- SMA Type III: Subjects with Later-onset Type III SMA, Longitudinal Analysis of Study CS2/CS12. Source: Summary of Clinical Efficacy, p. 73

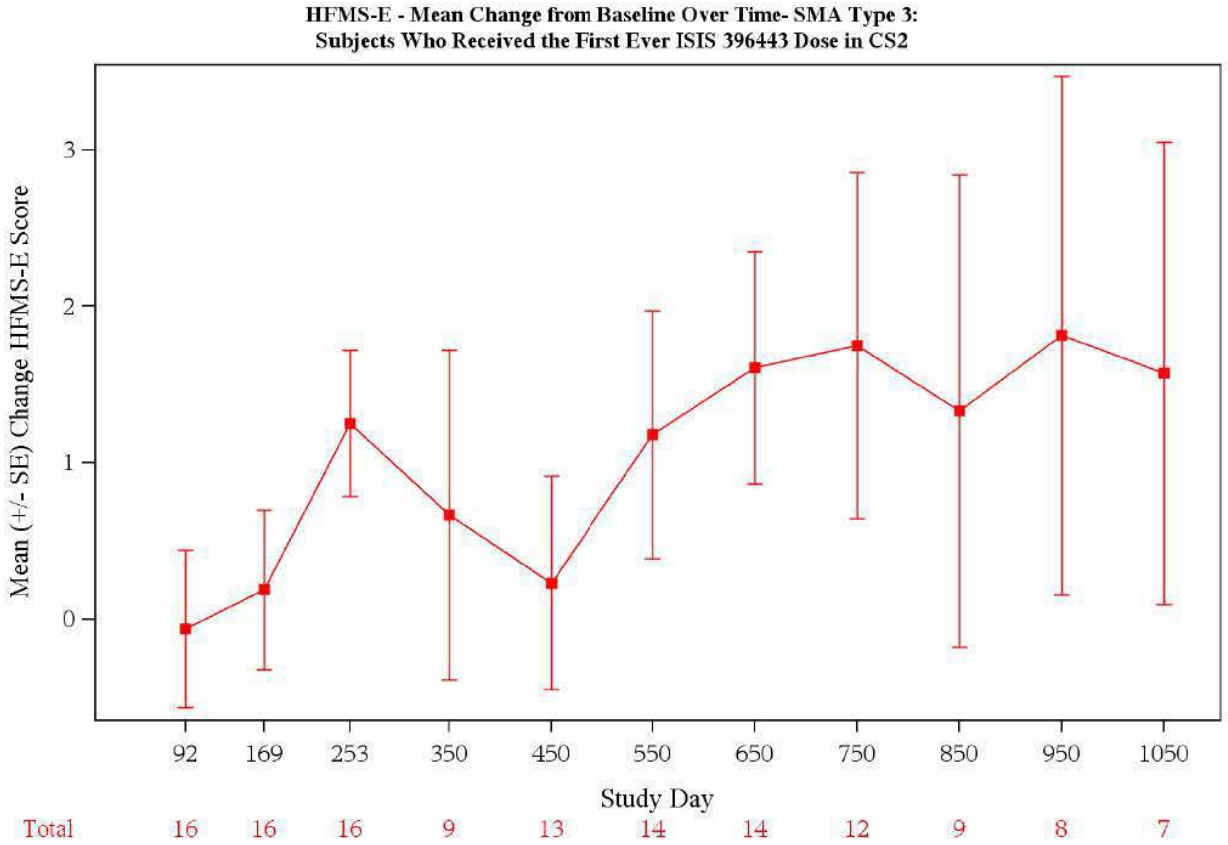


Figure 31: Upper Limb Module Mean Change From Baseline Over Time - SMA Type II, Longitudinal Analysis of Study CS2/CS12. Source: Summary of Clinical Efficacy, p. 75

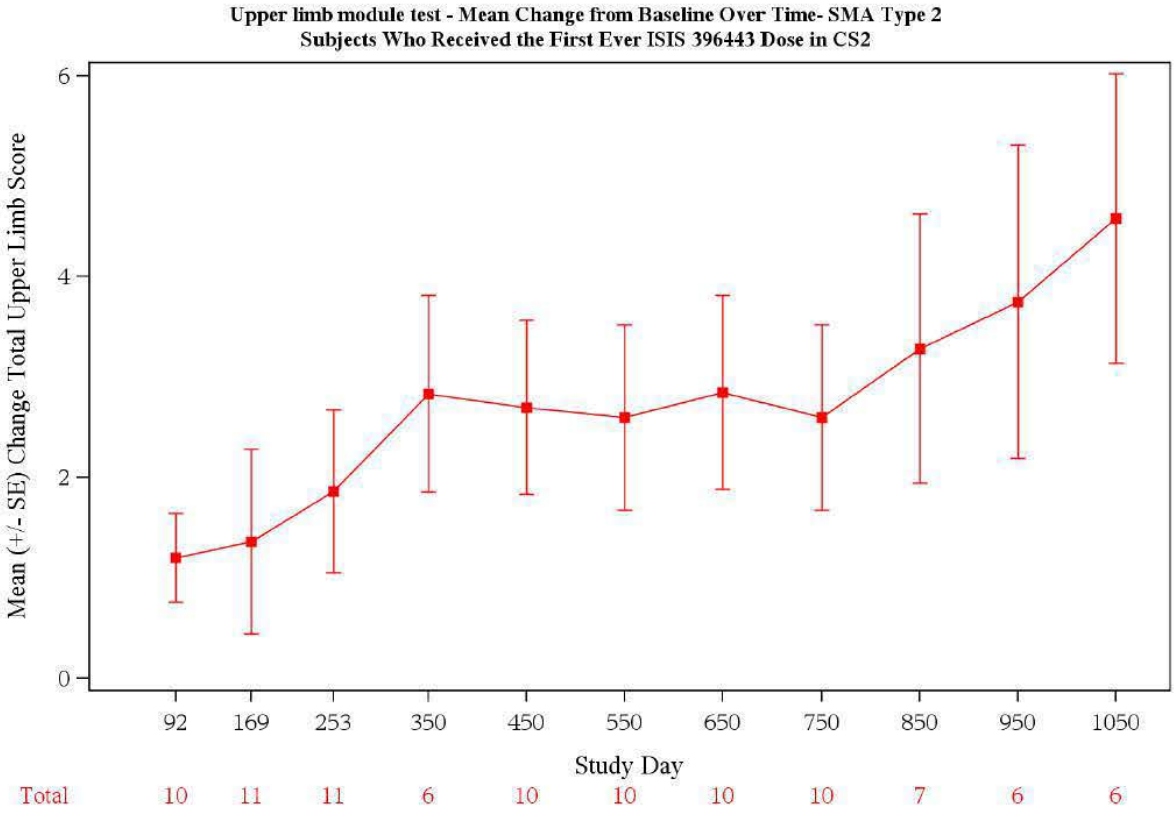
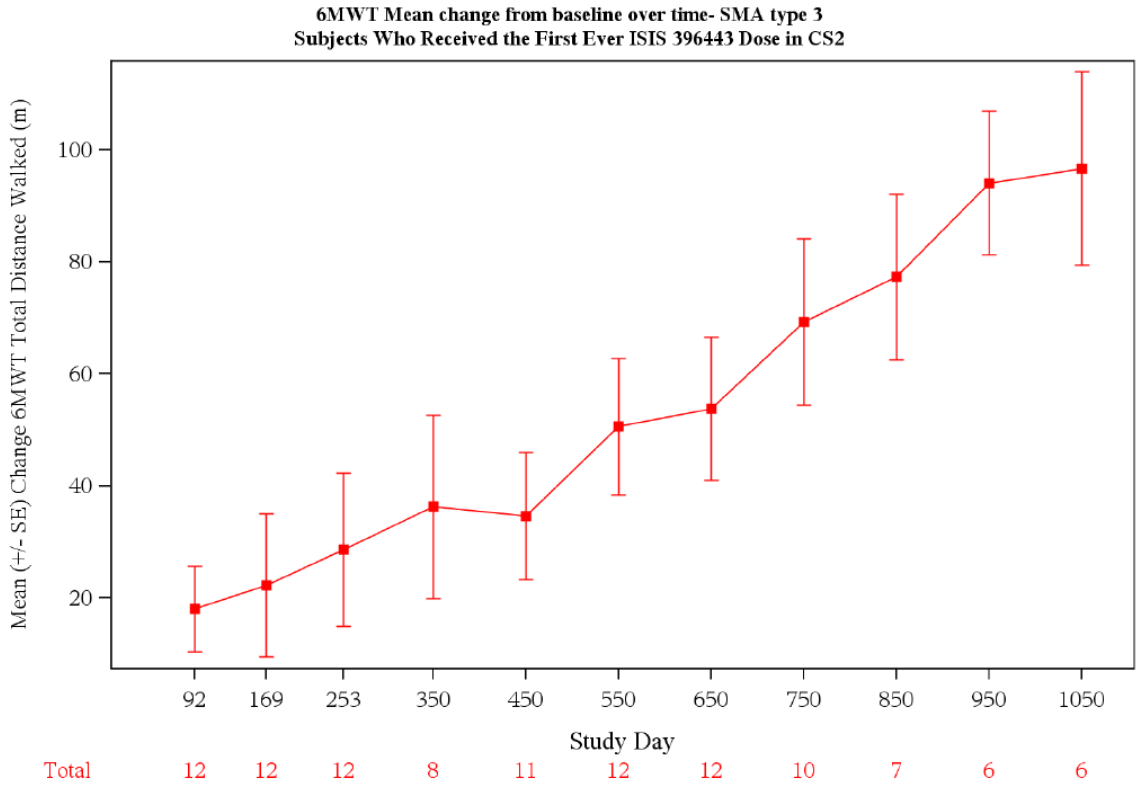


Figure 32: 6MWT Mean Change From Baseline Over Time - SMA Type III, Longitudinal Analysis of Study CS2/CS12. Source: Summary of Clinical Efficacy, p. 77



7.3. Integrated Assessment of Effectiveness

The Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness if FDA determines that such data and evidence are sufficient to establish effectiveness (Section 115(a) of the Modernization Act).

The sham-procedure controlled study CS3B is the one adequate and well-controlled efficacy study that can support approval of nusinersen for the treatment of infantile-onset SMA patients. It is a single well-designed multicenter study that has provided reliable and statistically strong ($p<0.0001$) evidence of an important clinical benefit, motor milestone development that is inconsistent with the natural course of the disease, with a numerical trend towards a beneficial effect on survival. A confirmatory sham-procedure controlled study in infantile onset SMA, who typically die by 2 years of age, would have been difficult to conduct

on ethical grounds.

In addition to the strongly positive primary endpoint for study CS3B, in which the motor milestone response was 40% for nusinersen and 0% for the sham-procedure control group ($p<0.0001$), there were numerically positive results (see Section 6.1.2, 7.1.2, and Appendix 13.8) for the additional endpoints of survival, neuromuscular function as measured by the CHOP INTEND score, and motor nerve function as measured by the CMAP amplitude.

The positive results of the single adequate and well-controlled study are lent further support by descriptive results in 6 open-label studies (see Section 6.2, 7.1.2, and Appendix 13.8) as well as a report of a statistically significant result ($p=0.0000002$) assessing motor function by HFMSE score in a sham-procedure controlled study (CS4 in Section 6.3, data not available for review) in later-onset SMA patients. The open-label trials (4 in later-onset SMA, 1 in presymptomatic infants, and 1 in infantile-onset SMA) and the report of the controlled trial CS4, while unable to support approval alone due to the uncontrolled nature of the former and the lack of submitted data for the latter, do not contradict the results of study CS3B. They provide confirmatory evidence of nusinersen's efficacy and allow reasonable extrapolation (See Section 7.2.2) of the use of nusinersen to the later-onset SMA population in addition to the infantile-onset patients studied in CS3B.

8 Review of Safety

The safety of nusinersen is reviewed by Dr. Evelyn Mentari in a separate review.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee is planned for this application.

10 Labeling Recommendations

10.1. Prescribing Information

As discussed in Section 4.5, OCP recommends a fixed-dose of 12 mg/5 mL for all subjects with loading doses at days (b) (4), followed by the same maintenance dose every 4 months

thereafter.

The reader is referred to the safety review by Dr. Evelyn Mentari for comments about safety in nusinersen labeling.

10.2. Patient Labeling

The reader is referred to the safety review by Dr. Evelyn Mentari for discussion of safety issues that might warrant a Medication Guide, patient package insert (PPI), or instructions for use. Note that nusinersen is not administered by patients themselves or their family members, but must be given intrathecally by a supervising physician.

10.3. Nonprescription Labeling

Not applicable to this application.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not proposed for this application. The reader is referred to Dr. Mentari's safety review.

12 Postmarketing Requirements and Commitments

There are no post-marketing efficacy requirements. For potential safety requirements, the reader is referred to Dr. Mentari's safety review.

13 Appendices

13.1. References

Arkblad, E., Tulinius, M., Kroksmark, A., Henricsson, M., & Darin, N. (2009, May). A population-based study of genotypic and phenotypic variability in children with spinal muscular atrophy. *Acta Paediatr, 98*(5), 865-872.

Arnold, W., Kassar, D., & Kissel, J. (2015, Feb). Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve, 51*(2), 157-167.

Bonadio, W. (1992, Jun). The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. *Pediatr Infect Dis J., 11*(6), 423-431.

De Sanctis, R., Coratti, G., Pasternak, A., & et al. (2016, Nov). Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord, 26*(11), 754-759.

Finkel, R., Bertini, E., Muntoni, F., & Mercuri, E. (2015, Jul). 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord, 25*(7), 593-602.

Finkel, R., McDermott, M., Kaufmann, P., & et al. (2014, Aug 26). Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology, 83*(9), 810-817.

Glanzman, A., Mazzone , E., Main, M., Pelliccioni, M., Wood, J., Swoboda , K., et al. (2010, Mar). The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord, 20*(3), 155-161.

Glanzman, A., O'Hagen, J., McDermott, M., Martens, W., Flickinger, J., Riley, S., et al. (2011, Dec). Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. *J Child Neurol, 26*(12), 1499-1507.

Gregoretti, C., Ottonello, G., Chiarini Testa, M., & et al. (2013, May). Survival of patients with spinal muscular atrophy type 1. *Pediatrics, 131*(5), e1509-1514.

Jedrzejowska, M., Milewski, M., Zimowski, J., & et al. (2010). Incidence of spinal muscular atrophy in Poland--more frequent than predicted? *Neuroepidemiology, 34*(3), 152-157.

Kang, P., Gooch, C., McDermott, M., & et al. (2014, May). The motor neuron response to SMN1 deficiency in spinal muscular atrophy. *Muscle Nerve, 49*(5), 636-644.

Kaufmann, P., McDermott, M., Darras, B., Finkel, R., & et al. (2012, Oct 30). Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology, 79*(18), 1889-1897.

Lewelt, A., Krosschell, K., Scott, C., & et al. (2010, Nov). Compound muscle action potential and motor function in children with spinal muscular atrophy. *Muscle Nerve, 42*(5), 703-708.

Matsuzawa, J., Matsui, M., Konishi, T., Noguchi, K., Gur, R., Bilker, W., et al. (2001, Apr). Age-related volumetric changes of brain gray and white matter in healthy infants and children. *Cereb Cortex, 11*(4), 335-342.

Mazzone, E., Mayhew, A., Montes, J., & et al. (2016, Oct 4). Revised upper limb module for spinal muscular atrophy: Development of a new module. *Muscle Nerve*.

Mercuri, E., Bertini, E., & Iannaccone, S. (2012, May). Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol, 11*(5), 443-452.

Mercuri, E., Finkel, R., Montes, J., & et al. (2016, Feb). Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. *Neuromuscul Disord, 26*(2), 126-131.

O'Hagen, J., Glanzman, A., McDermott, M., & et al. (2007, Oct). An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. *Neuromuscul Disord, 17*(9-10), 693-697.

Prior, T. (2010, Mar). Perspectives and diagnostic considerations in spinal muscular atrophy. *Genet Med, 12*(3), 145-152.

Shefner, J., Watson, M., Simionescu, L., & et al. (2011, Jul). Multipoint incremental motor unit number estimation as an outcome measure in ALS. *Neurology, 77*(3), 235-241.

Sugarman, E., Nagan, N., Zhu, H., & et al. (2012, Jan). Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet, 20*(1), 27-32.

Swoboda, K., Prior, T., Scott, C., & et al. (2005, May). Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol, 57*(5), 704-712.

Swoboda, K., Scott, C., Crawford, T., & et al. (2010, Aug 19). SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One, 5*(8), e12140.

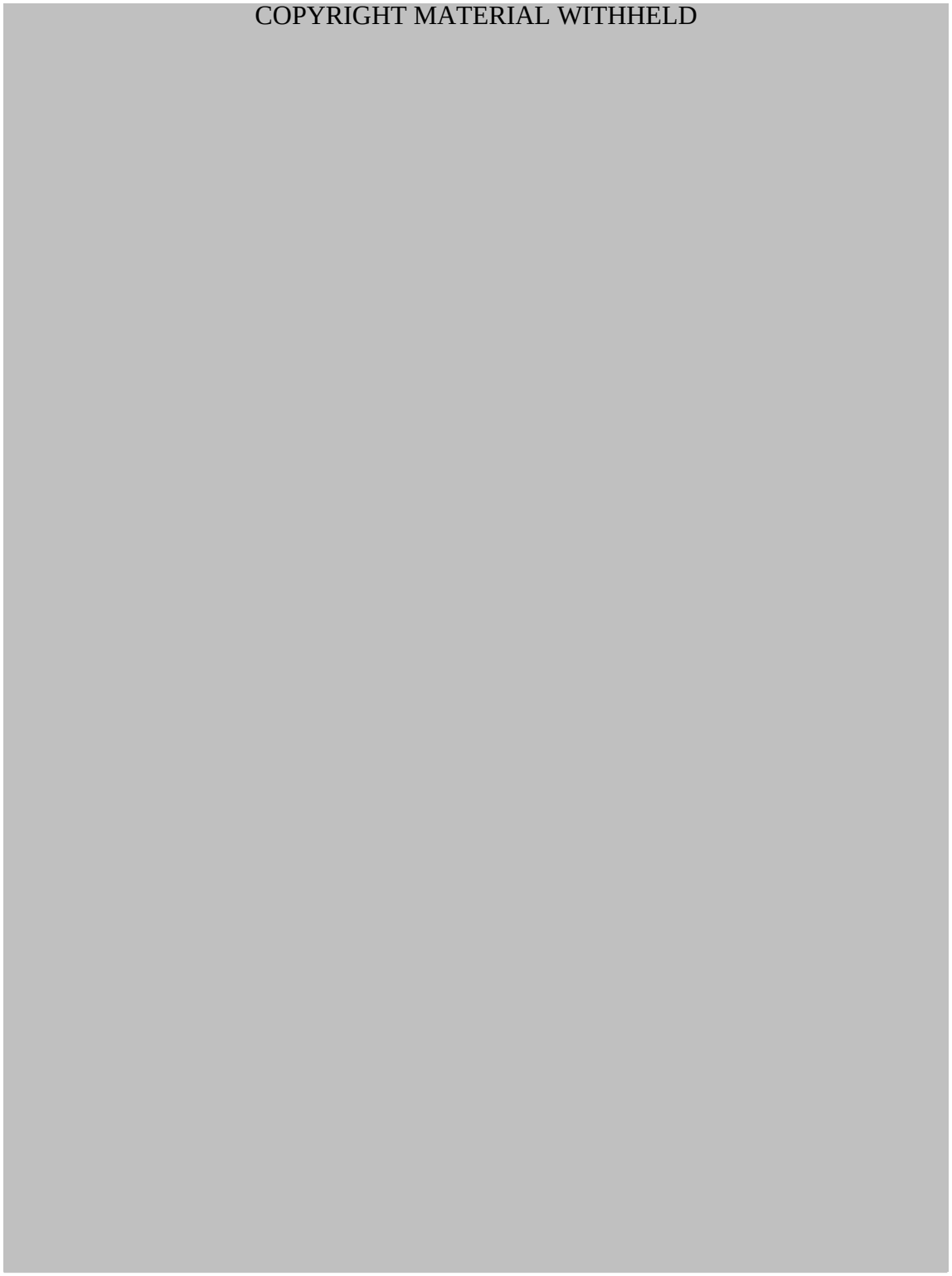
Wang, C., Finkel, R., Bertini, E., Schroth, M., Simonds, A., Wong, B., et al. (2007, Aug). Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol, 22*(8), 1027-1049.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): ISIS 396443- CS3b

Was a list of clinical investigators provided:	Yes x☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 321		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Not stated, but sponsor states that the 321 investigators above have no financial interests with IONIS or Biogen.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 23 investigators had missing financial disclosure forms.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 reported Significant payments of other sorts: 0 reported Proprietary interest in the product tested held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ No disclosable financial interests/arrangements reported.
Is a description of the steps taken to minimize potential bias provided:	Yes x☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 321		
Is an attachment provided with the reason:	Yes x☐	No ☐ (Request explanation from Applicant)

13.3. **CHOP INTEND Scoring Sheet. Source: Glanzman et al., 2010**



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13.4. Protocol Amendments

Table 55: Study CS3B Protocol Amendments

Protocol Version	Date	Changes
Original	25 November 2013	
Amendment 1	25 April 2014	• Finalized aspects of the study design.
Amendment 2	20 June 2014	• Added language explaining that all primary endpoint events were to be reviewed in a blinded fashion by a central, independent adjudication committee. • Added language to specify the segregation of responsibilities and blinding for personnel making decisions regarding subjects' ventilation and performing efficacy evaluations.
Amendment 3 (Japan only)	26 September 2014	• Clarification was made regarding the intention to continue safety follow up via scheduled study visits for subjects who discontinued treatment without withdrawal of consent. • Inserted main findings from nonclinical studies conducted with ISIS 396443. • Clarification was made that general anesthesia or sedation were not allowed to be used for LP procedures. In addition, clarification was made that local anesthesia (e.g., lidocaine) could be used for the LP procedure. • The HINE and Motor Milestones were added as appendices.
Amendment 3	22 April 2016	• Clarification was made to allow subjects who complete all study assessments to rollover into a long-term extension study in the scenario of the study being terminated early based on the assessment of risk-benefit of ISIS 396443 as a result of the interim

		analysis. • A statement was added related to unblinding of certain representatives from the study Sponsor during the conduct of the interim analysis. • Clarification was made on the adjustment of visit schedule for subjects who experience treatment delays as a result of an illness. • Changes were made to the primary and secondary efficacy endpoints based on new information from Phase 2 and natural history data and to improve ability to interpret some of the endpoints in the event that the study is terminated early. • A sample size justification was added based on the power analysis using the new primary endpoint of motor milestone responders. • Timing of the interim and final analyses was clarified. • Clinical experience was updated to reflect the most recent version of the Investigator's Brochure. • A definition for Interim Efficacy Set was added. • A description of the endpoints and timing of the interim analysis was added. • Details on the definitions of primary, secondary, and tertiary endpoints were added. • References related to analytical methods were added.
Amendment 3 (Turkey)	24 May 2016	• Clarification was made to allow subjects who complete all study assessments to rollover into a long-term extension study or transition to open-label study drug in the scenario of the study being terminated early based on the assessment of risk-benefit of ISIS 396443 as a result of the interim analysis. • A statement was added related to unblinding of certain representatives from the study Sponsor during the conduct of the interim analysis. • Clarification was made on the adjustment of visit schedule for subjects who experience treatment delays as a result of an illness. • Changes were made to the primary and secondary efficacy endpoints based on new information from Phase 2 and natural history data and to improve ability to interpret some of the endpoints in the event that the study is terminated early. • A sample size justification was added based on the power analysis using the new primary endpoint of motor milestone responders. • Timing of the interim and final analyses was clarified. • Clinical experience was updated to reflect the most recent version of the Investigator's Brochure. • A definition for Interim Efficacy Set was added. • A description of the endpoints and timing of the interim analysis was added. • Details on the definitions of primary, secondary, and tertiary endpoints were added. • References related to analytical methods were added.
Amendment 4 (Japan)	06 May 2016	• Clarification was made to allow subjects who complete all study assessments to rollover into a long-term extension study in the

		scenario of the study being terminated early based on the assessment of risk-benefit of ISIS 396443 as a result of the interim analysis. • Clarification was made that DSMB data review meetings are held on a quarterly basis. • A statement was added related to unblinding of certain representatives from the study Sponsor during the conduct of the interim analysis. • Clarification was made on the adjustment of visit schedule for subjects who experience treatment delays as a result of an illness. • Changes were made to the primary and secondary efficacy endpoints based on new information from Phase 2 and natural history data and to improve ability to interpret some of the endpoints in the event that the study is terminated early. • A sample size justification was added based on the power analysis using the new primary endpoint of motor milestone responders. • Timing of the interim and final analyses was clarified. • Clinical experience was updated to reflect the most recent version of the Investigator's Brochure. • A definition for Interim Efficacy Set was added. • A description of the endpoints and timing of the interim analysis was added. • Details on the definitions of primary, secondary, and tertiary endpoints were added. • References related to analytical methods were added.

DSMB = Data Safety Monitoring Board; HINE = Hammersmith Infant Neurological Exam; LP = lumbar puncture

13.5. Data tables from study CS3B for the tertiary efficacy endpoint "Change from baseline in growth parameters (weight for age/length, chest circumference, head to chest circumference ratio, and arm circumference)."

Table 56: Change from Baseline for Growth Parameters at day 394 - Interim Efficacy Set. Source: CS3B CSR, p. 331

Arm Circumference (cm)

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	16	16
Baseline mean	14.279		13.228	
Baseline median	14.200		13.300	
Mean	16.014	1.736	14.644	1.416
SD	1.3948	1.5692	2.0369	1.9806
Median	16.000	2.000	14.075	0.950
Min, Max	13.85, 18.50	-0.45, 3.20	11.60, 17.90	-0.70, 5.05

Chest Circumference (cm)

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	16	16
Baseline mean	41.529		39.397	
Baseline median	42.000		38.350	
Mean	46.564	5.036	45.766	6.369
SD	2.6132	3.3192	2.8356	4.2455
Median	46.600	5.600	45.650	6.150
Min, Max	43.15, 49.10	1.15, 10.70	40.60, 52.60	-1.15, 13.60

Weight (kg)

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	16	16
Baseline mean	7.454		6.634	
Baseline median	7.480		6.505	
Mean	11.371	3.917	9.691	3.057
SD	1.4316	1.1772	1.3263	1.4047
Median	11.800	3.930	9.398	2.940
Min, Max	8.99, 13.66	2.10, 5.71	7.90, 12.40	1.24, 5.80

Weight for Age Percentile

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	16	16
Baseline mean	33.807		28.386	
Baseline median	20.045		15.484	
Mean	60.830	27.023	28.526	0.140
SD	33.2022	29.3243	30.2695	36.4384
Median	77.035	24.245	15.606	-5.942
Min, Max	5.37, 96.56	-3.32, 72.11	0.51, 88.69	-55.85, 67.71

Body length (cm)

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	16	16
Baseline mean	67.386		65.369	
Baseline median	67.400		65.400	
Mean	87.943	20.557	78.875	13.506
SD	4.7999	3.3922	6.1874	5.9475
Median	87.000	20.000	78.150	15.275
Min, Max	81.40, 96.00	17.10, 26.65	69.10, 90.70	-3.20, 20.75

Head circumference (cm)

DAY 394				
n	7	7	16	16
Baseline mean	43.271		42.066	
Baseline median	42.900		42.600	
Mean	48.464	5.193	47.213	5.147
SD	1.6923	1.2775	1.3731	1.6404
Median	49.000	5.300	47.300	4.975
Min, Max	45.95, 50.90	3.45, 7.00	45.00, 50.60	2.80, 8.75

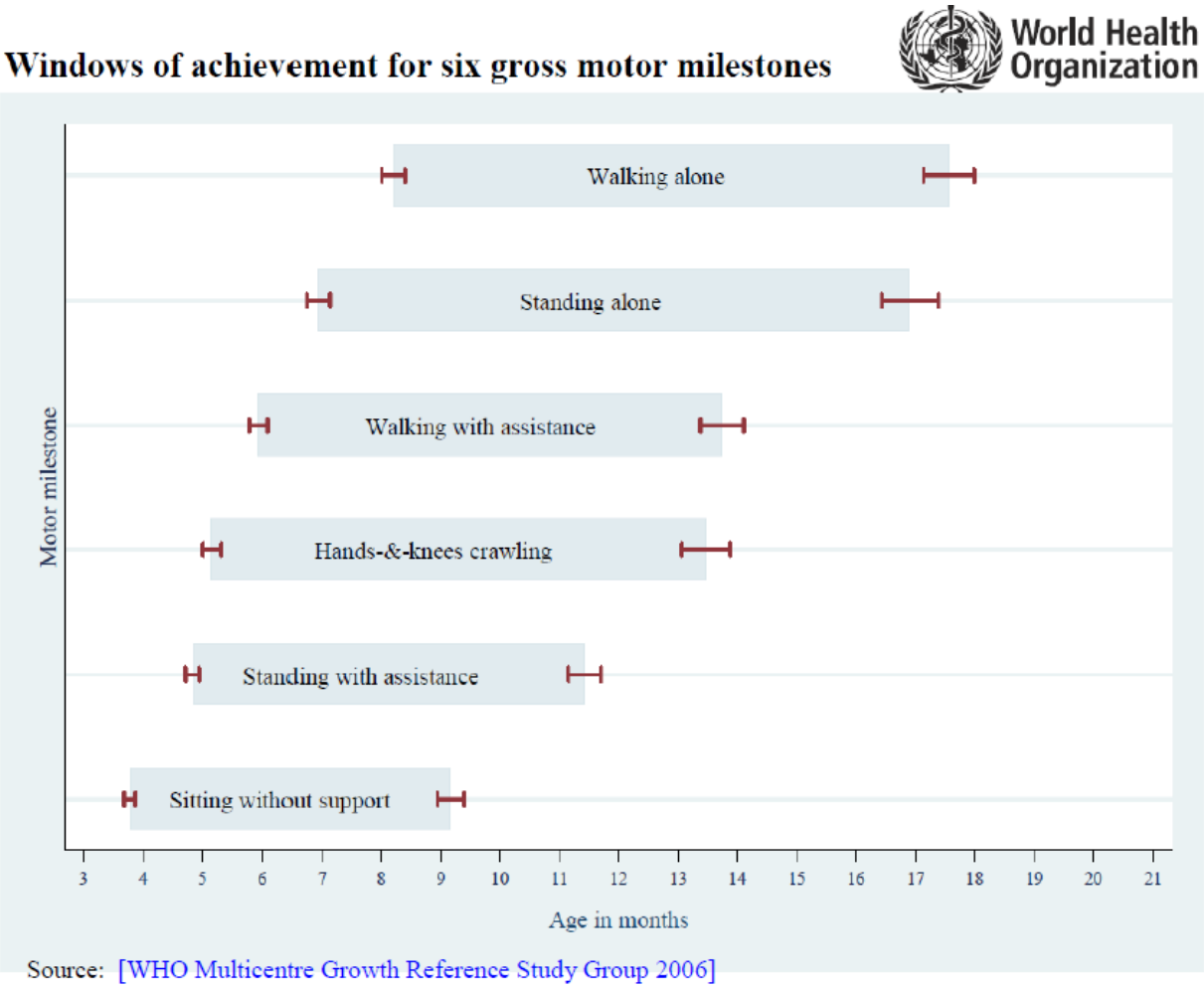
Head to chest circumference ratio

DAY 394				
n	7	7	16	16
Baseline mean	1.044		1.076	
Baseline median	1.030		1.075	
Mean	1.044	0.000	1.035	-0.041
SD	0.0586	0.0766	0.0609	0.1073
Median	1.040	0.010	1.025	-0.020
Min, Max	0.95, 1.13	-0.16, 0.07	0.96, 1.17	-0.27, 0.14

13.6. World Health Organization (WHO) Motor Milestones

"The WHO motor milestones are a set of 6 milestones in motor development, all of which would be expected to be attained by 24 months of age in healthy children. The individual milestones are as follows: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone, and walking alone. The WHO reported that, in approximately 90% of cases, the order of attainment followed a fixed sequence for 5 of the milestones, with only hands and knees crawling shifting between the earlier milestones" (SM201 CSR, p. 36).

Figure 33: WHO Motor Milestones Normal Achievement Time Range



13.7. Study CS1, Plasma Biomarker Panel Results, Excerpt from CS1 listing of labs, p. 1443

Sample Type	Lab Test	Day	Date Drawn	Draw Time	Result	Unit	Low	High	LDD	LLOQ	PK Code	Comments
Labid= (b) (4) Study/Treatment Group =Cohort 4, 9 mg Subject =1776-4001 First Dose Date = 09JUL2012												
Plasma (EDTA)	AXL Receptor Tyrosine Kinase (AXL)	Day 1 Predose	09JUL2012	8:01	17	ng/mL	6.9	21	0.055	0.12	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	17	ng/mL	6.9	21	0.055	0.12	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Apolipoprotein B (Apo B)	Day 1 Predose	09JUL2012	8:01	916	ug/mL	461	2670	8.8	42	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	918	ug/mL	461	2670	8.8	42	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	C-Reactive Protein (CRP)	Day 1 Predose	09JUL2012	8:01	0.041	ug/mL	0.27	15	0.017	0.039	Plasma SMA-MAP Sample Aliquot 1	

Note: The least detectable dose (LDD) was determined as the mean + 3 standard deviations of 20 blank readings. Results below the LDD will be more variable than results above the LDD. The LLOQ (Lower Limit of Quantitation) is the lowest concentration of an analyte in a sample that can be reliably detected and at which the tota error meets the laboratory's requirements for accuracy. In our case, the laboratory's requirement for accuracy is the concentration of an analyte at which the coefficient of variation of replicate standard samples is 30%. ND indicates Not Detected. N/A indicates Not Available.
SOURCE: \\isis.local\ogroups\cdmstats\396443\CS01\testdir\program\lsma_lab.sas DSCHULZ SASv9.2 (25SEP201317:24) EDC Date: 07JAN13
All Subjects Enrolled (N=28)

Sample Type	Lab Test	Day	Date Drawn	Draw Time	Result	Unit	Low	High	LDD	LLOQ	PK Code	Comments
Labid= (b) (4) Study/Treatment Group =Cohort 4, 9 mg Subject =1776-4001 First Dose Date = 09JUL2012												
Plasma (EDTA)	C-Reactive Protein (CRP)	Day 85	01OCT2012	11:18	0.18	ug/mL	0.27	15	0.017	0.039	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Cadherin-13 (T-cad)	Day 1 Predose	09JUL2012	8:01	8.5	ng/mL	13	35	1.6	1.8	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	8.7	ng/mL	13	35	1.6	1.8	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Cartilage Oligomeric Matrix Protein (COMP)	Day 1 Predose	09JUL2012	8:01	189	ng/mL	285	1270	6.3	14	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	234	ng/mL	285	1270	6.3	14	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed

Sample Type	Lab Test	Day	Date Drawn	Draw Time	Result	Unit	Low	High	LDD	LLOQ	PK Code	Comments
Labid= (b) (4) Study/Treatment Group =Cohort 4, 9 mg Subject =1776-4001 First Dose Date = 09JUL2012												
Plasma (EDTA)	Cathepsin D	Day 1 Predose	09JUL2012	8:01	259	ng/mL	223	521	115	88	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	439	ng/mL	223	521	115	88	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Complement Factor H _ Related Protein 1 (CFHR1)	Day 1 Predose	09JUL2012	8:01	2630	ug/mL	1160	6610	15	23	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	2900	ug/mL	1160	6610	15	23	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Complement component C1q receptor (C1qR1)	Day 1 Predose	09JUL2012	8:01	4.2	ug/mL	5.2	19	0.013	0.027	Plasma SMA-MAP Sample Aliquot 1	

Sample Type	Lab Test	Day	Date Drawn	Draw Time	Result	Unit	Low	High	LDD	LLOQ	PK Code	Comments
Labid= (b) (4) Study/Treatment Group =Cohort 4, 9 mg Subject =1776-4001 First Dose Date = 09JUL2012												
Plasma (EDTA)	Complement component C1q receptor (C1qR1)	Day 85	01OCT2012	11:18	5.1	ug/mL	5.2	19	0.013	0.027	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Dipeptidyl peptidase IV (DPPIV)	Day 1 Predose	09JUL2012	8:01	197	ng/mL	203	632	14	18	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	265	ng/mL	203	632	14	18	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed
	Endoglin	Day 1 Predose	09JUL2012	8:01	3	ng/mL	2.6	6.5	0.0084	0.012	Plasma SMA-MAP Sample Aliquot 1	
		Day 85	01OCT2012	11:18	3.4	ng/mL	2.6	6.5	0.0084	0.012	Plasma SMA-MAP Sample Aliquot 1	Sample Received Thawed

13.8. Endpoint Summary Across Trials

Table 57: Descriptive Summary of Endpoints and Results Across All Clinical Studies

Endpoint	Clinical Study						
	CS3B	CS3A	SM201	CS1	CS10	CS2	CS12
HINE (Motor Milestones)	Nusinersen: 40% responded, Control: 0% (p<0.0001) over ~ 13 months	13/20 subjects (65%) attained new motor milestones over ~2 years	100% attained new motor milestones by day 183				
CHOP INTEND	Nusinersen: 65% had >= 4-point improvement from baseline. Control: 4%	Mean change from baseline was 16.90 points at the Day 694 visits.	Mean (SD) change from Baseline at Day 302 was 5.2 (8.64) points				
Survival	12 subjects (15%) in nusinersen group and 13 subjects (32%) in control group died	65% event-free survival at 30 months of age	100% alive at 13 months of age				

Endpoint	Clinical Study						
	CS3B	CS3A	SM201	CS1	CS10	CS2	CS12
Growth	Control group had greater increase in weight (3.1 vs. 3.9kg control), body length (13.5 vs. 20.6cm control), and arm circumference (1.4 vs. 1.7cm control)		Growth failure in 4/17 subjects (weight for age decreased by ≥2 major percentiles)				
CMAP amplitude	Nusinersen: 43% had >=0.5mV (peroneal nerve) increase vs. Control: 0%	Mean change from baseline in nerve amplitude: 0.691 mV (415.4%, ulnar); 1.72 mV (388.3%, peroneal)	Mean (SD) change at day 302 from baseline amplitude (mV) 1.22 (1.825, ulnar); 0.07 (1.9, peroneal)	mean change from baseline at Day 85 = -0.2	Mean change from baseline at day 169 = -0.6mV	Mean (SD) change from baseline at day 253 = 0.4 (0.9) for 9mg dose; 0.0 (1.0) for 12mg dose	

Endpoint	Clinical Study						
	CS3B	CS3A	SM201	CS1	CS10	CS2	CS12
HFMSE				≥ 3 Point Increase in 7/10 (70.0%) subjects, 9mg dose	Mean change from baseline of 5.8 points (p = 0.008, 9mg dose)	Mean change from baseline at day 253 = 3.7 points (9mg dose); 2.3 points (12mg dose)	Mean (SD) change from baseline on day 715= -0.65 (8.49); median (25th percentile, 75th percentile) = 0.0 (-1.0, 3.0)
MUNE				Mean change from baseline at Day 85 = 16.9	Mean change from baseline at day 169 = 11.4	Mean change from baseline at day 253= 21.5 (20.5, 12mg dose)	
ULMT						Mean change from Baseline on day 253 = 1.6 points	Mean change from Baseline (SD) on day 715= 1.00 (1.11)

Endpoint	Clinical Study						
	CS3B	CS3A	SM201	CS1	CS10	CS2	CS12
myometry						On Day 253, mean increases from 0.5 to 1.5 lbs (5.9-16.9% change) were noted in all muscles tested	
6MWT						Mean (SD) increase of 34.8 (37.4) meters at Day 253 compared to baseline.	Change from baseline on day 715: Mean (SD, SEM)= -10.88 (82.55, 29.18); Median (P25, P75)= -18.50 (-47.50, 25.50)

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/s/

RAINER PAINE
12/12/2016

NICHOLAS A KOZAUER
12/14/2016