# Cross-Discipline Team Leader Review

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<th>December 8, 2016</th>
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<tbody>
<tr>
<td>From</td>
<td>Nick Kozauer, MD</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>NDA/BLA #</td>
<td>NDA 209531</td>
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<td>Supplement#</td>
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<tr>
<td>Applicant</td>
<td>Biogen, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>September 23, 2016</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>March 23, 2017</td>
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<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>Spinraza (nusinersen)</td>
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<tr>
<td>Dosage form(s) / Strength(s)</td>
<td>Solution for intrathecal injection, 12mg/5mL (2.4mg/mL)</td>
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<tr>
<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>Treatment of spinal muscular atrophy (SMA)</td>
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<td>Recommendation on Regulatory Action</td>
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<tr>
<td>Recommended Indication(s)/Population(s)</td>
<td>Treatment of spinal muscular atrophy (SMA)</td>
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1. **Benefit-Risk Assessment**
Benefit-Risk Summary and Assessment

Spinal muscular atrophy (SMA) is a rare genetic disorder characterized by atrophy of the voluntary muscles of the limbs and trunk. It is the most common genetic cause of death in infants. SMA is caused by a deletion or mutation of the survival motor neuron 1 (SMN1) gene located on chromosome 5q coding for the SMN protein, which helps to maintain motor neurons. A small amount of SMN protein is produced from a similar gene known as SMN2. However, most SMN2 mRNA transcripts lack exon 7, which leads to the production of a truncated protein that is easily degraded. Nusinersen (ISIS 396443) is a 2’-O-(2-methoxyethyl) antisense oligonucleotide (ASO) that is designed to bind to the SMN2 pre-mRNA and promote the inclusion of exon 7 in the mRNA transcript, thereby leading to the production of higher levels of the functional SMN protein.

The number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. Historically, patients were diagnosed as having Types 0, I, II, III, or IV SMA depending on their clinical presentation. This application refers to the clinical categories of SMA as presymptomatic, infantile-onset, and later-onset, respectively. Patients with infantile-onset SMA (the majority of all cases), consistent with having 2 copies of the SMN2 gene, uniformly fail to reach developmental motor milestones such as the ability to sit unassisted and rarely survive beyond 24 months of age in the absence of life-sustaining interventions. Patients with 3 copies of the SMN2 gene are generally unable to walk without assistance and approximately 70% are alive at 25 years of age. Patients with 4 or more copies of the SMN2 gene may have normal life expectancies and tend to experience a more varied clinical course ranging from mild weakness to the loss of previously attained motor milestones in adulthood (although some can still be more severely affected).

There are no FDA approved treatments for SMA, and treatment in clinical practice is supportive only.

This application has provided data from an interim analysis of a double-blind, sham-procedure controlled trial in infantile-onset SMA subjects having only 2 copies of the SMN2 gene. This trial demonstrated a clear and important benefit of nusinersen with 21/51 (41%) of nusinersen-treated subjects meeting a motor milestone development responder definition based on Section 2 of the Hammersmith Infant Neurological Examination (HINE) as compared to 0/27 (0%) of subjects receiving the sham-procedure control (p<0.0001). The results on the trial’s secondary endpoints, although only presented descriptively according to the SAP, consistently supported the effect on the primary endpoint. The results from Study CS3B were also supported by Study CS3A, an open-label trial in infantile-onset subjects where treatment with nusinersen was associated with the development of motor milestones that would be extremely unusual in the natural course of the illness (e.g., 7/20 subjects were able to sit without assistance, 5 of whom only had 2 copies of the SMN2 gene).

Results were also provided from additional open-label trials in later-onset SMA subjects having up to 4 copies of the SMN2 gene. Although the interpretation of these results is limited by the lack of a concurrent control group, these trials appeared to demonstrate a clinical course that was inconsistent with the expected clinical deterioration in these subjects in the absence of treatment. There would also be no obvious basis

Reference ID: 4026347
to expect that the mechanism of action of nusinersen would not plausibly be associated with efficacy in patients with differing numbers of SMN2 genes, particularly as clear evidence of effectiveness has been established in the most severely affected infantile-onset patients. This conclusion is also supported by summary findings from an interim analysis from in Study CS4 in later-onset SMA subjects with 3 copies of the SMN2 gene that was ongoing at the time of the application submission. Although data from Study CS4 were not available for review, and can therefore only provide additional context for consideration, scores on the primary endpoint of the Hammersmith Functional Motor Scale – Expanded (HFMSE) (a maximum score is 66-points; higher scores are better) were reported to be significantly higher in the nusinersen-treated group [4.0 (95% CI 2.9-5.1)] as compared to the sham-procedure control group [-1.9 (95% CI -3.8-0.0)] (p=0000002). Ultimately, the data provided with this application have established the efficacy of nusinersen for the treatment of all patients with SMA.

The safety reviewers have identified a number of potential risks with nusinersen including thrombocytopenia, proteinuria, decreases in serum bicarbonate, liver enzyme elevations, severe hyponatremia, growth retardation, rash/vasculitis, and QT prolongation. These risks are based on both observations from the clinical development program as well as the known class-effects with oligonucleotides having a phosphorothioate backbone. It is also possible that additional currently unidentified risks may become evident with long-term exposure. A description of these findings has been recommended for the WARNINGS AND PRECAUTIONS section of the prescribing information (PI), with monitoring recommendations intended to mitigate the risks. However, the serious nature of SMA justifies an approval action in the setting of the clinical efficacy that has been clearly established.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Analysis of Condition</td>
<td>• SMA is a rare and serious genetic disorder that results in atrophy of the voluntary muscles of the limbs and trunk. The condition results from a deletion or mutation of the SMN1 gene on chromosome 5q. The SMN2 gene also produces the SMN protein, but most of the copies of the SMN2 pre-mRNA lack exon 7 which leads to the production of a truncated protein that is easily degraded. Humans can have between 2-8 copies of the SMN2 gene, with less copies resulting in a more severe clinical course. 58% of patients have what has historically been referred to clinically as Type I SMA. 90% of these patients have only 2 copies of the SMN2 gene. In these patients, the disease has an onset ≤ 6 months of age, they do not attain developmental milestones like the ability to sit unassisted, and the disease is almost uniformly fatal before 24 months of age. SMA is the most common genetic cause of infant mortality.</td>
<td>SMA is a serious disease. Although some later-onset patients can have normal life expectancies, the majority have infantile-onset disease that almost uniformly leads to death before 24 months of age.</td>
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<td>Dimension</td>
<td>Evidence and Uncertainties</td>
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<tr>
<td>Current Treatment</td>
<td>• There are no FDA approved treatments for SMA. Treatment in clinical practice is only supportive and has no beneficial effect on motor milestone development.</td>
<td>There is a high unmet medical need for effective treatments for SMA.</td>
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<tr>
<td>Options</td>
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<td>Benefit</td>
<td>• Nusinersen is an anti-sense oligonucleotide (ASO) that is designed to increase the inclusion of exon 7 into the SMN2 mRNA, thereby leading to increase production of a functional SMN protein which can partially compensate for deletions/mutations of the SMN1 gene.</td>
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<td>• The applicant has provided data from an interim analysis of Study CS3B which was a double-blind, sham-procedure controlled trial in infantile-onset SMA subjects having 2 copies of the SMN2 gene. This trial demonstrated a clinically important and highly statistically significant effect on motor milestone development with 21/51 (41%) of nusinersen-treated subjects meeting a responder definition based on Section 2 of the Hammersmith Infant Neurological Examination (HINE) as compared to 0/27 (0%) of subjects receiving the sham-procedure control (p&lt;0.0001). Results on the trial’s secondary endpoints, reported descriptively according to the SAP, were consistently supportive of the primary endpoint findings. Study CS3B was stopped on the basis of these results, with all subjects being switched to active treatment.</td>
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<td>• Study CS3A, an open-label trial in infantile onset SMA subjects (17/20 (85%) of whom had 2 copies of the SMN2 gene) was very supportive of the CS3B results. 7/20 (35%) of the subjects were able to sit unassisted, including 5 subjects with only 2 copies of the SMN2 gene, which is a motor milestone that would be unexpected in this population.</td>
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<td>• Results from additional open-label trials conducted in SMA patients with up to 4 copies of the SMN2 gene were provided to support the efficacy of nusinersen across the range of SMA subtypes. The uncontrolled nature of these trials prevents them from providing the primary basis of efficacy in these subjects. However, the findings are</td>
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<td>Dimension</td>
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<tr>
<td>Risk</td>
<td>consistent with a beneficial effect of nusinersen in later-onset SMA patients, particularly in the context of the compelling findings of efficacy in infantile-onset subjects and a mechanism of action that would plausibly lead to efficacy in the SMA population, as a whole. The application also provided a summary of the interim analysis of the results from Study CS4 which was a double-blind, sham-procedure controlled trial in SMA subjects with 3 copies of the SMN2 gene. The trial was ongoing at the time of the application submission, so only summary data was provided for context. However, the reported results on the primary endpoint of the Hammersmith Functional Motor Scale – Expanded (HFMSE) (a maximum score is 66-points with lower scores being worse) were significantly higher in the nusinersen-treated group [4.0 (95% CI 2.9-5.1)] as compared to the sham-procedure control group [-1.9 (95% CI -3.8-0.0)] (p=0.000002). These results provide an additional degree of reassurance that nusinersen is effective across the range of SMA patients.</td>
<td></td>
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</tbody>
</table>
|           | • Drs. Mentari and Yasuda, the safety reviewers for this application, have identified a number of potential risks with nusinersen, including:  
  • Thrombocytopenia and coagulation abnormalities  
  • Proteinuria/low serum bicarbonate  
  • Severe hyponatremia  
  • Reduced growth (height/weight)  
  • Rash/vasculitis  
  • Liver toxicity  
  • QT prolongation  

These concerns were raised based on both observations in the clinical development program with nusinersen, as well as known class-effects with oligonucleotides with a phosphorothioate backbone. There was also a nonclinical concern about potential neurotoxicity based on findings in the monkey. | Drs. Mentari and Yasuda conclude that the safety issues that have been identified could potentially have life-threatening outcomes. Although 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. The serious nature of SMA justifies an approval action in the setting of the clinical efficacy that |
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<tr>
<td>Risk Management</td>
<td>• 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.</td>
<td>Drs. Mentari and Yasuda conclude that 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. They also recommend that WARNINGS and PRECAUTIONS contains information informing prescribers about hyponatremia, decreased growth, and rash/possible vasculitis.</td>
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2. Background

This application contains data in support of the efficacy of nusinersen (ISIS 396443), administered intrathecally (IT) via lumbar puncture (LP) for the treatment of spinal muscular atrophy (SMA). Nusinersen is a new molecular entity (NME) and has not been approved for any indication and has not previously been the subject of any marketing application. There are no FDA-approved treatments for SMA.

Spinal muscular atrophy (SMA) is a rare genetic disease characterized by atrophy of the voluntary muscles of the limbs and trunk. It is the most common genetic cause of death in infants. SMA is caused by a deletion or mutation of the survival motor neuron 1 (SMN1) gene located on chromosome 5q coding for the SMN protein, which helps to maintain motor neurons. A small amount of SMN protein is produced from a similar gene known as SMN2. However, most SMN2 mRNA transcripts lack exon 7, which leads to the production of a truncated protein that is easily degraded. Nusinersen is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO) that is designed to bind to the SMN2 pre-mRNA and promote the inclusion of exon 7 in the mRNA transcript, thereby leading to the production of higher levels of the functional SMN protein.

The number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype. Historically, patients were diagnosed as having Types 0, I, II, III, or IV SMA depending on their clinical presentation. This application refers to the clinical categories of SMA as presymptomatic, infantile-onset, and later-onset, respectively. The following table briefly summarizes the clinical/genetic characteristics of the clinically diagnosed SMA subtypes.

<table>
<thead>
<tr>
<th>Clinical SMA Diagnosis</th>
<th>% of SMA cases</th>
<th>Usual number of SMN2 copies</th>
<th>Typical age of symptom onset</th>
<th>Life expectancy</th>
<th>Motor development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>Very rare</td>
<td>1</td>
<td>In utero</td>
<td>Death occurs shortly after birth</td>
<td>None</td>
</tr>
<tr>
<td>Type I</td>
<td>58</td>
<td>2</td>
<td>≤ 6 months</td>
<td>≤ 24 months</td>
<td>Never able to sit unassisted</td>
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<tr>
<td>Type II</td>
<td>29</td>
<td>2-4 (80% have 3 copies)</td>
<td>≤ 18 months</td>
<td>70% alive at 25 years</td>
<td>Unable to walk without assistance</td>
</tr>
<tr>
<td>Type III</td>
<td>13</td>
<td>80% have 4 copies</td>
<td>May be normal</td>
<td>May be normal</td>
<td>Able to stand and walk without assistance, but lose this ability as the disease progresses</td>
</tr>
<tr>
<td>Type IV</td>
<td>&lt;5</td>
<td>≥ 4</td>
<td>20-30 years</td>
<td>Normal</td>
<td>Ambulatory. May experience mild muscle weakness.</td>
</tr>
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</table>

The applicant has provided data from an interim analysis of a double-blind, sham-procedure controlled clinical trial as the primary basis of support for the efficacy of nusinersen in SMA. Additional data from 6 completed and ongoing open-label trials are intended to support a broad indication covering all SMA subtypes (i.e., to include presymptomatic and later-onset disease). During the review period, the applicant conducted an interim analysis of what was an ongoing study in later-onset SMA (consistent with Type II SMA). A summary of these findings was also provided to the NDA for additional context.
The regulatory history for nusinersen is detailed in Dr. Rainer Paine’s clinical review and the reader is referred there for additional information.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson (Dr. Wilson’s review lists the entire OPQ team that was involved with the review of this application). Nusinersen is an 18-mer oligonucleotide, formulated as a solution for intrathecal administration via slow bolus injection. OPQ recommends approval of this NDA. Dr. Wilson’s review states that OPQ will grant a [b]1-month re-test period for the drug substance when stored [c] and a 30-month drug product expiration period when stored refrigerated in commercial packaging. There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

Dr. Wilson’s review outlines a number of post-approval quality agreements that have been reached between the applicant and OPQ during the review period. Her review provides comments for the action letter reminding the applicant of these agreements.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. Ed Fisher, with Dr. Lois Freed performing a secondary review. Dr. Fisher concludes that the application is approvable from a pharmacology/toxicology standpoint. The following are among the key conclusions from Dr. Fisher’s review:

- In the 13-week subcutaneous (SC) mouse study, histopathologic findings attributed to the expected effects of local and systemic accumulations of oligonucleotide and/or their pro-inflammatory effects were observed in a variety of tissues. These findings were generally not associated with evidence of necrosis, degeneration, or inflammation.

- No clear evidence of reproductive or developmental toxicity was seen in mouse and rabbit studies, and nusinersen was negative for genotoxicity in a standard battery of in vitro and in vivo assays.

- Carcinogenicity studies were not conducted. The applicant has requested a waiver based on the infeasibility of conducting lifetime studies in rodents by the IT route, but given the significant systemic exposure documented in clinical studies, it is recommended that a parenteral study in one species be conducted postmarketing.

- Neurotoxicity (decreased lower spinal reflexes) was observed following single doses ≥ 3 mg in both adult and juvenile monkeys but appeared to be reversible and did not increase in incidence or severity with continued dosing. Additionally, possible long-term effects on performance in a learning and memory test were observed in juvenile monkeys at the high-dose (HD) in the 1-year study, which could be related to drug-related hippocampal neurohistopathology. However, due to data variability and small group sizes, this neurobehavioral effect did not reach statistical significance. Neuronal vacuolation (graded slight to minimal) in the inferior region of the hippocampus was observed at the middle-dose
(MD) and HD in both studies. In some animals at both doses, this vacuolation was associated with low incidences of neuronal and glial cell necrosis and cellular debris. Hippocampal vacuolation and necrotic cells/cellular debris were still present following 12 and 24 weeks of recovery in the 14- and 53-week studies, respectively. The no-observed adverse effect level (NOAEL) for neurohistopathology in monkeys (0.3 mg/dose or 39 mg/year) is similar to the proposed human maintenance dose (36 mg/yr) when calculated on a yearly basis and was associated with tissue levels similar to those measured in patient tissue samples at autopsy.

The review team is recommending that the potential risk for neurotoxicity observed in the monkey be conveyed in the WARNINGS AND PRECAUTIONS section of the prescribing information (PI).

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Hobart Rogers (the primary reviewer), Dr. Atul Bhattaram, Dr. Christian Grimstein, Dr. Kevin Krudys, and Dr. Sreedharan Sabarinath (the clinical pharmacology team lead).

The following are among the key conclusions of the OCP review:

- 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) on the SMN2 pre-mRNA to enhance production of full length SMN protein.

- Nusinersen is distributed rapidly to the CNS and plasma. Plasma concentrations peak at 1-6 hours and decline rapidly because of extensive tissue distribution.

- 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.

- 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.

A focus of the OCP review was related to the proposed dosing recommendations for nusinersen. The applicant initially proposed a dose of 12mg/5mL (dosed in 4 loading doses, followed by a maintenance dosing schedule) for patients [b] (c)

However, the OCP review concluded that a fixed-dose of 12mg/5mL was appropriate for subjects [b] (c) with loading doses [b] (c), followed by maintenance doses every 4 months thereafter. This recommendation was based on the following considerations outlined in their review:

- 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.
- Fixed dosing is simpler and may reduce the potential for any dosing errors.

During discussions during the review period, the applicant agreed the 12mg/5mL dose would also be appropriate for patients < 2 years of age.

The OCP review contains a detailed analysis and discussion of the applicant’s proposed dosing recommendations, in terms of the dose level as well as the proposed dosing schedule. The OCP review comments that a visual assessment of the Day 183 and 305 data from the double-blind, sham-procedure controlled trial in patients with infantile-onset SMA (Study CS3B) suggests that higher doses or more frequent dosing would not have likely led to greater efficacy. However, the review cautions that this conclusion should be interpreted with some caution since all patients did not receive Day 183 assessments.

The OCP review also concludes that therapeutic individualization is not required for extrinsic factors because of the intrathecal route of administration and lack of a drug-drug interaction potential. The review further states that intrinsic factors such as hepatic and/or renal impairment are not expected to affect nusinersen exposure and are also not considered prevalent in the SMA patient population.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Rainer Paine was the clinical reviewer for this application. Dr. Tristan Massie was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead for this application.

The following graphic, copied from the application, illustrates the completed and ongoing clinical trials with nusinersen for the treatment of SMA:
Of the clinical trials depicted in the preceding figure, data from Studies CS3A and CS3B (infantile-onset SMA), CS1, CS2, CS10, and CS12 (later-onset SMA), and SM201 (pre-symptomatic infants), served as the basis for this application. Study CS3B, conducted in patients with infantile-onset SMA, was the only double-blind, sham-procedure controlled investigation submitted with the application and therefore provided the primary data for consideration. Data from the additional trials, all of which are open-label designs, were intended to provide support for the efficacy of nusinersen across a broad age-range of patients with SMA.

The results from Study CS3B will be described in the most detail, below. The findings from the additional open-label trials will be summarized more briefly as additional detail is available in Dr. Paine’s clinical review.

**Study CS3B in Infantile-Onset SMA**

Study CS3B was a 13-month, multicenter, randomized, double-blind, sham-procedure controlled trial in subjects with infantile-onset SMA. Approximately 111 subjects were to be randomized in a 2:1 ratio to receive either a scaled-equivalent 12mg dose of nusinersen, administered intrathecally by lumbar puncture (LP), or a sham-procedure control. Subjects received loading doses on Days 1, 15, 29, and 64 followed by maintenance doses on Days 183 and 302 (i.e., every 4 months). Randomization was stratified based on disease duration at Screening (≤ 12 weeks versus > 12 weeks). Subjects were required to have 2 copies of the SMN2 gene; consistent with a clinical diagnosis of Type I SMA.

As Dr. Massie’s review details, an interim analysis was to include all subjects that had a Day 183 visit at the time of the interim analysis cut-off date of June 15, 2016. Dr. Massie’s review observes that a total of 121 subjects had received at least one dose of nusinersen (n=80) or sham-procedure control (n=41), and were included in the ITT population, at that time. The interim analysis set (all subjects who had the opportunity for assessment at Day 183) included 78 subjects (51 randomized to nusinersen versus 27 randomized to the sham-procedure control).

The primary endpoint for the interim analysis was the between-group difference in the proportion of motor milestone responders based on a definition utilizing Section 2 of the Hammersmith Infant
Neurological Examination (HINE). Dr. Paine’s review details the specific definition of a responder on the scale, which was agreed to by the Division prior to the analysis. The applicant reported a highly statistically significant result on the primary endpoint, with 21/51 (41%) of subjects receiving nusinersen meeting the responder definition on the HINE as compared to 0/27 (0%) in the sham-procedure control group (p<0.0001; α = 0.032). Dr. Massie’s review discusses the fact that the Agency had preferred a definition of the ITT population for the interim analysis that included all patients who died or withdrew after baseline, regardless of whether they had the opportunity to be assessed at Day 183. Notably, the results of this analysis were similarly positive with 20/52 (40%) responders in the nusinersen group as compared to 0/30 (0%) in the sham-procedure control group (p<0.0001). Dr. Massie’s review comments that all of the sensitivity analyses that were conducted on the primary endpoint were supportive of the primary result.

An important observation with respect to motor milestone development, is that 5 patients in the nusinersen group were able to sit unassisted (as defined by the HINE), as opposed to 0 subjects in the sham-procedure control group. As Dr. Paine’s review describes, the achievement of this milestone would be extremely rare in patients historically diagnosed with Type I SMA. As subjects in the trial were required to have only 2 copies of the SMN2 gene, consistent with the over 90% of clinically defined Type I SMA patients, this finding also strongly supports the clinically important efficacy of nusinersen in this population.

Secondary endpoints included the proportion of patients who improved at least 4 points on the CHOP-INTEND (a 64-point motor development scale for SMA with higher scores being better), survival, event-free survival (i.e., the absence of death or permanent ventilation), and electrophysiological assessments. The results of these analyses were only reported descriptively as per the statistical analysis plan (SAP) for the interim analysis. The following are some of the most notable findings from these analyses as described by Drs. Paine and Massie:

- In the overall study population, there were 12/81 (15%) deaths in the nusinersen-treated group as compared to 13/41 (32%) deaths in the sham-procedure control group (HR = 0.44). As of a November 28, 2016 update, there was 1 additional death in the nusinersen-treated group and 3 additional deaths in the sham-procedure control group.

- In the overall study population, 27/80 (34%) of the subjects in the nusinersen group versus 20/41 (49%) of the subjects in the sham-procedure control group had died or required permanent ventilation (HR = 0.71).

- In the interim analysis data set, 33/51 (65%) of nusinersen-treated subjects met the prespecified responder definition for the CHOP-INTEND of a change from baseline of at least 4 points as compared to 1/27 (4%) of subjects in the sham-procedure control group. A worsening in CHOP-INTEND score of at least 4 points was observed in 2/51 subjects (4%) in the nusinersen group compared to 13/27 subjects (48%) in the sham-procedure control group.

- Findings on various electrophysiologic studies, detailed in Dr. Paine’s review, were supportive of the efficacy of nusinersen. For example, Dr. Paine comments that the improvement noted in compound muscle action potential (CMAP) amplitudes in the nusinersen group would not normally be expected in this population, as these patients will generally only decline on these assessments.
Following the highly positive results of the interim analysis, Study CS3B was stopped with all subjects being switched over to receive active treatment with nusinersen.

**Additional Clinical Trials**
The following table, adapted from the application, summarizes the 6 additional open-label trials that were submitted with the application (shaded to help visualize the population differences among the trials):

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CS3A</th>
<th>SM201</th>
<th>CS1</th>
<th>CS10</th>
<th>CS2</th>
<th>CS12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong> (all open-label)</td>
<td>Phase 2, multiple-dose</td>
<td>Phase 2, multiple-dose, single-arm</td>
<td>Phase 1, escalating-dose</td>
<td>Phase 1, single-dose</td>
<td>Phase 1, dose-escalation, multiple-dose</td>
<td>Phase 1, multiple-dose, single-arm</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Symptomatic, infantile-onset</td>
<td>Presymptomatic, infantile-onset (genetically diagnosed)</td>
<td>Symptomatic, later-onset</td>
<td>Symptomatic, later-onset</td>
<td>Symptomatic, later-onset</td>
<td>Symptomatic, later-onset</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>21</td>
<td>17</td>
<td>28</td>
<td>18</td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>Ongoing (note: Studies CS1, CS10, and CS2 all fed into CS12)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Motor milestones (HINE)</td>
<td>Time to death or respiratory intervention</td>
<td>Hammersmith Functional Motor Scale—Expanded (HFMSE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong> (all expressed as scaled equivalent doses and administered intrathecally via lumbar puncture)</td>
<td>Cohort 1: 6mg loading dose/12 mg maintenance</td>
<td>12mg</td>
<td>1, 3, 6, and 9 mg single doses</td>
<td>Cohort 1: 6mg on Day 1, 9mg on Day 1</td>
<td>Cohort 1: 3mg on Days 1, 29, and 85</td>
<td>Cohort 1: 12mg on Days 1, 169, 351, and 533 (subjects had already received loading doses in Studies CS1, CS10, and CS2)</td>
</tr>
<tr>
<td></td>
<td>Cohort 2: 12mg loading dose/12 mg maintenance</td>
<td>Loading doses on Days 1, 15, 29, and 64 with a maintenance dose on Days 183, 302, 421, 540, 659, and 778</td>
<td>Total duration approximately 2.4 years</td>
<td>Cohort 2: 9mg on Day 1</td>
<td>Cohort 2: 6mg on Days 1, 29, and 85</td>
<td>Total duration approximately 1.5 years</td>
</tr>
<tr>
<td></td>
<td>Loading doses on Days 1, 5, and 85 with a maintenance dose on Day 253 and every 4 months, thereafter</td>
<td>Total duration approximately 2.4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (median) age at Baseline</strong></td>
<td>155 days (36 to 210 days)</td>
<td>21.9 days (8 to 42 days)</td>
<td>6.1 years (2-14 years)</td>
<td>6.6 years (2-11 years)</td>
<td>7.4 years (2-15 years)</td>
<td>8 years (3-17 years)</td>
</tr>
<tr>
<td><strong>Mean (median) age at symptom</strong></td>
<td>Median 56 days</td>
<td>NA (presymptomatic)</td>
<td>Not summarized</td>
<td>Not summarized</td>
<td>Not summarized</td>
<td>Not summarized</td>
</tr>
<tr>
<td>SMN2 copy number</td>
<td>2 (n=17)</td>
<td>2 (n=12)</td>
<td>3 (n=25)</td>
<td>3 (n=17)</td>
<td>2 (n=1)</td>
<td>3 (n=39)</td>
</tr>
<tr>
<td>------------------</td>
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<td>----------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>Unknown (n=1)</td>
<td>3 (n=5)</td>
<td>4 (n=2)</td>
<td>4 (n=1)</td>
<td>3 (n=25)</td>
<td>4 (n=8)</td>
<td>4 (n=8)</td>
</tr>
</tbody>
</table>

Dr. Paine’s clinical review provides a detailed description of the efficacy findings reported for the trials outlined in the preceding table. Because of the open-label nature of these investigations, no formal statistical testing was possible and therefore, the results are not discussed by Dr. Massie in his biometrics review.

The following are among the most notable findings from these investigations that are described in Dr. Paine’s review:

**Study CS3A (infantile-onset SMA)**

This trial enrolled 17/20 subjects with 2 copies of the SMN2 gene, 2/20 subjects with 3 copies, and 1 subject with an unknown number of copies.

- 8/20 (40%) subjects were able to sit unassisted, 6 of whom had only 2 copies of the SMN2 gene. 2/20 (10%) subjects, both with 3 copies of the SMN2 gene, were able to walk (one with assistance and one independently). The achievement of these milestones is highly unexpected in the enrolled patient population.

- As of the initial application reporting date of January 26, 2016, 15/20 subjects were alive and continuing in the trial (1 had withdrawn and 4 had died). An update by the applicant confirmed that as of November 28, 2016, that only 1 additional subject had died and another subject had required permanent ventilation. 13/15 had not reached the point of requiring tracheostomy or permanent ventilation. 11/15 had lived to at least 36 months of age. These findings are highly inconsistent with the natural history of an SMA population primarily consisting of subjects with only 2 copies of the SMN2 gene.

**Study 201 (presymptomatic, genetically-diagnosed SMA)**

This trial enrolled 12/17 subjects with 2 copies of the SMN2 gene, 5/17 subjects with 3 copies.

- 0/17 subjects met the primary endpoint of death or a respiratory intervention (defined as invasive/noninvasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days, or tracheostomy).

- 4/10 subjects who had the ability to have assessments at Day 183 had manifestations of SMA clinically. As Dr. Paine notes, 3/4 of these subjects had 2 copies of the SMN2 gene, while 1/4 had 3 copies, which conveys a relatively less severe, although still debilitating, clinical course. However, the converse is that of the 7 subjects who had only 2 copies of the SMN2 gene, only 3 manifested clinical symptoms of SMA at the Day 183 assessment, which would be unexpected in this population. Importantly, no subjects lost any of the motor milestones that had been attained during the trial.

- As of the data cut-off for the interim analysis, all subjects were alive without permanent ventilation or chronic non-invasive ventilation. These subjects ranged from 74 to 380 days of
age at last visit. Dr. Paine comments in his review that less than 25% of patients in clinical practice who were clinically diagnosed with Type I SMA (as already noted, consisting of 90% of patients with 2 copies of the SMN2 gene) would be expected to survive to 13 months of age. Therefore, the fact that 7/7 subjects with 2 copies of the SMN2 gene and who had the opportunity to have at least Day 183 assessments were surviving at 13 months of age is highly inconsistent with the natural history of SMA in these patients. As no subject had met the combined primary endpoint of death or respiratory intervention, any survival benefit was not a consequence of intensive life-sustaining interventions.

- Dr. Paine notes the applicant’s observation that at Day 302, 5 subjects with 2 copies of the SMN2 gene had a World Health Organization (WHO) motor milestone assessment. 1/5 subjects 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. As Dr. Paine notes, these findings are highly inconsistent with the natural history of SMA in these patients.

**Studies CS1, CS10, CS2, and CS12 (later-onset SMA)**

The focus will be on the results from Studies CS12 and CS2, as Studies CS1 and CS10 were single-dose trials. Please refer to Dr. Paine’s review for a discussion of how patients from Studies CS1, CS2, and CS10, were transitioned into Study CS12. Study CS2 enrolled 1/34 subjects with 2 copies of the SMN2 gene, 25/34 with 3 copies, and 8/34 with 4 copies. Study CS12 enrolled 39/47 subjects with 3 copies of the SMN2 gene and 8/47 subjects with 4 copies.

- In Study CS2 there was a consistent trend of increasing HFMSE scores over time (including an apparent dose-response) (e.g., a mean positive change from baseline of 2 points [9.4%] in the 12mg/5mL group at the Day 253 assessment). Dr. Paine’s review notes that Kaufman (2012) reported a mean HFMSE decline of -0.54 points (95% CI -1.45 to 0.36) over 2 years in patients clinically diagnosed with Type 2 SMA. Therefore, a mean 2-point increase, complimented by an apparent dose-response in score improvement, suggests a benefit of treatment.

- Dr. Paine notes that there were small positive trends in the efficacy parameters in Study CS12, but also comments that the clinical significance of these small changes is uncertain given the generally more gradual progression in later-onset SMA patients. His review notes that mean HFMSE, 6-minute walk test (6-MWT), and upper-limb test (ULT) scores are all above baseline at Day 624. However, as with the preceding findings in Study CS2, the lack of a mean decline in scores across different endpoints in these subjects would not be inconsistent with a treatment benefit from nusinersen.

**Study CS4 (later-onset SMA)**

*(Note: this study was not described in the introductory table for this section, as results were not submitted with the application)*

Study CS4, which was a 15-month, double-blind, sham-procedure controlled trial in patients with later-onset SMA (consistent with patients who would have a clinical diagnosis of Type 2 SMA, with the majority having 3 copies of the SMN2 gene [range: 2-4]), was ongoing at the time of the NDA submission. Subjects received 12 mg loading and maintenance doses of nusinersen administered intrathecally. An interim analysis conducted based on a data cut-off of August 31, 2016, including 126
subjects (84 receiving nusinersen and 42 receiving sham-procedure control) was reported as revealing a highly statistically significant treatment effect. The study was stopped based on these findings, and all subjects in the sham-procedure control group were subsequently provided treatment with nusinersen. The applicant submitted a summary of the study findings to the NDA. With the important caveat that the data from Study CS4 have not been submitted for review, Dr. Paine describes the following key reported findings for context in his review:

- HFMSE scores were significantly higher in the nusinersen group [4.0 (95% CI 2.9-5.1)] as compared to the sham-procedure control group [-1.9 (95% CI -3.8-0.0)] (p=0000002). The applicant reports that all sensitivity analyses for the primary endpoint consistently supported this result.

- 57.3% of subjects in the nusinersen group achieved a 3-point or greater increase in HFMSE scores over baseline at 15 months compared to 20.5% in the sham-procedure control group. As with Study CS3B, alpha was only allocated to the primary analysis at the interim analysis, so findings for all of the additional endpoints were only presented descriptively.

**Efficacy Conclusions**

The 1998 FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products describes scenarios where evidence from a single clinical study can fulfill the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126. Specifically, the Guidance refers to section 115(a) of the FDA Modernization Act (1988) which makes clear that the Agency may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence of effectiveness in support of an approval of a marketing application.

The current application provides a quintessential example of a situation where the “single study plus confirmatory evidence” standard can and should be applied. Study CS3B, conducted in infantile-onset SMA, demonstrated a clinically important and highly statistically significant effect on motor milestone development that was consistently supported by the range of secondary endpoints, including a descriptive survival benefit. Results from Study CS3A, an open-label trial also conducted in in infantile-onset SMA, further support the efficacy of nusinersen in this population. Subjects in the trial reached developmental milestones that are universally thought not to be attained in SMA patients with only 2 copies of the SMN2 gene. As of December 5, 2016, the applicant has provided an update that 11/20 of the subjects in Study CS3A had survived past 36 months of age in a condition where the published survival beyond 24 months is historically 1.5%. Despite the lack of a concurrent control group, the results from Study CS3A provide strong confirmatory evidence for the controlled findings from Study CS3B and lead to a conclusion that nusinersen is effective for the treatment of infantile-onset SMA.

This application also provided data from uncontrolled, open-label trials conducted in genetically-diagnosed presymptomatic SMA (Study 201)(2-3 copies of the SMN2 gene) and later-onset SMA (Studies CS1, CS2, CS10, and CS12)(2-4 copies of the SMN2 gene). The open-label nature of these trials prevents their results from providing primary evidence of effectiveness in the context of the greater clinical heterogeneity in patients with increasing copies of the SMN2 gene. However, the findings from these trials suggest a clinical course that is inconsistent with the natural history of the disease. The summary results from the CS4 trial in subjects with 2 copies of the SMN2 gene provide an additional degree of reassurance that the open-label results in later-onset subjects are reflective of
a true treatment benefit. Of note, although more mild, adult-onset (i.e., clinically diagnosed Type IV SMA with an onset between age 20-30) SMA patients were not studied, these subjects constitute <5% of SMA cases and there is no obvious basis for concluding that nusinersen would not also be effective in these patients. Fundamental to this discussion is the fact that the mechanism of action of nusinersen, i.e., to increase the transcription of full-length SMN2 mRNA, would plausibly be expected to result in clinical efficacy across the disease spectrum. Therefore, the available evidence supports a reasonable conclusion that the benefit of nusinersen that was established in infantile-onset SMA would also be expected in presymptomatic and later-onset patients, supporting a broad indication for the treatment of SMA, as a whole.

An additional and related consideration is the appropriateness of the 12mg/5mL dose in older patients given the increase in CSF volume, and resultant decrease in nusinersen concentrations, with age. As Dr. Paine notes in his review, the average CSF volume in children/adolescents age 4 to 13 ranges from 65-140mL, while the average adult CSF volume ranges from 125-150mL, indicating an overlap between the average volumes in older adolescents and adults. Older adolescent and adult subjects were enrolled in the development program, including 9 subjects who reached ages ≥ 15 years in Study CS12, 4 of whom were ≥ 18 years old at the time of last dose, representing a range of mature CSF volumes. Inspection of the HFMSF results from these patients on an individual-patient level demonstrates a stability of progression that is not inconsistent with a treatment benefit in this population, as depicted in the following figure:

Therefore, although these trials, by design, were not capable of establishing a statistically significant treatment effect in older subjects alone, there is no evidence to suggest that the proposed 12mg/5mL dose would be ineffective in the SMA population overall as a function of reduced drug concentrations with age.

8. Safety

Dr. Evelyn Mentari was the safety team reviewer for this application. Dr. Sally Jo Yasuda, the safety team lead, has also written a comprehensive supervisory review.

Dr. Mentari’s review notes that a total of 173 subjects were exposed to nusinersen in the development program. These included 80 infantile-onset subjects who were exposed in the sham-procedure controlled trial (Study CS3B) and 93 subjects who were exposed in the additional open-
label trials discussed in Section 8 of this review. Of these subjects, 19/80 of the subjects in Study CS3B were exposed for ≥ 12 months, with 64/93 of the subjects in the open-label trials being exposed for ≥ 12 months, 62/93 of these subjects being exposed for ≥ 18 months, and 54/93 of these subjects being exposed for ≥ 24 months. The large majority of subjects were exposed to the 12mg dose intended for marketing. I agree with Drs. Mentari and Yasuda that the overall subject exposure is acceptable in the context of the rare nature of SMA.

Dr. Mentari’s review finds that the coding of adverse events in the application was appropriate. However, her review comments on a number of deficiencies in the laboratory assessments in the development program including the lack of quantitative urine protein measurements, the lack of routine evaluation of serum bicarbonate levels, the lack of coagulation laboratory measurements in the controlled trials (and only post-baseline in Study CS2), and the fact that GGT was not measured to assess hepatic toxicity.

The following are the key safety results (including deaths, serious adverse events [SAEs], discontinuations due to adverse events [AEs], other AEs, results of laboratory tests, and immunogenicity) that were identified by Drs. Mentari and Yasuda in their reviews.

**Deaths**
Deaths were observed during the development program including in 12 of 80 (15%) of nusinersen-treated subjects compared to 13 of 41 (32%) sham-procedure control subjects in Study CS3B. In all studies, 16 of 173 (9%) nusinersen-treated subjects died. However, Drs. Mentari and Yasuda note that all deaths occurred in subjects with symptomatic infantile-onset SMA and appeared related to complications of SMA (mostly respiratory disorders or cardio-respiratory arrest). Dr. Mentari comments on one nusinersen-treated subject (ID 2037-5167) in Study CS3B who had an unclear cause of death. However, this death was associated with “weight stagnation” which is commonly noted in non-sitting SMA patients.

**Bleeding Risk**
Thrombocytopenia has been associated with other phosphorothioate oligonucleotides. As noted by both Drs. Mentari and Yasuda, in Study CS3B, 6/56 (11%) of nusinersen-treated subjects had a platelet level below the lower limit of normal (LLN), compared to 0/28 sham-procedure control treated subjects. 3/145 (2%) of all nusinersen-treated subjects had platelet counts < 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. Prolonged activated partial thromboplastin time (aPTT) has also been described with other phosphorothioate oligonucleotides. However, Dr. Mentari notes that coagulation laboratory data with nusinersen are limited, although 10/53 (19%) of all subjects with these measures assessed had a shift from baseline to a high aPTT.

**Renal Toxicity**
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. There were no adverse events associated with renal toxicity identified in the development program. However, Dr. Mentari describes treatment-emergent elevated urine protein levels and low serum bicarbonate levels in some nusinersen-treated subjects; both findings that are associated with proximal renal tubule dysfunction.

**Neurologic Toxicity**
As already discussed in Section 4 of this review, Dr. Fisher describes nonclinical findings of neurotoxicity including hippocampal vacuolization and necrotic cells, as well as possible treatment-related changes in learning test performance in juvenile cynomolgus monkeys. Although Dr. Mentari has attempted to assess signs of drug-related neurologic toxicity in the development program, it is difficult, if not impossible, to discern the extent to which these findings would not primarily be associated with the underlying SMA disease process itself (particularly in infantile-onset patients who are incapable of self-report).

**Safety Issues Related to Lumbar Puncture**

Dr. Mentari comments that ultrasound guidance was necessary during the intrathecal administration of nusinersen in 99% of the subjects in Study CS3B. Not unexpectedly, AEs such as back pain, post-lumbar puncture syndrome, headache, vomiting, and nausea were often reported within 120 hours of nusinersen administration (mostly by later-onset subjects capable of self-report). Complications associated with anesthesia (e.g., atelectasis) were also observed in 11/80 (14%) of nusinersen-treated subjects in Study CS3B as compared to 2/41 (5%) of the sham-procedure control treated subjects. However, because of the risk of thrombocytopenia and potential coagulation abnormalities with nusinersen (discussed above), Dr. Mentari concludes that there is an increased risk of related adverse reactions following lumbar puncture.

**Rash and Possible Vasculitis**

Dr. Mentari notes that the pro-inflammatory effects of antisense nucleotides have been described in the published literature and has identified 3 cases of possible vasculitis with nusinersen. Drs. Mentari and Yasuda also comment that although distal necrosis has been rarely reported in SMA, 2 cases have been observed in the 173 nusinersen-treated subjects in the development program.

**Growth Retardation**

Dr. Mentari notes that in Study CS3B, nusinersen-treated subjects had reduced growth related to sham-procedure control treated subjects. Her review comments that although height/weight measurements may be theoretically easier to obtain in infants with decreased mobility, the finding of a weight difference further supports the possibility that there is a negative impact of treatment with nusinersen on growth.

**Hepatic Effects**

Nusinersen, like all antisense oligonucleotides, is deposited in the liver and therefore has the potential for hepatic toxicity. Dr. Mentari observes that there was no clear signal of hepatic enzyme elevations (ALT, AST, alkaline phosphatase, and bilirubin) in the development program. However, there were 2 cases of elevated ALT where a contribution of nusinersen could not be ruled out.

Dr. Patrick Lynch from the Office of Biotechnology Products (OBP) conducted an immunogenicity review for this application and concludes that there are no drug-induced immune response issues that would preclude an approval action for this application. Dr. Lynch does recommend a post-marketing requirement (PMR) to conduct a study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with nusinersen.

There is no foreign marketing experience.

Drs. Mentari and Yasuda both conclude that if efficacy is established for nusinersen and the benefits are determined to outweigh the risks, that nusinersen should be approved with labeling language,
including WARNINGS AND PRECAUTIONS, to mitigate these risks. I agree and find that the clearly established efficacy of nusinersen in a serious and fatal disease like SMA, even when viewed in the context of the preceding potential safety concerns, supports an approval action for this NDA.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable (the target population is largely pediatric, and discussed in the preceding sections of this memo).

11. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Paine’s review.
- Dr. Paine concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Office of Scientific Investigations (OSI) has inspected three clinical investigator sites. According to their review, these inspections did not reveal any significant regulatory violations and no Form 483s were issued. OSI concludes that based on results of these clinical investigator inspections, it appears that the data submitted by the applicant in support of the pending application for these sites are acceptable and the studies appear to have been conducted adequately.
- The Controlled Substance Staff (CSS) reviewer for this application is Dr. Martin Rusinowitz. Dr. Rusinowitz concludes that there are no data indicating that nusinersen has abuse potential or induces physical dependence.

12. Labeling

Please refer to the final negotiated product label. The following are among the key labeling issues that have been considered during this review:

- The applicant’s proposal that nusinersen be indicated for the treatment of all patients with SMA is supported by the data submitted with the application.
- The proposed 12mg/5mL dose, administered intrathecally via lumbar puncture, is acceptable.
- The Agency is recommending a number of WARNINGS AND PRECAUTIONS for the PI, including:
  - Thrombocytopenia and Coagulation Abnormalities
  - Renal Toxicity
The CLINICAL STUDIES section of the labeling should only provide detailed information from the double-blind, sham-controlled trial in infantile-onset SMA (Study CS3B). As only the primary endpoint from Study CS3B was analyzed statistically, consideration will need to be given to the appropriateness of presenting any compelling descriptive results on the secondary endpoints in the PI. The contribution of the additional open-label trials that were submitted with the application will only be described briefly without the presentation of any results given the lack of a placebo (sham-procedure) control.

13. Postmarketing Recommendations

The Division of Risk Management (DRISK) reviewer for this application is Dr. Robert Pratt. Dr. Pratt concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for nusinersen.

The following are the recommended post-marketing requirements:

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) A nonclinical carcinogenicity study.

Additional comments to the applicant regarding recommended post-marketing pharmacovigilance for an action letter should this application be approved as described in Section 14 of this review.

14. Recommended Comments to the Applicant

Dr. Yasuda’s review recommends that in ongoing or future clinical trials and through postmarketing surveillance, the applicant should continue to monitor for adverse events of special interest. These should include thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, effect on growth, rash and possible vasculitis, neurologic toxicity, hepatic effects and QT prolongation.

Dr. Wilson’s OPQ summary reviews outlines comments for the action letter, should an approval decision be made. Specifically, these remind the applicant of several post-approval quality agreements included in the amendment dated November 29, 2016 (SD 39) as well an agreement to update the carton and container labels to include the salt equivalency statement on the next printing and to submit this change as a CBE labeling supplement.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICHOLAS A KOZAUER
12/12/2016