APPLICATION NUMBER:

209531Orig1s000

OFFICE DIRECTOR MEMO
# Office of Drug Evaluation-I: Decisional Memorandum

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<th>December 23, 2016</th>
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<td>From</td>
<td>Ellis F. Unger, MD</td>
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<td>Director</td>
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<td>Office of Drug Evaluation-I</td>
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<td>Subject</td>
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<tr>
<td>New Drug Application (NDA) #</td>
<td>209531</td>
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<tr>
<td>Applicant Name</td>
<td>Biogen Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>September 23, 2016</td>
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<td>PDUFA Goal Date</td>
<td>May 23, 2017</td>
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<tr>
<td>Proprietary Name/Established (USAN) Name</td>
<td>Spinraza™ nusinersen injection</td>
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<td>Dosage Forms/ Strengths</td>
<td>12 mg/5mL (2.4 mg/mL)</td>
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<td>Final Indication</td>
<td>“SPINRAZA is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients”</td>
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**Material Reviewed/Consulted - Action Package, including:**

- Project Manager: Yuet (Fannie) Choy
- Clinical Efficacy: Rainer Paine
- Clinical Safety: Evelyn Mentari, Sally Jo Yasuda
- Clinical Pharmacology/Pharmacometrics: Hobart Rogers, Atul Bhattaram, Christian Grimstein, Kevin Krudys, Sreedharan Sabarinath, Mehul Mehta
- Office of Biostatistics: Tristan Massie, Kun Jin, Hsien Ming Hung
- Pharmacology Toxicology: J. Edward Fisher, Lois Freed, Paul Brown
- Office of Biotechnology Products: Patrick Lynch
- Office of Pharmaceutical Quality: Monica Cooper, Mariappan Chelliah, Denise Miller, Gerlie Gieser, Erin Kim, Aditi Thakur, Dahlia Woody, Wendy Wilson-Lee, Kui Yang, Caryn McNab, Martha Heimann
- Office of Scientific Investigations: Cara Alfaro, Susan Thompson, Kassa Ayalew, Janice Pohlman, Lakisha Williams, Yolanda Patague
- Method Validation: Michael Hadwiger
- Statistical Review – Stability data: Monica Cooper, Kasturi Srinivasachar, Mariappan Chelliah, Wendy Wilson-Lee
- Office of Prescription Drug Promotion: Aline Moukhtara
- Division of Medication Error Prevention and Analysis: John Morris, Lolita White
- Division of Risk Management: Robert Pratt, Jamie Wilkins Parker
- Associate Director for Labeling: Tracy Peters
- Controlled Substance Staff: Martin Rusinowitz, Michael Klein
- Cross-Discipline Team Leader: Nicholas Kozauer
- Deputy Director, Division of Neurology Products: Eric Bastings
1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Spinal muscular atrophy is a rare (1:10,000 births) autosomal recessive disease characterized by loss of motor neurons in the anterior horn of the spinal cord, resulting in progressive wasting of the voluntary muscles of the limbs, trunk, and diaphragm. SMA is caused by deletions or point mutations of the survival motor neuron 1 (SMN1) gene located on chromosome 5q. The gene codes for SMN protein, which is necessary for survival of motor neurons. SMN2 is a related gene on chromosome 5, which, because of variation in a single nucleotide, produces a protein that undergoes alternative splicing, such that only 10-20% of transcripts encode a fully functional SMN protein; most produce abnormal truncated protein that is rapidly degraded.

The severity of SMA is generally related to the ability of the SMN2 genes to compensate for the loss of SMN1, and the number of copies of the SMN2 gene is the best predictor of clinical phenotype. Whereas normal individuals have 2 copies of the SMN2 gene, the number can range from 1 to 4 in patients with SMA; the greater the number of SMN2 copies, the milder the disease. Type I (infantile-onset) SMA is fatal, usually by 2 years of age. Individuals with Type IV SMA typically live into adulthood. Historically, patients have been diagnosed with SMA Types 0, I, II, III, or IV on the basis of their clinical presentation.

This application includes data from a planned interim analysis of a double-blind, sham-controlled trial in subjects with infantile-onset SMA who had 2 copies of the SMN2 gene (Study CS3B). The trial demonstrated a clear and important benefit of nusinersen, with 21/51 (41%) of nusinersen-treated patients meeting a responder definition (based on achievement of motor milestones), vs. 0/27 (0%) of controls ($p<0.0001$). Secondary endpoints, although presented only descriptively according to the statistical analysis plan, consistently support a treatment benefit. The study has many of the important characteristics of an adequate and well-controlled study that can, by itself, provide substantial evidence of effectiveness, as outlined in FDA’s 1998 Guidance for Industry: “Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products” (see pages 15-16). Other data submitted in the NDA provide additional support for efficacy, and support for the generalization of efficacy to all age groups and severities/types of SMA.

In considering the benefit, it is important to convey realistic expectations with respect to the effect size. Although a 41% response rate (compared to 0%) sounds impressive on face, it means that 41% of nusinersen-treated patients had some response. Although the response was clearly important, perhaps life-changing in a few cases (6% of patients gained the ability to sit without assistance, a feat that almost never occurs in individuals with only 2 copies of the SMN2 gene), the majority of patients had a modest response or no response at all.

Thus, most (94%) patients were not able to sit, no patient was able to stand unassisted, and no patient achieved walking. Compared to motor development in normal individuals, the response to nusinersen would have to be considered disappointing. In Study CS3B, motor milestones...
were determined based on evaluation of 7 aspects of the Hammersmith Infant Neurological Examination (HINE): ability to kick, crawling, head control, rolling, sitting, standing, and walking (see Table 2). Ratings could range from zero (no milestones) to 23 (maximum milestone development). Treatment was initiated at a mean age of ~6 months, and the interim analysis was based on assessments at (mean) 12 months of age. At 12 months of age, a healthy baby would typically achieve a motor milestone score of approximately 22 points on this scale. In contrast, the mean motor milestone score in nusinersen-treated patients increased from approximately 1 point (prior to treatment) to approximately 4 points at 12 months – a difference of ~3 points over 6 months. Because some patients can exhibit more extreme responses, consideration of only the mean effect can underestimate the true importance of a therapy, and, as noted above, a few (6%) nusinersen-treated patients achieved unassisted sitting. But it should be kept in mind that the vast majority of patients did not achieve this milestone, and no patient became able to stand unassisted or walk (one patient could stand with assistance). Thus, although the drug represents an unprecedented advance for individuals with SMA, it does not represent a cure.

With the exception of patients who do extremely well and those who do poorly (i.e., develop respirator-dependence), patients/caregivers will not be able to tell whether or not nusinersen is actually helping to improve and/or preserve muscle function in an individual with SMA. Thus, for most patients, treatment will likely be life-long. Patients who develop important toxicity may have a difficult time deciding whether to continue nusinersen treatment in the face of toxicity, or whether to abandon treatment.

Overall, given the type of benefit demonstrated and the magnitude of the benefit, the potential harms are justified from both a population standpoint and a regulatory decision-making standpoint, and should be largely acceptable to individual patients/parents. The potential harms identified include thrombocytopenia, procedural bleeding, renal toxicity, growth reduction, and potential neurologic toxicity. These risks are based on observations from the clinical development program and preclinical studies, as well as known class-effects of related oligonucleotides. Based on our current knowledge, these harms are reversible and can be mitigated effectively with the monitoring recommended in the prescribing information and through enhanced pharmacovigilance. But given the small number of patients exposed to the drug, rare toxicities have not been well characterized. It seems likely that other toxicities may be become evident during marketing, as well as more severe manifestations of known toxicities.

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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| Analysis of Condition      | - SMA is a rare and serious genetic disorder that results in atrophy of the voluntary muscles of the limbs and trunk. The underlying genetic abnormality is described above.  
- SMA Type I, the most severe and the most common type (60% of all SMA patients), is usually diagnosed during the first 6 months of life. Most (90%) patients have 2 copies of the SMN2 gene. These patients do not attain developmental milestones such as the ability to walk. | 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. |
### Evidence and Uncertainties

- to sit unassisted. The disease is almost uniformly fatal before age 2.
  - SMA Type II is usually diagnosed between 6 and 24 months of age. Most (80%) patients have 3 copies of the SMN2 gene. The first sign is often a delay in achieving motor milestones, or failing to meet milestones entirely. Patients can typically sit up without help, but are unable to walk without assistance.
  - SMA Type III is usually diagnosed between 18 and 36 months of age. Most (80%) patients have 4 copies of the SMN2 gene. Patients are initially able to walk, but lose this ability as the disease progresses.
  - SMA type IV is very rare. Initial symptoms of mild motor impairment appear in adulthood.

### Current Treatment Options

- There are no FDA-approved treatments for SMA. Treatment in clinical practice is only supportive and has no beneficial effect on motor milestone development.

### Conclusions and Reasons

- There is a high unmet medical need for effective treatments for SMA.

### Benefit

- Nusinersen is an antisense oligonucleotide designed to increase the inclusion of exon 7 into the SMN2 mRNA, and to increase production of a functional SMN protein that can partially compensate for deletions/mutations of the SMN1 gene.
- This application includes data from an interim analysis of a double-blind, sham-controlled trial in infantile-onset SMA patients who have 2 copies of the SMN2 gene (Study CS3B). This trial demonstrated a clear and important benefit of nusinersen, with 21/51 (41%) of nusinersen-treated patients meeting a motor milestone development responder definition, vs. none of the control patients \( (p<0.0001) \). Study CS3B was stopped on the basis of these results, with all subjects being switched to active treatment. Secondary endpoints, although only presented descriptively according to the analysis plan, consistently support a treatment benefit.
- During the review, the applicant provided the topline results of Study CS4, a double-blind, sham-controlled trial in patients with later-
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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| Risk            | Onset SMA, with the majority of patients having 3 copies of the SMN2 gene (range: 2-4). The study was stopped at an interim analysis with a highly statistically significant ($p<0.001$) treatment effect on the Hammersmith Functional Motor Scale - Expanded. The applicant reported that sensitivity analyses consistently supported this result. The findings of this study, although not yet independently reviewed by FDA, are supportive of efficacy in later-onset SMA patients.  
• 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 limits their interpretability to some extent, but the findings are nevertheless consistent with a beneficial effect of nusinersen in later-onset SMA patients.                                                                 | Safety issues identified to date have potentially life-threatening outcomes, although monitoring will likely mitigate the risk. Nevertheless, based in the types of harms observed, there is the potential for irreversible harm. Although no irreversible harms were observed that were thought to be drug-related, relatively few patients have been studied. Despite recommended monitoring, we would predict irreversible harm during marketing in rare cases. |
| Risk Management | Drs. Mentari and Yasuda, the safety reviewers for this application, identified a number of potential harms with nusinersen, including thrombocytopenia and bleeding, proteinuria, and adverse effects on growth. These concerns were raised based on observations in the clinical development program, 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. | Warnings and Precautions will describe the risks and provide recommendations for monitoring.                                                                                         |
2. Background

The applicant is seeking marketing approval of nusinersen with the indication: “SPINRAZA is indicated for the treatment of Spinal Muscular Atrophy (SMA).” The application has been carefully considered by the Division of Neurology Products, and they recommend approval with various changes to the prescribing information and certain post-marketing requirements. I agree with their assessments and conclusions.

Nusinersen is a new molecular entity that has not been approved in any country. Current treatment for SMA is supportive; there are no specific approved treatments for the disease.

Spinal muscular atrophy is a rare (1:10,000 births) autosomal recessive disease characterized by loss of motor neurons in the anterior horn of the spinal cord, resulting in progressive wasting of the voluntary muscles of the limbs, trunk, and diaphragm. SMA is caused by deletions or point mutations of the survival motor neuron 1 (SMN1) gene located on chromosome 5q. The gene codes for SMN protein, which is necessary for survival of motor neurons. SMN2 is a related gene on chromosome 5, which, because of variation in a single nucleotide, produces a protein that undergoes alternative splicing, such that only 10-20% of transcripts encode a fully functional SMN protein; most produce abnormal truncated protein that is rapidly degraded.

The severity of the disease is generally related to the ability of the SMN2 genes to compensate for the loss of SMN1, and the number of copies of the SMN2 gene is the best predictor of clinical phenotype. Whereas normal individuals have 2 copies of the SMN2 gene, the number can range from 1 to 4 in patients with SMA; the greater the number of SMN2 copies, the milder the disease.

Historically, patients have been diagnosed with SMA Types 0, I, II, III, or IV on the basis of their clinical presentation. The NDA refers to the clinical categories of SMA as pre-symptomatic, infantile-onset, and later-onset. Table 1 summarizes the clinical/genetic characteristics of the clinically diagnosed SMA subtypes.

<table>
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<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>
</tr>
<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></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>
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The principal evidence of efficacy was provided by an interim analysis of a double-blind, sham-controlled trial in patients with infantile-onset SMA, with supporting data from 6 completed and ongoing open-label trials in a broader range of patients. The indication sought by the applicant would cover all SMA subtypes (i.e., to include pre-symptomatic and later-onset disease).

Nusinersen is a 2′-O-(2-methoxyethyl) antisense oligonucleotide. Its putative mechanism of action is 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 functional SMN protein, enhanced survival of motor neurons, and improved motor function.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of this NDA. The review states that OPQ will grant a 1-month re-test period for the drug substance when stored and a 30-month drug product expiration period when stored refrigerated in commercial packaging. No outstanding issues were identified in the OPQ review, and all manufacturing facilities were found to be acceptable.

A number of post-approval agreements were reached between the applicant and OPQ during the review period, and these will be included in the approval letter.

4. Nonclinical Pharmacology/Toxicology

The application is approvable from a pharmacology/toxicology standpoint. Key conclusions from the pharmacology-toxicology review:

- Decreased lower spinal reflexes were observed following single doses of ≥ 3 mg in both adult and juvenile monkeys, but appeared to be reversible and did not increase in incidence or severity with continued dosing. There were possible treatment-related deficits in performance on a learning and memory test in a 1-year repeat-dose study in juvenile cynomolgus monkeys, but the data were variable and the sample size was small. Neuronal vacuolation (minimal to slight) was observed in the inferior hippocampus at the mid and high doses in both studies. Vacuolation was associated with neuronal and glial cell necrosis in a few animals, and persisted following recovery. The no-observed adverse effect level (NOAEL) for neurohistopathology in monkeys (39 mg/year) is similar to the proposed human maintenance dose (36 mg/year), and was associated with tissue levels similar to those measured in human autopsy samples.

  The potential risk for neurotoxicity observed in monkeys will be conveyed in the section 8.4 of the prescribing information (PI).

- In the 13-week mouse study, the expected effects of local and systemic accumulation of oligonucleotide and pro-inflammatory effects were observed in a variety of tissues, without evidence of necrosis or degeneration.

- There was no clear evidence of reproductive or developmental toxicity in mice or rabbits, and a standard battery of in vitro and in vivo assays was negative for genotoxicity.
• Carcinogenicity studies were not conducted; the applicant requested a waiver based on the infeasibility of conducting lifetime studies using the IT route of administration in rodents. Given the significant systemic exposure documented in clinical studies, however, we are requesting a parenteral 2-year carcinogenicity study in one species as a postmarketing requirement. There is also an ongoing pre- and post-natal development study in mouse; completion of this study will also be a postmarketing requirement.

5. **Clinical Pharmacology**

The Office of Clinical Pharmacology (OCP) recommends approval from a clinical pharmacology perspective.

The following are the chief conclusions of their review:

- Following intrathecal injection, nusinersen’s bioavailability is 100%, with rapid distribution to the CNS and plasma. Plasma concentrations peak at 1.7 to 6 hours and decline rapidly because of extensive tissue distribution.

- Nusinersen is metabolized by exonucleases, primarily at the 3’ end of the oligonucleotide.

- The mean terminal elimination half-life in the cerebrospinal fluid (CSF) is 4.4 to 5.8 months, which supports an every 4-6 months maintenance dose schedule. Nusinersen is mainly excreted in the urine as chain-shortened metabolites (N-1,2,3) that are not thought to be active. Urinary excretion of intact nusinersen represents only a small fraction of the dose (<1%).

- Nusinersen neither inhibits nor induces any of the major CYP enzymes or transporters.

- Neither hepatic nor renal impairment are expected to affect nusinersen exposure, and such impairment is uncommon in the SMA patient population.

- Given that CSF volume increases from birth through 24 months, the applicant had initially proposed a dose of 12 mg/5 mL for patients The OCP review concluded, however, that a fixed-dose of 12 mg/5 mL would be appropriate for all patients based on modeling and clinical data that showed substantial inter-patient variability in C_{max} as well as substantial overlap between the lower and higher proposed doses. The applicant conducted its own analyses and agreed with OCP; the 12-mg dose will be recommended for all patients. Other points in favor of one dose for all patients: 1) there was no evidence of dose-related toxicity; 2) exposure-response findings from a phase 2 study showed a higher proportion of responders in the infantile-onset SMA population at the higher exposure; and 3) fixed dosing is simpler and should reduce the potential for dosing errors.

- OCP provided detailed analyses and discussion of the applicant’s proposed treatment regimen, in terms of both dose and dosing interval. The review comments that data from the double-blind, sham-controlled trial in patients with infantile-onset SMA (Study CS3B) suggest that...
higher doses or more frequent dosing would not likely have enhanced efficacy. Their assessment is primarily based on the exposure-response data shown in Figure 1. The review cautions, however, that this conclusion should be interpreted with some uncertainty, given that not all patients completed Day 183 assessments. The review suggests that these assessments should be revisited after obtaining clinical response data from all patients at Day 302, to determine whether there is a need for further optimization of the dosing regimen.

I agree with the cautionary tone of the OCP review: these data do not seem definitive, either in showing an exposure-response or showing the lack of an exposure-response, i.e., a plateau in response at higher concentrations. Revisiting the dosing regimen after all Day 302 data are submitted should be a high priority.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical – Efficacy

The clinical and statistical review teams agree that the applicant has provided substantial evidence of efficacy and support approval of the NDA.

Figure 2, adapted from the application, illustrates the scheme of completed and ongoing clinical trials with nusinersen for the treatment of SMA.
Study CS3B, conducted in patients with infantile-onset SMA, was the double-blind, sham-controlled investigation that provided the primary evidence of effectiveness. Study CS4, in later-onset SMA, was stopped at a recent interim analysis for efficacy. Although the CS4 data have not been reviewed, the topline results show efficacy in an older SMA population. The additional trials, all of which are open-label, were intended to provide support for the efficacy of nusinersen across a broad age-range of patients with SMA. (Studies CS1 and CS10 evaluated a single dose of nusinersen, and are not discussed in detail.)

Study CS3B in Infantile-Onset SMA

Study CS3B was a multinational, randomized, double-blind, sham-controlled trial in subjects with infantile-onset SMA. Approximately 111 subjects were to be randomized in a 2:1 ratio to receive either 12-mg nusinersen administered intrathecally by lumbar puncture or a sham-procedure (pin-prick with bandage). Lower doses were to be used for younger patients. 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 by 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, although a small number of patients had Type II SMA. The original 1° endpoint was time to death or need for permanent mechanical ventilatory support.
A Type-C guidance meeting was held with the sponsor when the trial was ongoing (September 15, 2015). At the meeting, the Agency recommended revision of the analytic plan to include an interim analysis based solely on the achievement of motor milestones. FDA’s thinking was that such an analysis might demonstrate a robust treatment effect with far fewer patients than originally estimated; and positive results from the interim analysis, combined with the results of Study CS3A, might support an NDA filing. It was agreed that for the interim analysis, the 1st endpoint would be a responder analysis based on achievement of motor milestones.

Motor milestones were to be determined using Section 2 of the Hammersmith Infant Neurological Examination (HINE) at screening and at Days 64, 183, 302, and 394. The HINE is comprised of 8 tests: ability to kick, crawling, head control, rolling, sitting, standing, voluntary grasp, and walking (Table 2). Each element is scored from 0 (meaning inability to perform a task) to 2, 3, or 4 (meaning full milestone development, depending on the task), and the scores are added. For this study, voluntary grasp was not included in the efficacy assessment; therefore, the maximum attainable score was 23 (minimum = 0).

The interim analysis included all subjects with a Day 183 visit at the time of the cut-off date (June 15, 2016). A stage-wise hierarchical strategy was applied to control the overall Type-I error rate across the interim and final analyses, with alpha = 0.035 allocated to the interim analysis.

For the motor milestone responder endpoint, achievement of a response was based on meeting both of these criteria:

- Improvement in at least one category (voluntary grasp not included), with improvement defined as ≥ 2-point increase in the motor milestones category of ability to kick, or achievement of maximal score

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<thead>
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<th>Table 2: The Hammersmith Infant Neurological Examination (HINE)</th>
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<td><strong>Milestone</strong></td>
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on that category (touching toes), or a 1-point increase in one of the other motor milestones, AND:

- The subject demonstrated improvement in more categories than worsening among the 7 motor milestone categories (voluntary grasp not included).

This milestone-based endpoint is considered to be clinically relevant and interpretable, and the separation between milestones is thought to permit assessment of a meaningful functional difference. Time to death or need for permanent assisted ventilation, adjudicated by a central, blinded, independent Event Adjudication Committee, was the second primary efficacy endpoint, and has obvious clinical meaningfulness.

As detailed in the statistical review, the difference in the percentage of responders between the nusinersen and sham groups was compared using logistic regression with the number of motor milestones at baseline, age at symptom onset, and disease duration at screening as covariates. Subjects who died or withdrew from the study were considered non-responders. Fisher’s exact test was planned if the number of responders was <5. (In fact, there were no responders in one of the treatment groups; therefore, Fisher’s exact test was used per the prospective plan.)

**Results:** At the time of the interim analysis, 121 subjects had received at least one dose of nusinersen (n=80) or a sham procedure (n=41), and were included in the intent-to-treat (ITT) analysis population. The interim analysis set included 78 of these subjects: 51 and 27 in the nusinersen and sham groups, respectively.

Of the 78 subjects in the interim analysis population, 55% were female and 45% were male. Age at first treatment ranged from 30 to 262 days (median 181). Eighty-six percent (86%) of subjects were Caucasian, 3% were Black, and 4% were Asian. Sixty-two percent (62%) of the population was enrolled in North America (United States and Canada), 33% in Europe, and 5% in the Asia-Pacific region. Baseline demographics were balanced between the nusinersen and control groups with the exception of age. The mean age of subjects in the nusinersen group was less than that in the control group (median age 175 vs. 205 days, respectively).

The nusinersen and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number (2 copies known in 97% of subjects in both groups). Median disease duration was 13.4 weeks. There was some imbalance in age at symptom onset with 88% of subjects in the nusinersen group and 74% in the control group experiencing symptoms within the first 12 weeks of life. Median age at symptom onset was 7 weeks in the nusinersen group and 8 weeks in the control group.

At baseline, 81% of subjects were unable to maintain their head upright, 72% were unable to kick, 94% were unable to roll, and 96% were unable to sit. No subject was able to crawl, stand, or walk. The groups were generally similar in their baseline motor milestone achievements with minor differences in individual categories that did not appear to favor either group overall.

The applicant reported a statistically significant result on the primary endpoint, with 21/51 (41%) responders in the nusinersen group compared to 0/27 (0%) in the sham group ($p<0.0001$). An FDA
preferred interim analysis 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 compared to 0/30 (0%) in the sham group ($p<0.0001$). Other sensitivity analyses conducted by the statistical reviewer were supportive of the primary efficacy results, and insensitive to all but very extreme worst case imputations for missing data.

The Day 183 data from the interim analysis are displayed in Figure 3, to show the full distribution of responses. Responses in the nusinersen group are shifted to the right of the figure, towards improvement.

Importantly, 5 subjects in the nusinersen group improved their motor abilities to the point where they were able to sit unassisted, versus none in the control group. As discussed by the review team, the ability to sit unassisted is extremely rare in patients with Type I SMA, and these data are also supportive of efficacy of the product. (It is possible that some of the patients who achieved that milestone have Type II SMA.)

The statistical review notes a better response rate for females (56%) than males (24%), and a better response rate for younger (47%) than older (32%) patients (age dichotomized at median = 181 days). Given the exploratory nature of these analyses, no conclusions can be drawn with respect to differential
efficacy by sex or age, and there were certainly too few Asian and Black subjects to reach any conclusions on efficacy by race.

The results of 2° analyses were reported descriptively as per the statistical analysis plan for the interim analysis; results are supportive of the 1° analysis:

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

- In the overall study population, 34% of subjects in the nusinersen group versus 49% of subjects in the sham group died or required permanent ventilator support (HR = 0.71).

- In the interim analysis data set, 65% of subjects in the nusinersen group met the responder definition for the Children’s Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) of a change from baseline of ≥ 4 points as compared to 4% of subjects in the sham group. Worsening of the CHOP-INTEND score by ≥ 4 points was observed in 4% of subjects in the nusinersen group versus 48% of subjects in the control group.

- Findings on various electrophysiologic studies were also supportive of nusinersen’s efficacy. 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 positive results of the interim analysis, Study CS3B was stopped and all subjects were switched over to receive active treatment with nusinersen.

**Study CS4: Another Sham-controlled Study in Later-Onset SMA**

During the review cycle, the applicant provided topline results of Study CS4, which was ongoing at the time of NDA submission. This is a 15-month, double-blind, sham-controlled study in patients with later-onset SMA. Most patients in Study CS4 would have had a clinical diagnosis of Type 2 SMA, with the majority having 3 copies of the SMN2 gene (range: 2-4). The nusinersen dosing regimen was the same as in Study CS3B. The applicant conducted an interim analysis at a cut-off date of August 31, 2016, including 84 subjects in the nusinersen group and 42 control subjects. The study was stopped based on a highly statistically significant treatment effect. The applicant’s analyses show that Hammersmith Functional Motor Scale – Expanded (HFMSE) scores were significantly higher in the nusinersen group (4.0) than in the control group (-1.9). The applicant also reports that sensitivity analyses for the 1° endpoint consistently supported this result. Fifty-seven percent (57%) of subjects in the nusinersen group achieved a ≥ 3-point increase in HFMSE scores over baseline at 15 months versus 21% of controls. The findings of this study, although not yet independently reviewed by FDA, are supportive of efficacy in later-onset SMA patients.

**Additional Open-Label Clinical Trials**

The applicant has conducted several additional open-label studies, covering age groups from presymptomatic infantile-onset (genetically diagnosed) SMA to later-onset SMA. Findings from these studies were generally supportive of efficacy, with patients achieving milestones not expected for the
study population, including ability to walk in patients with 3 copies of the SMN2 gene, maintenance of milestones to ages at which they would be expected to be lost, and survival to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies. These studies are discussed in greater detail in Dr. Paine’s clinical review and Dr. Kozauer’s CDTL memorandum.

**Efficacy Conclusions**

The applicant has submitted results of a single adequate and well-controlled trial (CS3B) as evidence of efficacy. Even given the modest sample size and lack of full study data (the study was stopped at the interim analysis), Study CS3B has many of the characteristics of an adequate and well-controlled study that could, by itself, provide substantial evidence of effectiveness, as outlined in FDA’s 1998 Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products.*

The study is relatively large (given the disease prevalence) and multinational. On 1° endpoint – motor milestone response – the results are statistically persuasive with a clinically meaningful effect size, and there is consistency across centers and important subsets. The results are robust to exploration and sensitivity analyses. Multiple 2° endpoints are consistent with the result of the 1° endpoint.

The originally planned 1° endpoint – time to death or permanent ventilatory assistance – was intended to assess a related but different type of effect. Although there was a trend in favor of the nusinersen group, the study did not reach statistical significance on this endpoint at the interim analysis. The lack of a statistically significant finding was expected, given that the study was stopped at the interim analysis.

As noted in Guidance, “...reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.” In the end, therefore, a reasonable way to consider whether Study CS3B (alone) provides substantial evidence of effectiveness is to consider whether it would be ethical to conduct a second study, wherein some patients would be randomized to a sham procedure. Based on the considerations above, I do not believe that investigators and/or the medical community would have equipoise to participate in such a study; I do not believe that such a study would be ethical or practicable. In light of the above, it seems clear that study CS3B provides substantial evidence of effectiveness.

Congress amended section 505(d) of the Act to clarify that FDA may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence of effectiveness. Thus, we typically look for confirmatory evidence of effectiveness when considering approval based on a single adequate and well-controlled trial.

Study CS3A, an open-label trial also conducted in infantile-onset SMA, further supports the efficacy of nusinersen in this population. Subjects reached developmental milestones that are universally thought not to be attained in SMA patients with only 2 copies of the SMN2 gene. The applicant provided a December 5, 2016 update noting that 11 of 20 subjects (55%) had survived beyond 36 months of age in a condition where survival beyond 24 months is historically 1.5%. Despite the lack of a concurrent control group, Study CS3A provides strong confirmatory evidence for the findings from the controlled Study CS3B, leading to a conclusion that nusinersen is effective for the treatment of infantile-onset SMA.
This application also provided data from uncontrolled trials conducted in genetically-diagnosed pre-symptomatic SMA (Study 201; 2 to 3 copies of the SMN2 gene) and later-onset SMA (Studies CS1, CS2, CS10, and CS12; 2 to 4 copies of the SMN2 gene). These open-label trials cannot provide primary evidence of effectiveness in the context of the greater clinical heterogeneity in patients with multiple copies of the SMN2 gene. The findings, however, suggest a better clinical course than would be expected based on the natural history of the disease.

The high-level summary results from Study CS4 in subjects with 2 copies of the SMN2 gene provide an additional measure of reassurance that the open-label results in later-onset subjects are reflective of a true treatment effect in this population. Of note, although more mild, adult-onset (i.e., clinically diagnosed Type IV SMA with onset at age 20 to 30) SMA patients were not studied, these subjects constitute <5% of SMA patients, and the available evidence provides reasonable support for the concept that the benefit of nusinersen would be expected in both pre-symptomatic and later-onset patients, supporting a broad indication for the treatment of SMA as a whole.

Together, these additional studies constitute the “confirmatory evidence” that would be needed for an approval action based on a single adequate and well-controlled trial, which is also supported by the statistical strength of the Study CS3B result. Moreover, the submitted studies cover a broad range of ages of disease onset, from pre-symptomatic through adult-onset SMA, such that the efficacy findings can be generalized to adult-onset SMA.

Based on the “single study with confirmatory evidence” standard, and in agreement with the Division, I believe there is no doubt that the efficacy of nusinersen for SMA has been demonstrated.

**Limitations of Treatment**

It is important to keep the magnitude of nusinersen’s treatment effect in perspective. Given that a baby with infantile-onset SMA would never be able to sit without assistance, the ability to sit is clearly a life-changing breakthrough. Five of 81 treated subjects in Study CS3B (6%) were able to sit unassisted, which is thought to almost never happen in individuals with only 2 copies of the SMN2 gene. Moreover, in the longer open-label study (CS3A) in similar subjects, 6 of 17 subjects (35%) with 2 copies of the SMN2 gene were able to sit unassisted.

But the treatment effect of nusinersen is importantly limited. Although 41% of nusinersen-treated patients in Study CS3B showed improvement in their motor milestones, 59% of treated patients did not exhibit a response. Moreover, compared to normal individuals, the response would have to be considered disappointing. As shown in figure 8 of the clinical efficacy review, the mean HINE milestone score for the nusinersen group was 1.3 at screening, increasing to 4.2 at Day 183 – an improvement of approximately 3 points over 6 months. The median age of subjects in Study CS3B was approximately 6 months at baseline, and therefore 12 months at Day 183. Based on data reported by Haataja L, et. al. (*J Pediatr* 1999; 135:153-61), a healthy infant would typically reach a HINE motor milestone score of approximately 14 points by 6 months of age, increasing to 22 points at 12 months of age – a change of 8 points over 6 months.

Thus, although the drug represents an unprecedented advance for individuals with SMA, it does not represent a cure. Possible reasons for less-than-complete development/preservation of motor function
could include a number of factors, including inadequate drug concentrations, inadequate drug levels at the appropriate site(s) in motor neurons, production of a less than fully functional protein, and need for earlier treatment to prevent motor neuron damage. The latter issue is particularly important, because time of treatment initiation is a variable that can be controlled.

Some have speculated that damage to motor neurons begins even before birth, such that early treatment is critical for success. Some of the subgroup analyses are consistent with this concept, suggesting that earlier initiation of treatment improves outcome. Specifically, the statistical review found that 47% of nusinersen-treated patients below the median age were motor milestone responders as compared to 32% of those above the median age. The clinical review noted (Figure 26) that treatment effects for patients with disease duration ≤ 12 weeks and >12 weeks were approximately 0.51 and 0.34 units, respectively.

Figure 4 considers the individual patient responses in the nusinersen treatment group as a function of age at treatment initiation. Note that the correlation includes only surviving patients, and is therefore biased. There is a trend for greater treatment effect with initiation at younger ages, but the R-value is only -0.27 for the correlation. At the risk of over-interpreting the data, initiation of treatment before 200 days of life could be important. The point here is that other factors, beyond age at time of treatment initiation, appear to be operational in determining the drug’s effect, and the applicant should be encouraged to perform additional research to attempt to improve the treatment response.

Finally, the Division concluded that the 12 mg/5 mL nusinersen dose is appropriate for all age groups, as there is considerable overlap in mean CSF volume between children and adults. Although the rationale
of the review team seems sound, there are clearly some unknowns here in terms of predicting responsiveness to treatment, and, in the absence of important dose-related toxicity, the applicant should be encouraged to study higher doses. As noted above, the final data from Study SC3B could be helpful in this regard.

8. **Safety**

I agree with the Division that the size of the safety database is acceptable for this indication. Of 173 patients in the database, 82 were exposed for ≥ 12 months, mostly at the 12-mg to-be-marketed dose.

I agree with the Division and the Office of Surveillance and Epidemiology that a risk evaluation and mitigation strategy (REMS) is not needed for nusinersen, considering the specialized setting under which nusinersen will be administered, with regular visits required for drug administration. I agree that risk management can be accomplished through appropriate labeling and enhanced pharmacovigilance for thrombocytopenia, glomerulonephritis, nephrotic syndrome and nephrotic range proteinuria.

The review team identified a number of significant safety issues, to be described in the prescribing information:

- **Thrombocytopenia and Coagulation Abnormalities**: Other phosphorothioate oligonucleotides have been found to cause thrombocytopenia. Thrombocytopenia was reported in 11% of nusinersen-treated patients in Study CS3B, and not reported in any control patients. Two percent of nusinersen-treated patients had platelet counts < 100,000/µL; none had a count below 50,000/µL. Given that thrombocytopenia can lead to excessive bleeding, and given that lumbar puncture can be technically difficult in this age group, there is concern regarding procedurally related bleeding in this patient population. In clinical studies, 5 of 173 (3%) nusinersen-treated patients reported a hemorrhagic complication of lumbar puncture. Complications included subdural hematoma, spinal cord hematoma, epidural hemorrhage, and spinal subarachnoid hemorrhage. All agree that laboratory testing should be performed prior to each injection, to include platelet count, prothrombin time, and activated partial thromboplastin time.

- **Renal Toxicity**: Nusinersen accumulates in the kidney, and important renal toxicity has been observed with other antisense oligonucleotides. In Study CS3B, 33% of nusinersen-treated patients had elevated urine protein, compared with 20% of controls. In a group of later-onset SMA patients (mean treatment exposure 34 months), 36 of 52 patients (69%) had elevated urine protein. Because of the potential for renal toxicity of nusinersen spot quantitative urine protein testing should be obtained prior to each injection of nusinersen.

- **Hyponatremia**: Prolonged and severe hyponatremia was reported in a patient treated with nusinersen. Treatment included salt supplementation for 14 months.

- **Hepatic Effects**: Nusinersen is deposited in the liver and therefore has the potential for hepatic toxicity; however, Dr. Mentari found no clear signal of hepatic enzyme elevations in the development program. Some 4% of nusinersen-treated subjects in Study CS3B had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0% of control subjects, but these elevations were isolated, and there were potential mitigating factors.
Logistically, therefore, it will be important for health care providers to obtain the following studies prior to lumbar puncture for administration of nusinersen: platelet count, coagulation studies (PT, aPTT), and a spot urine protein.

- **Effects on growth:** In Study CS3B, the safety review reported that nusinersen-treated subjects had reduced growth compared with control subjects. At Day 394, mean change from baseline in height/length was 13 cm for nusinersen-treated patients, compared with 21 cm in control patients; mean change from baseline in height/length percentile for age was -26 for nusinersen-treated patients, compared with +26 in controls; mean change in weight from baseline was 3.1 kg for nusinersen-treated patients, compared with 3.9 kg in controls. The potential for slowing of growth will be noted in labeling.

- **Rash and Possible Vasculitis:** Pro-inflammatory effects of antisense nucleotides have been described in the literature, and 3 nusinersen-treated subjects had symptoms consistent with vasculitis. One patient developed painless red macules on the forearm, leg, and foot, 8 months after starting nusinersen, with ulceration and scabbing. A second subject developed red macules on the cheek and hand ten months after the start of nusinersen treatment. One nusinersen-treated subject had a cerebral infarction possibly related to vasculitis. Drs. Mentari and Yasuda also comment that although distal necrosis has been rarely reported in SMA, 2 cases were observed in 173 nusinersen-treated subjects in the development program. Although vasculitis was suspected, vasculitis was not proven in biopsy sections, and the rashes resolved despite continued treatment, the latter arguing against the likelihood of vasculitis.

- **Neurotoxicity:** As described above, neurotoxicity, including hippocampal vacuolization and necrotic cells, was observed in monkeys. No clinical correlates were observed, but they would not have been easy to identify in the SMA population. The monkey findings will be noted in Section 8.4 of labeling.

- **Immunogenicity**

  Sera from all clinical studies were analyzed for anti-drug antibodies (ADA). Five patients had positive ADA samples; antibodies were transient in four patients, and persistent in one. No adverse events were thought to be caused by the presence of ADA in these patients. The ability of ADA to cross-react with nucleic acids was not evaluated. The applicant will have a post-marketing requirement to conduct a study to assess the presence of antibodies to native double-stranded DNA in patients treated with nusinersen.

- **QT effects**

  Given the IT route of drug administration, a thorough QT study was not feasible. Moreover, no small therapeutic protein is known to inhibit the hERG channel directly and cause QTc prolongation. Thus, the utility of a thorough QT study, even if feasible, would be dubious.

- **Safety Issues Related to Lumbar Puncture**

  Ultrasound guidance was utilized during the intrathecal administration of nusinersen in 99% of 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-reporting). The Division considered whether the prescribing information should recommend image-guided lumbar puncture for some patients, particularly younger patients, but decided that such procedural details reflect the individual practice of medicine and should be left to the discretion of the physician; therefore, labeling will be silent here.

- **Continued Monitoring**
  I agree with Dr. Yasuda’s recommendation that the applicant continue to monitor for adverse events of special interest in ongoing and future trials and through post-marketing surveillance. These events include thrombocytopenia and coagulation abnormalities, renal toxicity, hyponatremia, adverse effects on growth, rash and possible vasculitis, neurologic toxicity, and hepatic effects.

9. **Advisory Committee Meeting**

This application was not referred for review to an advisory committee, based on the strength of the efficacy findings, and the lack of safety issues for which the advice of an advisory committee would be necessary.

10. **Pediatrics**

Not applicable; the target population is largely pediatric.

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) inspected three clinical investigator sites. These inspections did not reveal any significant regulatory violations, and Form 483s were not issued. OSI concluded that the data submitted by the applicant from these sites were acceptable and the studies appear to have been conducted adequately.

- The Controlled Substance Staff (CSS) review concluded that there are no data indicating that nusinersen has abuse potential or induces physical dependence. Nusinersen should not bind to receptors known to be involved in drug abuse, and the intrathecal route of administration is unlikely to have a potential for abuse.

12. **Labeling**

- There are no outstanding labeling issues. As discussed by the review team, the label will include *Warnings and Precautions* for thrombocytopenia and coagulation abnormalities and renal toxicity. Hyponatremia, rash, and growth reduction will be described in *Adverse Reactions*. The potential for neurotoxicity will be described in Section 8.4 of labeling, *Pediatric Use*. 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). I favor display of some of the descriptive results on the 1st endpoint, as in Figure 3, above. The contribution of the additional open-label trials submitted with the NDA will be described only briefly given the lack of a placebo (sham-procedure) control. Study CS4 in later-onset SMA cannot be described at this point, because the study was recently completed and has not been reviewed by FDA.

13. Postmarketing Recommendations

As noted above, I agree with the review team that a risk evaluation and mitigation strategy (REMS) is not needed for nusinersen.

There will be 3 post-marketing requirements:

- A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with nusinersen. The study may be conducted with plasma samples from patients treated with nusinersen in the clinical development program, including ongoing studies, but should include samples from patients who test negative as well as patients who test positive for antibodies to nusinersen. Among patients who develop anti-drug antibodies, samples should be included from patients shortly after seroconversion as well as from sustained responders. A sensitive assay should be used to assess presence of antibodies to double-stranded (ds) DNA in patient samples.
- A two-year carcinogenicity study in one rodent species (CD-1 mice) with subcutaneous administration of nusinersen.
- A pre-and postnatal development (including maternal function) study of nusinersen in rodent.

Given the modest efficacy of the drug and the lack of dose-related side effects, it will be essential to revisit the dosing regimen after Day 302 data are submitted from Study CS3B. These data may better define the exposure-response of the drug, and could support the utility of studying higher nusinersen doses for enhanced efficacy.

14. Recommended Comments to the Applicant

The OPQ review provided comments for the action letter, to remind the applicant of several post-approval quality agreements included in the amendment dated November 29, 2016, 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.

15. Other

Despite the considerable workload of the Division of Neurology Products, they completed an outstanding review of this NDA in 90 days, enabling a regulatory action fully 5 months in advance of the PDUFA goal date. I would like to recognize all of the individuals on the review team for their extraordinary efforts on the review of this application.
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/s/

ELLIS F UNGER
12/23/2016