

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209531Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template
PMR 3143-1

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA #	NDA 209531
Product Name:	SPINRAZA (nusinersen)

PMR/PMC Description: A two-year carcinogenicity study in one rodent species (CD-1 mice) with subcutaneous administration of nusinersen.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/31/2017</u>
	Study/Trial Completion:	<u>12/28/2020</u>
	Final Report Submission:	<u>3/31/2021</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The clinical data demonstrate efficacy for a serious indication (spinal muscular atrophy) and warrant approval at this time. This issue is appropriate for a PMR rather than a pre-approval requirement in part because the theoretical concern is secondary to the risk posed by the life-threatening indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study is required to identify an unexpected, serious risk of adverse effects of nusinersen, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals* July 1997

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A two-year carcinogenicity study in one rodent species with subcutaneous administration of nusinersen.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

PMR 3143-2

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA #	NDA 209531
Product Name:	SPINRAZA (nusinersen)

PMR/PMC Description: A pre-and postnatal development (including maternal function) study of nusinersen in rodent

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Study is complete
	Study/Trial Completion:	Study is complete
	Final Report Submission:	01/31/2017
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The clinical data demonstrate efficacy for a serious indication (SMA) and support approval of SPINRAZA at this time, and an adequate nonclinical pre-and postnatal study has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A pre- and postnatal development (including maternal function) study in rodent is required to identify an unexpected, serious risk of adverse effects of nusinersen, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pre-and postnatal development (including maternal function) study of nusinersen in rodent.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template
PMR 3143-3

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # NDA 209531
Product Name: SPINRAZA (nusinersen)

PMR/PMC Description: A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with Spinraza (nusinersen). The study may be conducted with plasma samples from patients treated with Spinraza (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 Spinraza (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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/30/2018</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

There is a theoretical concern for Spinraza (nusinersen) to induce anti-drug antibodies that cross-react with native dsDNA. In theory, antibodies recognizing the unique structure of the oligonucleotide drug may give rise to anti-dsDNA antibodies, possibly through epitope spreading, during prolonged use of Spinraza (nusinersen). Autoimmune disorders such as systemic lupus erythematosus are associated with anti-dsDNA autoantibodies. This issue is appropriate for a PMR rather than a pre-approval requirement in part because the theoretical concern is secondary to the risk posed by the life-threatening indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Clinical study data indicate that Spinraza (nusinersen) oligonucleotide product can induce anti-drug antibodies in the patient population. It is unclear whether anti-drug antibodies cross-react with native double-stranded (ds) DNA. Drug-induced anti-dsDNA antibodies may increase risk for eventual development of autoimmune disorders such as systemic lupus erythematosus or lupus-like syndrome. The goal of the study is to collect data from multiple patients who test positive for anti-drug antibodies so that an assessment of risk for cross-reactivity to dsDNA can be made.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with Spinraza (nusinersen). The study may be conducted with plasma samples from patients treated with Spinraza (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 Spinraza (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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

 - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☒ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)

 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY U YASUDA
12/22/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: December 21, 2016

To: Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Acting Associate Director for Labeling, DNP

Fannie Choy, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **NDA 209531**
OPDP labeling comments for SPINRAZA (nusinersen) injection, for intrathecal use (Spinraza).

In response to DNP's consult request dated September 27, 2016, OPDP has reviewed the draft product labeling (PI) for Spinraza.

OPDP's comments are based on the substantially complete version of the draft PI provided by DNP (Fannie Choy) on December 18, 2016, and are provided below.

OPDP comments on the draft carton and container labeling were provided under a separate cover on November 14, 2016.

If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on this material.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALINE M MOUKHTARA
12/21/2016



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 8, 2016

From: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, MD, PhD
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Fannie Choy, Regulatory Project Manager
Division of Neurology Products

Subject: QT-IRT Consult to NDA 209531

This memo responds to your consult to us dated 12/1/2016. The QT-IRT received and reviewed the following materials:

- Your consult;
- Response to Clinical Information Request (received 11/30/2016);
- Highlights of Clinical Pharmacology and Cardiac Safety;
- CSR for Study CS3B; and
- Summary of Clinical Safety.

In a clinical study, 4 of 80 (5%) of nusinersen patients had a QTc value above 500 milliseconds (ms) and an increase of >60 ms from baseline, compared to 0 of 41 control patients. In 2 of the patients, the prolonged QT was observed within 6 hours after the dose and in 2 of the patients, the prolonged QT was observed within 24 hours after the dose. The Sponsor has provided additional information about these 4 patients in the attached response to an information request that clarifies when the finding was observed with respect to doses administered. Each episode was an isolated finding in each of the 4 patients; also ECGs were not measured with every dose that was given. Prolonged QT intervals (compared to baseline) were not observed in the other clinical studies that were open label studies.

Do you recommend including information about QT prolongation in the labeling of this product and if so do you recommending adding the language to Section 5 (Warnings and Precautions) or

Section 6 (adverse reactions) in addition to Section 12? Do you recommend using caution when co-prescribing with drugs that could prolong the QT interval? Please provide any recommended language.

QT-IRT Response

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

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

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

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

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

For the USPI, we recommend that the QTc data are described in Section 12.2 (Pharmacodynamics). We do not recommend including statements in Section 5 (Warnings and Precautions) because there is uncertainty in these clinical QTc data. We defer the final labeling decisions to the Division.

Section 12.2 Pharmacodynamics

QTc Interval Prolongation

In 120 patients with spinal muscular atrophy randomized to receive either SPINRAZA or sham-control, QTcF values > 500 ms and change from baseline values > 60 ms were observed in 5% of

patients receiving SPINRAZA. There were not any differences from the sham-control in the incidence of cardiac adverse reactions associated with delayed ventricular repolarization.

BACKGROUND

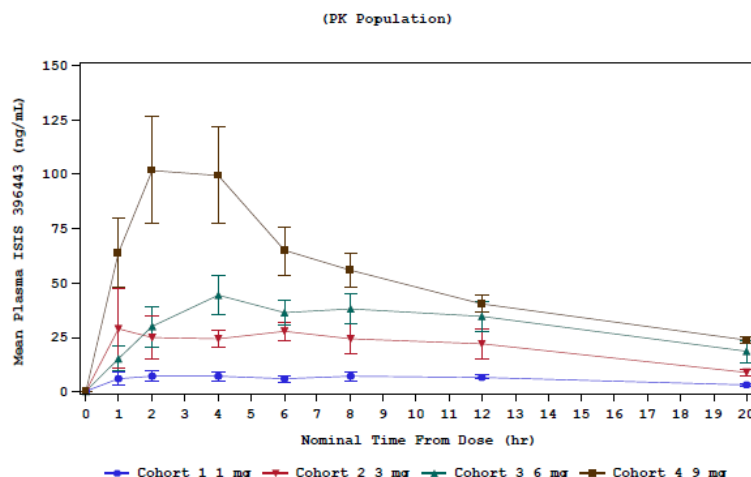
ISIS 396443 is an 18-base residue (18-mer) phosphorothioate antisense oligonucleotide. ISIS 396443 is designed to support intrathecal chronic administration for the treatment of patients with spinal muscular atrophy (SMA), independent of clinical phenotype.

The pharmacokinetics (PK), safety, and efficacy of ISIS 396443 were evaluated in the clinical development program across a broad range of SMA phenotypes. Data were collected in 10 clinical studies that enrolled newborns up to subjects aged 15 years of age at first dose who had a genetic diagnosis of 5q SMA and multiple copies of the SMN2 gene.

Key clinical PK properties of the ISIS 396443 when administered intrathecally (IT) by lumbar puncture include:

- Following IT administration, ISIS 396443 is rapidly transferred from CSF into the systemic circulation, with a median time to maximum concentration (T_{max}) of 1.7 to 6.0 hours in plasma in both later-onset subjects and infants diagnosed with SMA. ISIS 396443 trough concentrations in plasma were relatively low compared to those in CSF.
- After reaching the peak level, plasma concentrations of ISIS 396443 declined rapidly followed by a much slower decline, indicating a biphasic disposition in plasma. The rapid decline in plasma concentrations is likely due to extensive distribution to systemic tissues.
- There was an approximately dose proportional increase in maximum concentration (C_{max}) and area under the concentration-time curve (AUC) values in plasma over the evaluated dose range. C_{max} and AUC were greater in infants diagnosed with SMA than in subjects with later-onset SMA given the same dose, consistent with their lower body weight. The terminal elimination half-life in plasma was estimated to be 63 to 87 days in subjects with later-onset SMA and could not be calculated in infants due to the limited sample collection postdose.
- Based on peak (C_{max}) or total exposure (AUC_{0-4hr}, AUC_{0-6hr}, and AUC_{0-20hr}), no accumulation of ISIS 396443 was evident in plasma after multiple doses.
- The metabolites of ISIS 396443 observed in CSF, plasma, and urine samples from subjects with later-onset SMA following multiple IT administrations suggest that ISIS 396443 is metabolized slowly by exonuclease (3'- and 5')-mediated hydrolysis, which is not dependent on the liver.

Sponsor's Figure 2: Mean ($\pm$ SE) Plasma Concentrations of ISIS 396443 Versus Time (0-20 hour Profile) Following Single IT Administration on Day 1 by Cohort, Study ISIS 396443-CS1



Safety Pharmacology

No in vitro analyses were completed.

In vivo analyses included a safety pharmacology study in male rats using an osmotic pump for continuous IT infusion into the lumbar region of the spinal cord at dose levels of 0.14, 0.42, and 1.4 mg/week for up to 25 days (Study ISIS396443-AS04). Blood pressure (systolic, diastolic, and mean arterial) and heart rate were measured for at least 30 minutes on Day 19, 22, 23, or 25 of the study. Cardiovascular parameters (ECG and heart rate) were also evaluated in the single-dose (1, 3, and 7 mg), 14-week (0.3, 1, and 3 mg/dose) and 53-week (0.3, 1, and 4 mg/dose) GLP IT toxicology studies in cynomolgus monkeys.

There were no cardiovascular effects observed in rats using continuous IT infusion for 25 days, or effects on any cardiovascular measurement in the single or repeat-dose IT toxicology studies in monkeys.

QT Assessment in Study CS3B

Study CS3B is a phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset SMA. Subjects randomized to the ISIS 396443 treatment group received a single IT LP injection of study drug as a slow bolus (1 to 3 minutes) using a spinal anesthesia needle and 5-mL syringe on Study Days 1, 15, 29, 64, 183, and 302. Each subject received a 12-mg scaled equivalent dose based on CSF volume.

ECGs were collected at baseline (D-21 to D-1) and on-treatment on Day 2, 29 and 394 (end of treatment/early termination).

There were no large mean increases in QTcF change from baseline (CSR CS3B, Table 135). Mean values on Days 2, 29 and 394 were +5 ms, +6 ms and +13 ms for the sham-controlled group compared to -3 ms, -5 ms and -5ms for ISIS 396443 group. The variability in change in

QTcF data was large (SD ~40 ms) in both groups, and percentage of subjects with values >60 ms was similar (7% in control group vs. 6% in the ISIS 396443 group, CSR CS3B, Table 136). Five subjects in the ISIS 396443 group had QTcF >500 ms and 4 subjects of these subjects also had QTcF change of >60 ms. None of the subjects in the sham-controlled group had a QTcF >500 ms.

- Subject 2007-5360 had a QTcF of 550 ms on Day 2 which corresponds to a change from baseline of +120 ms. The subject's last exposure to ISIS 396443 was on Day 1. The subject reported atelectasis of moderate severity on Day 2. On Day 29, the QTcF value was 436 ms.
- Subject 2010-5063 had a QTcF of 504 ms on Day 2 which corresponds to a change from baseline of +123 ms. The subject's last exposure to ISIS 396443 was on Day 1. No adverse events were reported on Day 2. On Day 29, the QTcF value was 444 ms.
- Subject 2037-5063 had a QTcF of 566 ms on Day 29 which corresponds to a change from baseline of +144 ms. The ECG was considered abnormal and showed sinus tachycardia with a ventricular rate of 180 bpm. No follow-up ECGs were reported. The subject received ISIS 396443 approximately 3 hours earlier in the day.
- Subject 2112-5018 had a QTcF of 510 ms on Day 29 which corresponds to a change from baseline of +69 ms. The subject received ISIS 396443 approximately 14 hours earlier in the day. No follow-up ECGs were reported.

Of the four subjects with clinically important increases in QTcF, one subject (2037-5063) had an AE of cardiopulmonary arrest on Day 112. The subject's most recent study exposure prior to the event was on Day 70 and the abnormal ECG was obtained on Day 29. The subject recovered and continued in the study, with last exposure on Day 183 (no subsequent ECG results have been reported yet). The other three subjects did not have cardiac AEs.

There were no reports of torsade de pointes. The incidence of cardiac SAEs was similar between arms (12% for control vs. 11% for ISIS 396443). One ISIS 396443-treated subject had ventricular tachycardia; the last dose prior to the event was on Day 29 and the event occurred on Day 59. At the time, the subject also had a respiratory infection and difficulty breathing, and was treated with an antibiotic. The event resolved, and the subject continued to participate in the study. Of note, this subject had a QTc of 527 ms at screening, prior to exposure to ISIS 396443, which decreased to 400 ms on Day 2 and 490 ms on Day 2.

Twelve subjects (15%) in the ISIS 396443 group and 13 subjects (32%) in the control group died during the study. Majority of the deaths were due to respiratory and nervous system disorders. Two subjects in each group (3% vs. 5%) died of cardiorespiratory arrest. One subject in each group died of unknown causes.

- One ISIS 396443-treated subject (2037-5167) died during sleep on Day 82. This subject had no ECG values above 500 ms nor any increase of >30 ms (baseline 408 ms, Day 2 404 ms, Day 29 415 ms).
- One control group subject (1835-5103) died on Day 31. The subject's last ECG showed QTc of 460 ms, which was an increase of 40 ms from baseline and 57 ms from the previous ECG on Day 2.

Sponsor's Table 135. Summary of ECGs: Change from Baseline by Visit - Safety Set

	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
SCREENING				
n	41		80	
Mean	418.54		430.58	
SD	35.082		34.077	
Median	420.00		426.00	
25 th , 75 th percentiles	399.0, 436.0		414.0, 443.0	
Min, Max	312.0, 503.0		354.0, 563.0	
DAY 2				
n	41	41	80	80
Baseline mean	418.54		430.58	
Baseline median	420.00		426.00	
Mean	423.88	5.34	427.26	-3.31
SD	42.761	45.926	33.050	44.003
Median	424.00	3.00	430.00	2.00
25 th , 75 th percentiles	410.0, 447.0	-16.0, 26.0	412.5, 440.0	-12.0, 16.0
Min, Max	202.0, 492.0	-166.0, 122.0	297.0, 550.0	-167.0, 123.0
DAY 29				
n	36	36	74	74
Baseline mean	418.67		431.15	
Baseline median	420.50		427.50	
Mean	424.64	5.97	426.35	-4.80
SD	29.333	37.704	32.836	41.144
Median	423.50	3.50	426.50	-3.50
25 th , 75 th percentiles	410.0, 447.5	-8.0, 21.5	410.0, 440.0	-22.0, 11.0
Min, Max	316.0, 474.0	-76.0, 121.0	346.0, 566.0	-141.0, 144.0
	Control		ISIS 396443	
	Actual result	Change from baseline	Actual result	Change from baseline
DAY 394				
n	7	7	15	15
Baseline mean	417.29		435.80	
Baseline median	421.00		433.00	
Mean	430.29	13.00	430.47	-5.33
SD	20.328	14.259	19.878	36.594
Median	427.00	5.00	435.00	-3.00
25 th , 75 th percentiles	412.0, 451.0	2.0, 28.0	416.0, 446.0	-21.0, 17.0
Min, Max	401.0, 457.0	1.0, 36.0	388.0, 458.0	-99.0, 60.0

Sponsor's Table 136: Incidence of Outliers in ECGs Based on Corrected QT Interval - Safety Set

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

Sponsor's Table 38: Serious Adverse Events, Safety Set (N=121), for Cardiac Disorders

System Organ Class Preferred Term	Control		ISIS 396443	
	Subjects (%)	Events (%)	Subjects (%)	Events (%)
Cardiac disorders	5 (12)	7 (6)	9 (11)	9 (4)
Cardio-respiratory arrest	3 (7)	4 (3)	5 (6)	5 (2)
Cardiac arrest	2 (5)	2 (2)	2 (3)	2 (<1)
Cyanosis	1 (2)	1 (<1)	1 (1)	1 (<1)
Ventricular tachycardia	0	0	1 (1)	1 (<1)

Thank you for requesting our input into the development of this product under NDA 209531. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE E GARNETT
12/08/2016

NORMAN L STOCKBRIDGE
12/08/2016



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Biotechnology Research and Review II
Silver Spring, MD 20993
Tel. 301-796-2400

Memorandum of Review

STN: 209531

Type: NDA 505(b)(1)

Subject: Immunogenicity review

Submission Date: September 23, 2016

Review Date: December 2, 2016

Primary Reviewer: Patrick Lynch, Ph.D.
DRRII/OBP/CDER

RPM: Fannie Choy

Consults: Immunogenicity

Applicant: Biogen, Inc.

Product: ISIS 396443 (nusinersen) is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO) designed to bind to a specific sequence in the intron downstream of exon 7 of the *SMN2* transcript.

Route of administration: Intrathecal (IT)

Indication: Spinal muscular atrophy (SMA)

Proposed proprietary name: SPINRAZA™

Action Date: December 23, 2016

Table of Contents

I. SUMMARY BASIS OF RECOMMENDATION:	3
A. RECOMMENDATION:	3
B. JUSTIFICATION	3
II. COMMENTS TO SPONSOR:	3
III. REVIEW SUMMARY:	4
1. ANALYSIS OF CLINICAL IMMUNOGENICITY RESULTS	5
2. VALIDATION OF ANTI-DRUG ANTIBODY SCREENING ASSAY	9
2.1 Background	9
2.2 Validation parameters	9
2.3 Materials and controls	9
2.4 Validation exercises	10
2.4.1 Screening and Titration Cut Points	11
2.4.2 Confirmatory cut-points (CCP)	15
2.4.3 Assay sensitivity and positive controls	16
2.4.4 Prozone effect	18
2.4.5 Precision	19
2.4.6 Selectivity	21
2.4.7 Drug tolerance	23
2.4.8 Specificity	23
2.4.9 Precision of confirmatory cut-point	24
2.4.10 Precision of titration	25
2.4.11 Stability: antibody	25
APPENDIX 1: Clinical studies overview	26
APPENDIX 2: Anti-ISIS 396443 antibody status	28
APPENDIX 3: ISIS 396443 levels in ADA positive patients	30

I. SUMMARY BASIS OF RECOMMENDATION:

A. RECOMMENDATION:

From the immunogenicity perspective, I recommend approval of this NDA for ISIS 396443 (“Spinraza”).

B. JUSTIFICATION

There are no drug-induced immune response issues that preclude approval of the NDA. The sponsor monitored immunogenicity and provided data from seven clinical studies in the SMA patient population. Design of the studies was appropriate to assess immunogenicity development over time and from repeat exposure. The sponsor validated an ELISA method to screen for and confirm anti-drug antibody (ADA) in patient plasma. Confirmed ADA positive samples were assessed for titer in a validated assay. These methods were appropriate to assess ADA incidence, duration, and titer in clinical samples. In total, 5 patients were identified as positive for ADA after treatment with ISIS 396443 that yields an overall incidence rate of 4%. Duration of ADA was transient in 4 out of 5 patients and persistent in 1 out of 5 patients. Titer of ADA was low overall with a range of 1 to 16 across all positive samples. Titer values for the only persistent ADA instance were low with a range of 2 to 4 and did not increase over the course of 351 days. Development of ADA occurred over several months after initial exposure. Four out of 5 patients first tested positive for ADA at or by 169 days on study. Neutralizing activity of ADA was not evaluated, but the potential for antibodies to impact safety and efficacy was considered. The presence of ADA was not found to correlate with loss of safety or efficacy, and did not impact levels of ISIS 396443 in cerebrospinal fluid. For the oligonucleotide drug in this case, it is not clear that assessment of neutralizing antibody activity by an *in vitro* assay would provide meaningful information for transient and low titer samples. The ability of ADA to cross-react with nucleic acids was not evaluated. Drug-induced development of anti-dsDNA antibodies could increase risk for autoimmune disorders. A request for the sponsor to assess potential development of antibodies to dsDNA in post-marketing studies will be sent.

II. COMMENTS TO SPONSOR:

None

III. REVIEW SUMMARY:

Biogen is seeking approval for ISIS 396443 (also referred to in the submission as nusinersen or SPINRAZA) for the treatment of spinal muscular atrophy (SMA). SMA is caused by mutations that lead to survival of motor neuron (SMN) protein deficiency. SMA is a progressive disease associated with loss of motor function. Clinical phenotypes range from death soon after birth to asymptomatic survival into adulthood. The majority of patients die or are disabled early in life. ISIS 396443 (nusinersen) is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO). The mechanism of action is mediated through binding of target *SMN2* pre-mRNA that in turn modifies splicing and enhances production of full-length survivor of motor neuron 2 (SMN2) proteins. The ASO molecular mechanism is thought to involve inhibition of a splicing silencer from accessing the 5' splice site of exon 7 for *SMN2*. ISIS 396443 is an 18-base residue phosphorothioate oligonucleotide with 2'-O-(2-methoxyethyl)-D-ribose (MOE) on all 18 sugar residues. The drug is supplied as a 12 mg/5 ml (2.4 mg/ml) solution in vials for intrathecal (IT) chronic administration.

The sponsor monitored immunogenicity from multiple clinical studies in the SMA population, including the pivotal phase III CS3B study. Plasma samples were screened for binding ADA by an anti-ISIS 396443 ELISA assay. Positive screened samples were then analyzed in a confirmatory assay. Confirmed positive samples were assessed for titer. The screening assay exhibited good sensitivity at 50 ng/ml. The drug tolerance of the assay was measured 4 mcg/ml, which is well above the expected levels of ISIS 396443 in clinical samples. During the review cycle, FDA requested the sponsor re-calculate the confirmatory cut-point using a 1% false positive rate as opposed to the 0.1% false positive rate reported in the submission. This request was sent on November 21, 2016, and the company provided a response by email on November 28, 2016. As a result of the re-calculated cut-point, 1 additional patient was identified as having drug-induced ADA. Unless otherwise indicated, clinical ADA results discussed in this review are based on the re-calculated 1% false positive rate.

A low overall incidence rate of 4% was determined for ISIS 396443-induced ADA. All ADA positive events occurred in studies CS3B, CS3A, and CS12. In response to FDA request dated November 21, 2016, Biogen reported that 5 out of 125 (4%) of SMA patients who received drug testing negative for ADA at baseline and positive for ADA post-treatment. For these 5 patients, ADA developed after several months of treatment. In most cases, ADA were not observed for nearly 6 months. The duration of ADA response was transient in most subjects; however 1 patient out of 5 developed a persistent response. Of note, the patient with persistent positive ADA was first treated in study CS2 and found to have no ADA, but developed ADA at the time of screening for enrollment in extension study CS12. The persistent ADA positive samples exhibited an overall low titer that either remained stable or potentially decreased over time from 4 to 2. The two-fold difference in titer is near the limit of assay precision. Low titer was observed for all cases, with a maximum value of 16. The low numbers of ADA events limited ability to conduct a thorough analysis of correlations between ADA and adverse events. However, presence of ADA was not found to impact safety or efficacy in the 5 patients who

developed antibodies. The sponsor also determined that ADA did not significantly impact levels of ISIS 396443 in cerebrospinal fluid (CSF). A potential, albeit inconsistent, impact of ADA on plasma levels of ISIS 396443 was noted; however, this observation was considered unlikely to be clinically meaningful because the ISIS 396443 levels in CSF near the site of action were unaffected.

The sponsor did not evaluate ADA for cross-reactivity to dsDNA or for neutralizing activity. The predominant risk for neutralizing activity is from high titer persistent ADA, which were not observed in the clinical studies. ISIS 396443 may induce ADA that cross-react with dsDNA. Given that anti-dsDNA present risk for autoimmune disorders, a request for evaluation of anti-dsDNA in post-marking studies was recommended.

1. ANALYSIS OF CLINICAL IMMUNOGENICITY RESULTS

Clinical immunogenicity overview

Clinical immunogenicity information in SMA patients was provided from 7 clinical studies. The overall clinical development program included 10 studies. However, immunogenicity data from studies CS4, CS11, and SM2020 were not provided because these studies were ongoing and blinded at the time of submission. A schematic outlining the overall clinical development program is provided in Appendix 1 of this review memo. All immunogenicity data were collected in the patient population, which the sponsor grouped into symptomatic (infantile-onset and later onset) and genetically diagnosed presymptomatic. Study CS3B is pivotal to development of ISIS 396443 and ongoing at the time of submission. Immunogenicity was measured using enzyme-linked immunosorbent assays (ELISA) that included screening, confirmation, and titer components. Review of ADA incidence primarily focused on data from studies CS3B, CS3A, SM201, and C12. No ADA were detected in patient samples collected in studies CS1, CS2, or CS10; however, subjects from studies CS2 and CS10 were subsequently enrolled in long-term extension study CS12 (see Appendix 1). The table below provides a summary of dosing and immunogenicity sample collection times for these studies.

Study	Dosing	Status	Immunogenicity sampling (study day)
CS3B	Multi-dose, 12 mg level	Ongoing	Pre-dose D1, D64, D183, D302, D394
CS3A	Multi-dose, 6 or 12 mg level	Ongoing	Pre-dose D1, D85, D169, D252, D337, D442, D568, D694, D820, D946, D1072, D1198, D1352
CS12	Multi-dose, 12 mg level	Ongoing	Pre-dose D1, D85, D169, D351, D533, D715
SM201	Multi-dose, 12 mg level	Ongoing	Pre-dose D1, D15, D29, D64, D183, D302, D421, D540, D659, D778

Table prepared by reviewer

ADA incidence

Immunogenicity data generated in the above clinical studies were initially evaluated in ELISA assays designed for a 0.1% false positive rate. These analyses found a relatively low incidence of treatment emergent ADA as follows: 1 out of 113 (0.88%) positive

patients in study CS3B, 2 of 47 (4.3%) positive patients in study CS12, 1 out of 20 (5%) positive patients in study CS3A, and 0 out of 14 (0.0%) positive patients in study SM201. One patient in study CS3B tested positive for ADA only at baseline, and was thus considered unrelated to treatment and not included in the above values. Of these four ADA positive patients, three were characterized as transient. One patient in study CS12 exhibited persistent ADA at four consecutive sampling times. In response to an Agency request to re-evaluate clinical samples using a 1% false positive rate recommended in Guidance¹, the sponsor identified two additional subjects in study CS3B that tested positive for ADA. For one of the two newly-identified ADA-positive patients, ADA was unrelated to treatment because that patient did not receive drug. Table 2 below was provided in response to an FDA information request, and summarizes ADA incidence rates found in treatment groups using a 1% false positive rate.

Table 2: Incidence of Anti-ISIS396443 Antibodies in Subjects Dosed with ISIS 396443 (1% False Positive Rate)

	Pre-symptomatic (Study SM201)	Infantile-onset		Later-onset (Studies CS1, CS2, CS10, CS12) (e)	All subjects dosed
		Study CS3A	Study CS3B		
Positive at baseline (a)	0/14	0/18	1/74 (1)	0/42	1/148 (<1)
Positive post-baseline irrespective of baseline positivity (b)	0/10	1/19 (5)	2/58 (3)	2/56 (4)	5/143 (3)
Positive post-baseline but negative at baseline (c)	0/10	1/18 (6)	2/55 (4)	2/42 (5)	5/125 (4)
Positive at any time (baseline or post-baseline) (d)	0/14	1/19 (5)	3/77 (4)	2/56 (4)	6/166 (4)

SOURCE: ISIS396443/ISS/FDA-REQ-21-NOV-2016/T-ANTIBODY-1PER.SAS

DATE: 26NOV2016

Collectively, the data indicate an overall ADA rate of 4% (5 out of 125) in patients receiving ISIS 396443.

Reviewer Comments:

The data support an overall incidence rate of 4% ADA induced by ISIS 396443 treatment. All ADA positive subjects were dosed at the 12 mg level with the exception of one patient in CS3A, who was in the 6 mg cohort. When considering only patients dosed with ISIS 396443, similar rates were observed in studies CS3B, CS3A, and CS12. Both ADA positive patients in the “Later-onset (Studies CS1, CS2, CS10, CS12)” column of the above table were identified in study CS12. The patient testing positive only at baseline and the patient testing positive in the sham group are not included in the ADA rate calculation because they are not attributable to drug exposure. It’s plausible that these two results are false positives, which may occur given the number of subjects (treatment and sham groups), and the number of samples from each subject that are tested for ADA.

ADA development

¹ Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. CDER, April 2016.

The table below provides the immunogenicity testing results for each patient that received ISIS 396443 and tested positive for ADA.

Patient No. (Study)	Negative ADA result (Day)	Positive ADA result (Day)	Titer	SAE (preferred term)
2000-5203 (CS3B)	D1			• Aspiration • Hypoventilation • Pneumonia • Respiratory distress • Viral upper respiratory tract infection • Wound dehiscence
	D64			
		D183	Not tested	
	D302			
	D394			
2006-5071 (CS3B)	D1			• Atelectasis • Delayed recovery from anaesthesia • Increased bronchial secretion • Lower respiratory tract infection • Respiratory arrest • Respiratory distress • Viral infection
		D64	8	
	D183			
1843-1301 (CS3A)	D1			• Respiratory distress
	D85			
	D169			
		D253	16	
	D337			
	D442			
	D568			
	D694			
		D820	2	
	D946			
1776-3201 (CS2-CS12)	D1			
	D85			
		D169	1	
	D351			
1778-4206 (CS2-CS12)		D1	4	
		D85	4	
		D169	2	
		D351	2	

Table prepared by reviewer

The sponsor's summary ADA testing results were provided in response to an information request sent on November 21, 2016 and are provided in Appendix 2 of this review. ADA testing results in the Interim Reports for each study were also reviewed. Four of the five treatment-emergent ADA events were transient. One of the five ADA positive subjects developed a persistent response. This patient (1778-4206) in study CS12 tested positive at all four sampling times. As seen in the anti-ISIS 396443 status table provided in Appendix 2, this patient had been previously exposed to ISIS 396443 at the 12 mg level in study CS2. Listings of adverse events for each ADA positive subject were also provided in Biogen's response dated November 28, 2016. Only those events flagged as severe are included in the above table. The sponsor states that "review of AEs of subjects with anti-ISIS 396443 did not yield any event of interest. In addition, all cases of drug hypersensitivity reported in ISIS 396443-treated subjects were due to other drugs."

Reviewer Comments:

The ADA to ISIS 396443 are mostly transient, of low titer, and take several months to develop. In 4 of the 5 subjects, ADA were not observed until after 169 days. Persistent ADA developed in 1 patient (1778-4206, also identified as patient 1447 in the submission). This patient tested negative for ADA in study CS2 out to the 169 Day visit. The titer for this patient was relatively low with a range of 2-4, and showed a trend towards decreasing titer at later sampling points. No clear relationship between ADA presence or titer and severe adverse events was observed for this patient or any ADA positive subjects.

The sponsor did not evaluate ADA for neutralizing activity. The submission does not include a neutralizing antibody (NAb) assay or an in vitro cell-based potency for use in evaluating NAb activity. NAb could impact uptake of ISIS 396443 into target cells. Biogen evaluated ADA positive samples for impact on ISIS 396443 levels in plasma and CSF (see Appendix 3). This analysis found no significant difference between ADA positive patients and group mean for ISIS 396443 levels in CSF. Patients with persistent high titer ADA responses are at highest risk for developing NAb, but such instances were not found in the clinical study data. Upon review of data from the single patient with persistent ADA, Biogen found no impact on safety or efficacy of ISIS 396443. Considering the ADA incidence rate, titer, and overall transient nature of the anti-ISIS 396443 ADA, the risk for NAb to impact efficacy appears low. It is also uncertain whether development of an in vitro assay to assess neutralizing activity would provide meaningful information. However, in the event that persistent ADA responses of high titer are found in ongoing or future studies, I recommend advising the sponsor to evaluate NAb activity in an in vitro assay. This approach was discussed in consultation with FDA subject matter experts.

The sponsor did not evaluate ISIS 396443 for cross-reactivity to dsDNA. The unique structure of ISIS 396443 oligonucleotides has potential to induce ADA that react with dsDNA. Such anti-dsDNA antibodies would raise concern for development of autoimmune disease. For these reasons, the sponsor should be asked to evaluate ADA positive samples for cross-reactivity to dsDNA post-marketing. Notably, FDA has previously made this request a PMR for an oligonucleotide product.² To evaluate anti-dsDNA, the sponsor may consider using commercial assays deemed suitable for intended use.

2. VALIDATION OF ANTI-DRUG ANTIBODY SCREENING ASSAY**2.1 Background**

ELISA to screen for and confirm anti-ISIS 396443 ADA in human plasma were developed at Isis Pharmaceuticals, Inc. and validated at (b) (4)

² Refer to Approval Letter for Kynamro (mipomersen sodium), located at www.accessdata.fda.gov.

Test facility

(b) (4)

Method principle

An ELISA-based method is used to both screen for and confirm the presence of ISIS 396443 ADA in human plasma samples. The free amine version of ISIS 396443 is covalently coated onto 96-well amino plates to serve as the ADA capture reagent. Coated plates are then washed and blocked with blocking buffer (3% dry milk in 1X PBS, 1M NaCl). Human plasma samples diluted 1:50 in blocking buffer are added to the coated plates in duplicate to allow potential ADA to bind immobilized antigen. Plates are washed prior to addition of purified recombinant protein A/G conjugated to HRP, which serves as the detection reagent for captured anti-ISIS 396443 antibodies. Tetramethylbenzidine (TMB) substrate is added to provide a substrate for HRP activity. The HRP reacts with TMB, which is quenched with acid to yield a chromophore measurable at OD_{450nm/650nm}. Signal intensity is proportional to amount of bound ADA present in the plasma. This assay allows for detection of IgG, IgM, IgE, and IgA isotypes. Samples testing equal to or above the screening cut-point are analyzed in a confirmatory assay using the same ELISA platform. In this assay, antibodies are tested for target specificity using cold-competition against unbound ISIS 396443. ADA specific to ISIS 396443 are competed off by binding to excess free ISIS 396443 in solution, which results in signal inhibition. Samples testing equal to or above the confirmatory cut point are then evaluated for titer in the same ELISA assay.

2.2 Validation parameters

The ELISA assay was validated for screening cut-point, confirmatory cut-point, titer cut-point, system suitability criteria, sensitivity, selectivity, drug tolerance, precision, and stability. The individual validation parameters are reviewed in section 2.4 of this review memo.

2.3 Materials and controlsMaterials

The table below provides critical reagents used for positive controls and for ADA capture and confirmation.

Reagent	Concentration	Supplier
Anti-ISIS 396443 (Rabbit polyclonal IgG)	1.0 mg/ml	(b) (4)
ISIS 606568 (ISIS 396443 Free Amine; Coating Material)	300 µg/ml	Sponsor
ISIS 396443	11.6 mg/ml	Sponsor

ISIS 489192	9.15 mg/ml	Sponsor
Purified recombinant Protein A/G Peroxidase Conjugated	0.5 mg/ml	(b) (4)

Table prepared by reviewer

The table below provides the matrices used for validation exercises.

Matrix	Anticoagulant	Supplier	Number of Lots
Pooled Normal Human Plasma	K ₂ EDTA	(b) (4)	27
Individual lots of Normal Human Plasma—Male	K ₂ EDTA		29
Individual lots of Normal Human Plasma—Female	K ₂ EDTA		29
Individual lots of Normal Human Plasma—Male/Female	K ₂ EDTA and K ₃ EDTA		20 (10 male, 10 female)
Individual lots of Disease State Human Plasma	K ₂ EDTA	Sponsor	24

Table prepared by reviewer

Controls

System suitability controls are included on each analytical run. High positive control (HPC) and low positive control (LPC) samples are prepared neat in pooled human plasma matrix and then diluted 1:50 in blocking buffer. Pooled human plasma is used for negative control (NC). Preliminary PC sample concentrations were initially used. Final PC sample concentrations were determined from statistical evaluation of data generated during method validation studies. System suitability run acceptance criteria are provided in the submission with the analytical procedure.

Reviewer Comments:

The system suitability controls are acceptable for their intended use in the binding assay. Raw data for assay controls from each validation run are provided in the MV09 Study Report (Tables 1-4). Acceptance criteria for controls include quantitative limits that were defined statistically during validation exercises. This includes defined ranges for NC values (0.03 to 0.078), ratio of LPC to NC (1.3 to 5.0), and HPC to NC (28.2 to 68.2).

2.4 Validation exercises

2.4.1 Screening and Titration Cut Points

Patient plasma samples are evaluated for presence of ADA signal above the statistically determined cut-point of the assay. The sponsor first determined the screening assay cut-point (CP) through statistical analysis of treatment-naïve normal human plasma samples and then confirmed the CP in treatment-naïve disease human plasma samples. Separate cut-points for use in screening and titration assays were calculated in parallel using 5% and 1% false-positive rates, respectively. Normalization factors (i.e. correction factor) for use with screening (NF) and titration (TNF) assays were calculated based on the cut-

points and variation of negative control (NC) values established during pre-study validation exercises. Floating, plate-specific cut-points (PSCP) for use in-study are thus determined by multiplying plate-specific median negative control (NC) values by the pre-study correction factors (NF or TNF). The table below summarizes the validation outcomes.

Assay	Plasma Sample (No.)	Data Scale, Distribution	Cut-point Method	Cut-Point	Correction Factor	Floating CP
Screening	50	Log, non-normal	Non-parametric, 95 th percentile	0.075	NF = 1.398	= NC _(Plate) x NF
Titer	50	Log, non-normal	Non-parametric, 99 th percentile	0.093	TNF = 1.733	= NC _(Plate) x TNF

Table prepared by reviewer

Raw data and statistical analyses used to support validation of CP, TCP, and associated correction factors are provided in Section 5.3.1.4 (MV09 Study Report) of the BLA. These data are reviewed in more detail below, in this section of the review memo.

Normal Human Plasma Screening CP

Fifty individual lots of normal human plasma, derived from an equal number of men (n=25) and women (n=25) were analyzed to determine the screening cut-point (CP) OD value. Individual human plasma samples were diluted 1:50 and analyzed in six runs by two analysts (3 runs each) using a balanced design. Each run represents 3 plates containing a complete set of 50 plasma samples evaluated together on an occasion. In summary, the entire data set consists of 300 values collected from 18 total plates run on six separate occasions.

The CP was determined using statistical methods described in Appendix 7 of MV09 study report. The following stepwise statistical analyses and results were reported. First, to determine the scale (original or log-transformed) for subsequent analyses, raw OD values were evaluated for normality using the Shapiro-Wilk test. Data distribution was found non-normal and skewed for both original and log-transformed scales. As a result, the sponsor selected log-transformed data for further analyses on grounds that data were less skewed compared to the original scale. Second, to select outliers for removal from the dataset, log(OD) values were assessed using box-plot criteria. Samples were deemed outliers if their residuals fell above the 75th percentile plus 1.5 times the interquartile range, or below the 25th percentile minus 1.5 times the interquartile range. Eight analytical and two biological outliers were identified and removed from CP calculations. Third, using the mixed effects ANOVA model, data were evaluated for differences in means and variances across runs following outlier exclusion. This analysis found a significant difference between mean values, but no significant difference in variances across runs. Therefore, the sponsor selected a common CP for use with a normalization factor (i.e., floating cut-point). Using a non-parametric approach set at the 95th percentile, the following screening CP was calculated: 0.075.

Disease State Human Plasma Screening CP

The sponsor confirmed that the pre-study screening CP of 0.075 for normal plasma is suitable for use on in-study disease state human plasma. Twenty lots of normal human plasma (10 male, 10 female) and 20 lots of disease state plasma were evaluated for differences in means or variances between populations. Pre-dose disease state plasma samples used in the evaluation were collected as part of protocol 396443-CS1. Raw OD values were generated in a single run by a single operator. Table 9 below provides the raw OD values from the two populations.

Table 9 Data for Screening Cut-point Evaluation for the Detection of Anti-ISIS 396443 Antibodies in Normal and Disease State Human Plasma

Sample	Population	Run	Plate	Value
BRH775245	Normal	1	Val-36	0.053
BRH775246	Normal	1	Val-36	0.052
BRH775247	Normal	1	Val-36	0.044
BRH775248	Normal	1	Val-36	0.063
BRH775249	Normal	1	Val-36	0.046
BRH775250	Normal	1	Val-36	0.048
BRH775251	Normal	1	Val-36	0.044
BRH775252	Normal	1	Val-36	0.048
BRH775253	Normal	1	Val-36	0.047
BRH775254	Normal	1	Val-36	0.135
BRH775285	Normal	1	Val-36	0.050
BRH775286	Normal	1	Val-36	0.057
BRH775287	Normal	1	Val-36	0.046
BRH775288	Normal	1	Val-36	0.076
BRH775289	Normal	1	Val-36	0.049
BRH775290	Normal	1	Val-36	0.052
BRH775291	Normal	1	Val-36	0.044
BRH775292	Normal	1	Val-36	0.048
BRH775293	Normal	1	Val-36	0.047
BRH775294	Normal	1	Val-36	0.055

Table 9 Data for Screening Cut-point Evaluation for the Detection of Anti-ISIS 396443 Antibodies in Normal and Disease State Human Plasma

Sample	Population	Run	Plate	Value
1004 Day 1 Predose	Disease	1	Val-36	0.049
1005 Day 1 Predose	Disease	1	Val-36	0.046
1006 Day 1 Predose	Disease	1	Val-36	0.058
2001 Day 1 Predose	Disease	1	Val-36	0.048
2002 Day 1 Predose	Disease	1	Val-36	0.044
2003 Day 1 Predose	Disease	1	Val-36	0.049
2004 Day 1 Predose	Disease	1	Val-36	0.054
2005 Day 1 Predose	Disease	1	Val-36	0.066
2006 Day 1 Predose	Disease	1	Val-36	0.051
3001 Day 1 Predose	Disease	1	Val-36	0.058
3002 Day 1 Predose	Disease	1	Val-36	0.047
3003 Day 1 Predose	Disease	1	Val-36	0.057
3004 Day 1 Predose	Disease	1	Val-36	0.043
3005 Day 1 Predose	Disease	1	Val-36	0.053
3006 Day 1 Predose	Disease	1	Val-36	0.046
4001 Day 1 Predose	Disease	1	Val-36	0.057
4002 Day 1 Predose	Disease	1	Val-36	0.057
4003 Day 1 Predose	Disease	1	Val-36	0.047
4004 Day 1 Predose	Disease	1	Val-36	0.047
4005 Day 1 Predose	Disease	1	Val-36	0.068

Outliers in the dataset were identified using the box-plot method as described for normal human plasma cut-point analysis above. Two outliers were identified in the normal population (*highlighted by reviewer in Table 9 above*), and no outliers were found in the disease population. Comparison of means and variances between populations by ANOVA found no significant differences with reported P-values of 0.0938 and 0.1944, respectively.

Titration Cut Point (TCP)

Antibody titer is defined as the highest dilution factor to produce a mean OD value above the method cut point. The TCP was calculated from the same 50 lots of human normal plasma sample values analyzed and reported for the screening CP. Using a non-parametric approach set at the 99th percentile, the following TCP was calculated: 0.093.

Normalization Factors

Floating cut-points are calculated by multiplying background from each assay by a normalization factor, which is determined during pre-study validation exercises. Normalization factors are used to account for inter-assay variation in background signals. The sponsor derived a separate screening normalization factor (NF) and titration normalization factor (TNF). Raw data and methods used to derive the NF and TNF are provided in the submission and reviewed in this section below.

Screening Cut-Point Normalization Factor

An overall normalization factor (NF) for use in routine calculation of plate-specific cut-points (PSCP) was determined using the normal human plasma cut-point validation dataset. Median OD (A_{450nm}) values of negative control (NC) were calculated for each run (i.e., occasion) using the 8 replicates of pooled normal human plasma (PNHP) run on each plate. Using the statistically determined 0.075 screening CP described above, the NF for each of 6 runs was calculated as follows:

- $NF = CP/NC_{(Median\ OD)}$

The overall NF of 1.398 was established as the average NF from 6 runs. Table 12 below provides the NC results used to determine the screening assay NF.

Table 12 **Determination of the Normalization Factor (NF)**

Occasion #1		Occasion #2		Occasion #3		Occasion #4		Occasion #5		Occasion #6	
Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl
Val-01	0.077	Val-11	0.049	Val-16	0.070	Val-21	0.048	Val-26	0.049	Val-31	0.066
Val-02	0.067	Val-12	0.049	Val-17	0.053	Val-22	0.050	Val-27	0.052	Val-32	0.056
Val-03	0.070	Val-13	0.051	Val-18	0.051	Val-23	0.050	Val-28	0.047	Val-33	0.051
Median											
NF Run ^a	0.070	0.049		0.053		0.050		0.049		0.056	
	1.071	1.531		1.415		1.500		1.531		1.339	
Mean NF ^c						1.398					

Titration Cut-Point Normalization Factor

A specific titration normalization factor was calculated using pre-study validation results from normal human plasma as described above for the screening NF. The TNF was calculated using the following formula:

- $TNF = TCP/NC_{(Median\ OD)}$

The overall TNF of 1.733 was established as the average TNF from 6 runs. Table 12 below provides the NC results used to determine the screening assay NF.

Table 13 Determination of the Titration Normalization Factor (TNF)

Occasion #1		Occasion #2		Occasion #3		Occasion #4		Occasion #5		Occasion #6	
Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl	Assay ID	Median Neg Ctrl
Val-01	0.077	Val-11	0.049	Val-16	0.070	Val-21	0.048	Val-26	0.049	Val-31	0.066
Val-02	0.067	Val-12	0.049	Val-17	0.053	Val-22	0.050	Val-27	0.052	Val-32	0.056
Val-03	0.070	Val-13	0.051	Val-18	0.051	Val-23	0.050	Val-28	0.047	Val-33	0.051
Median	0.070	0.049	0.053	0.050	0.049	0.056					
TNF Run ^a	1.329	1.898	1.755	1.860	1.898	1.661					
Mean TNF ^c	1.733										

Reviewer Comments:

The data support a validated screening CP of 0.075 that is suitable to detect ADA in disease state human plasma samples collected in-study. This CP is intended for use in calculating the floating CP. For the validation of screening CP in normal human plasma, the number of samples (n=50) and design of the exercise (balanced design, 2 operators, 6 runs, on 6 days) is reasonable to ensure a statistically meaningful CP. The statistical methods used to derive the validated screening CP in normal human plasma, and then confirm this CP on in-study disease state human plasma samples, are consistent with recommendations.³ Given that the data are non-normal distributed, the sponsor's approach to derive a CP using non-parametric analysis on transformed data (i.e., less skewed) is reasonable. All raw OD values are provided in the submission. As shown in Table 9 above, after removing the highlighted outliers, similar OD value ranges of 0.044 to 0.063 for normal plasma and 0.044 to 0.068 for disease state plasma are observed. Collectively, the data and methodology are considered sufficient to support the screening CP.

The data also support a validated titration CP of 0.093 that is suitable to assess titer in ADA-positive patient samples. This TCP is intended for use in calculating a floating CP for titer analyses. The use of a higher CP for titer relative to screening is appropriate because the screening CP is near background levels (see Section 2.4.3 of this memo), wherein the assay is less sensitive to differences in 2-fold dilution factors (i.e. titer).

2.4.2 Confirmatory cut-points (CCP)**Normal Human Plasma CCP**

The confirmatory assay is based on loss of ADA signal during cold-competition with excess drug. To determine the CCP, 50 individual lots of normal human plasma samples (25 males and 25 females) were spiked with ISIS 396443 competitor at a final concentration of 50 µg/ml. Plasma samples were run in parallel with and without spiked ISIS 396443. The analysis was performed on data from a total of 6 runs conducted on different occasions by two analysts (3 runs each) using a balanced design. The percent signal inhibition was calculated for each sample using the following formula:

³ Shankar, G., et.al. 2008. Journal of Pharmaceutical and Biomedical Analysis. 48:1267-1281.

- % Inhibition = 100 [1-(spiked sample/unspiked sample)]

Raw OD values for each unspiked and spiked sample can be found in the submission in Table 8 (MV09 Study Report). Percent Inhibition values were subjected to the same stepwise statistical evaluations and methods described above for the screening cut-point. The statistical methodology and results are located in Appendix 7 of the MV09 Study Report. Investigation of distribution found non-normal distributed data less skewed in original scale. Twenty-seven analytical outliers were excluded from individual runs according to box-plot criteria. Comparison of runs by ANOVA found similar means and different variances. Therefore, the sponsor calculated separate CCPs for each run. Different CCP approaches (parametric or non-parametric) were considered for each run based on evaluation of the run data distribution.

Cut-points were determined to give 0.1% false positives using the 99.9th percentile for runs evaluated by non-parametric approach, or the following formula for runs evaluated by parametric approach:

- Mean % signal inhibition + 3.09*SD

Table 5 below provides the determined CCP for % inhibition by cold-competition from each run.

Text Table 5
CP and CCP Summary Results

Parameter	Cut-point	Selected Approach	Run	Calculated Value
OD	CP	Non Parametric	1 to 6	0.0750
% Inhibition	CCP	Non Parametric	1	15.3846
			4	15.3846
		Parametric	2	13.8499
			3	26.4647
			5	15.8330
			6	18.3654

The average CCP across 6 runs, calculated by the reviewer, is: 17.5470.

Disease State Human Plasma CCP

Twenty lots of normal human plasma (10 male, 10 female) and 20 lots of disease state plasma were evaluated by ANOVA for differences between populations. This analysis revealed a statistically significant difference in variation between normal and disease state populations. Consequently, the sponsor calculated a separate CCP for the disease state samples using a non-parametric approach set at the 99.9th percentile. This exercise yielded a CCP for the disease state of 17.5439.

The sponsor reports the following CCP for use in-study:

- CCP = 17.5%

Reviewer comments:

The concentration of drug used to validate the cut-point should be determined based on data demonstrating inhibition in the presence high levels of ADA. The drug tolerance

limit data (see section 2.4.7 below) demonstrate that 50 mcg/ml of ISIS 396443 inhibits detection of the high antibody concentration. Based on these data, the 50 mcg/ml concentration of drug used for cut point validation is acceptable.

Given that the same CCP value out to one decimal point after rounding was found in both normal and disease populations, the sponsor's approach for using a single fixed CCP is reasonable. However, the CCP was determined using a 0.1% false positive rate, which is lower than the 1% rate recommended in Guidance. The 0.1% rate may be too narrow to ensure all potential ADA positive samples are detected in the assay. To address this concern, the sponsor was asked to re-calculate the confirmatory cut-point using more stringent criteria (a 1% false positive rate instead of 0.1%), and to re-evaluate clinical study samples that screened positive.

2.4.3 Assay sensitivity and positive controls

To determine assay sensitivity, 6 dilution series of 16 serial 2-fold dilutions spanning the screening CP were prepared in PNHP matrix. Dilution series were performed by two analysts on three different days using a balanced design for a total of six runs. Test concentrations of anti-ISIS 396443 positive control antibody ranged from 100 µg/ml to 3 ng/ml. Table 16 below provides the raw OD values used to determine assay sensitivity (LLPC) and LPC.

Table 16 Sensitivity and Hook Effect Assessment Results for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

Assay ID		Val-05	Val-15	Val-20	Val-25	Val-30	Val-35					
Mean NC A _{450nm}		0.073	0.052	0.053	0.052	0.049	0.053					
Plate Cut-point ^b		0.100	0.073	0.072	0.076	0.068	0.075					
Dilution Factor	Initial Concentration (ng/mL)	Concentration after MRD (ng/mL)	A _{450nm}						N	Mean	SD	CV (%)
1	100000.000	2000.000	3.270	3.314	3.278	3.273	3.261	3.292	5	3.285	0.018	0.6
2	50000.000	1000.000	3.292	3.343	3.299	3.267	3.263	3.311	5	3.302	0.028	0.8
4	25000.000	500.000	3.216	3.299	3.271	3.203	3.213	3.266	5	3.251	0.040	1.2
8	12500.000	250.000	3.084a	3.190	3.115	2.854	3.123	3.168	5	3.082	0.134	4.4
16	6250.000	125.000	2.647	2.876	2.735	2.039	2.848	2.977	5	2.655	0.367	13.8
32	3125.000	62.500	1.829	2.165	1.802	1.423	2.248	2.296	5	1.903	0.342	18.0
64	1562.500	31.250	1.201	1.380	1.069	0.882	1.361	1.412	5	1.189	0.221	18.6
128	781.250	15.625	0.699	0.826	0.649	0.513	0.770	0.926	5	0.723	0.160	22.1
256	390.625	7.813	0.335	0.467	0.345	0.315	0.475	0.521	5	0.397	0.092	23.1
512	195.313	3.906	0.192	0.231	0.192	0.171	0.272	0.303	5	0.218	0.052	24.0
1024	97.656	1.953	0.137	0.152	0.125	0.105	0.158	0.178	5	0.139	0.028	19.8
2048	48.828	0.977	0.119	0.113	0.085	0.080	0.113	0.117	5	0.103	0.019	18.2
4096	24.414	0.488	0.095	0.067	0.064	0.060	0.073a	0.076	5	0.072	0.014	19.3
8192	12.207	0.244	0.085	0.061	0.056c	0.054	0.062	0.065	5	0.064	0.012	19.3
16384	6.104	0.122	0.073	0.055	0.053	0.057	0.055	0.055	5	0.059	0.008	13.9
32768	3.052	0.061	0.084	0.058	0.058	0.063	0.058	0.066	5	0.066	0.011	16.3
TPSCP ^f			0.124	0.091	0.089	0.094	0.085	0.093	-	-	-	-
Final Titer Fold ^e			1024	2048	1024	1024	2048	2048	-	-	-	-
Mean PC Concentration at Plate Cut-point (ng/mL)			41.034	22.046	24.124	35.402	d	14.426	5	27.406	10.696	39.0
										LLPC (ng/mL) ^d		
										50.211		
										LPC (ng/mL) ^d		
										67.485		

Assay sensitivity with 95% consistency was calculated from the mean interpolated concentration at the screening cut point from five of the six runs. According to the sponsor, Assay Val-30 (see Table 16) was not included in calculations because “no interpolated value was available.” The following formula was used to calculate sensitivity (LLPC):

- $LLPC = \text{Mean}_{(\text{PC concentration at PSCP})} + t_{0.05,df} \times SD$

Based on this calculation, assay sensitivity was determined:

- $LLPC = 50 \text{ ng/ml}$ (in undiluted matrix)

Data from the sensitivity exercise were used to determine the low positive control (LPC), which was designed to fail the assay (i.e., fall below cut point) 1% of the time. The following formula was used to statistically define the LPC:

- $\text{Mean}_{(\text{PC concentration at PSCP})} + t_{0.01,df} \times SD$

Based on this formula, the LPC was statistically defined at 68 ng/ml in undiluted matrix. However, in the validation acceptance criteria for LPC, the sponsor states that “due to low variability observed in the method development runs and the potential for the LPC value to be within 2-fold of the LLPC, the LPC level was the greater of the two values...” of 68 ng/ml or 3 times the LLPC (i.e. 50 ng/ml). Therefore, the LPC was set at 3 times LLPC:

- $LPC = 150 \text{ ng/ml}$ (in undiluted matrix)

The high positive control (HPC) was defined by the sponsor as “the concentration that produced the signal on the upper end of the linear response of the full positive control dilution curve.” Based on the data shown in Table 16 above, the HPC was set at:

- $HPC = 6250 \text{ ng/ml}$ (in undiluted matrix)

Reviewer comments:

The assay sensitivity of 50 ng/ml is acceptable. The methods used to calculate assay sensitivity and LPC are consistent with recommendations provided in Draft Guidance.⁴ At 50 ng/ml, the assay is considered relatively sensitive. For reference, FDA recommends an assay sensitivity of at least 100 ng/ml.

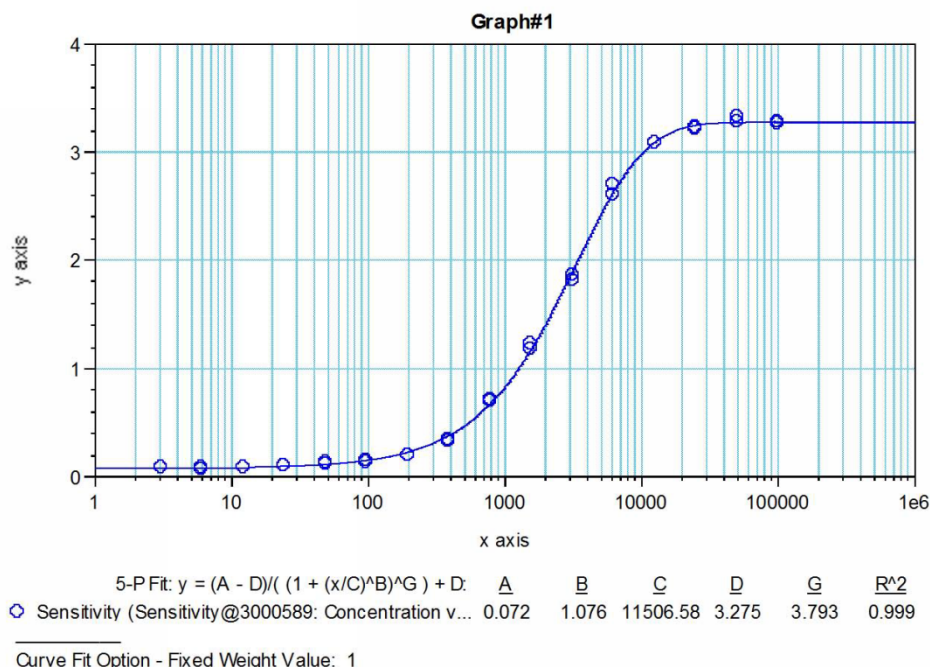
The LPC and HPC values of 150 ng/ml and 6250 ng/ml, respectively, are reasonable. The statistically determined LPC based on a 1% failure rate is recommended.⁴ However, the 150 ng level (3 x LLPC) falls at the lower end of the linear range (see also Figure 1 below). Given that the LPC level is near the cut-point, and that the LLPC level is included in routine runs per the analytical procedure, the selected LPC is considered reasonable to ensure assay sensitivity is monitored.

⁴ Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. CDER, April 2016.

2.4.4 Prozone effect

Prozone effect (referred to in the submission as “hook effect”) is defined as a reduction in signal that may occur in presence of high ADA concentrations. The sponsor assessed potential prozone effect in the same experiment used to determine sensitivity. A serial dilution series of 2-fold dilutions of positive control antibody ranging from 100 µg/ml to 3 ng/ml was evaluated on one occasion. Figure 1 below provides the positive control dilution curve.

Figure 1 Graphical Representation of Hook Effect Data



Reviewer comments:

The data support absence of prozone effect in the assay, as evidenced by the observed plateau of signal at the highest concentrations of positive control.

2.4.5 Precision

Intra-assay precision and inter-assay precision were evaluated using replicates of PC samples at the following concentrations:

- LLPC = 50 ng/ml
- LPC = 150 ng/ml
- HPC = 6250 ng/ml

To assess intra-assay precision, PC samples were evaluated in replicates of 6, each one in duplicate on 2 occasions, performed by 2 analysts, using a balanced design. To assess inter-assay precision, PC samples were evaluated in replicates of 3, each one in duplicate on 6 occasions, performed by 2 analysts, using a balanced design. These experiments were also used to establish quantitative LPC and HPC limits for in-study system suitability.

Intra-assay precision acceptance criteria (on each occasion):

- Mean A_{450nm} values of all PCs $\geq$ PSCP
- $\leq 25\%$ CV for LPC and HPC levels
- $\leq 30\%$ CV for LLPC level

Inter-assay precision acceptance criteria (global values):

- $\leq 25\%$ CV for LPC and HPC levels
- $\leq 30\%$ CV for LLPC level

Criteria to define quantitative LPC and HPC limits

- Upper limit = mean PC/(mean NC) ratio + $t_{0.05,df} \times SD$
- Lower limit = mean PC/(mean NC) ratio - $t_{0.05,df} \times SD$

Table 17 below provides results from precision exercises at LLPC, LPC, and HPC concentrations (*highlight added by reviewer*).

Table 17 Intra- and Inter-assay Precision of Positive Controls Results for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

PC Level	Assay ID	Mean A _{450nm}										Inter-assay Precision	Mean NC	Ratio ^c	
		Mean Duplicates						Intra-assay Precision							
		1	2	3	4	5	6	Mean	SD	CV (%)	N				
LLPC (50 ng/mL)	Val-40	0.079	0.076	0.076	0.074	0.074	0.076	0.076	0.002	2.4	6	Global Mean	0.091	0.051	1.5
	Val-41	0.098	0.084	0.076	-	-	-	0.086	0.011	12.9	3	SD	0.013	0.053	1.6
	Val-42	0.083	0.080	0.079	0.085	0.082	0.091	0.083	0.004	5.2	6	CV (%)	13.8	0.047	1.8
	Val-43	0.096	0.102	0.101	-	-	-	0.100	0.003	3.2	3	N	8	0.052	1.9
	Val-44	0.088	0.090	0.103	-	-	-	0.094	0.008	8.7	3			0.051	1.8
	Val-45	0.086	0.095	0.080	-	-	-	0.087	0.008	8.7	3			0.052	1.7
	Val-48	0.100	0.097	0.153	-	-	-	0.117	0.032	27.0	3			0.070	1.7
	Val-51	0.077	0.091	0.087	-	-	-	0.085	0.007	8.5	3			0.053	1.6
Mean														1.7	

Table 17 Intra- and Inter-assay Precision of Positive Controls Results for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

PC Level	Assay ID	Mean A _{450nm}										Inter-assay Precision	Mean NC	Ratio ^c	
		Mean Duplicates						Intra-assay Precision							
		1	2	3	4	5	6	Mean	SD	CV (%)	N				
LPC (150 ng/mL)	Val-40	0.147	0.138	0.145	0.156	0.129	0.131	0.141	0.010	7.3	6	Global Mean	0.168	0.051	2.8
	Val-41	0.155	0.146	0.150	-	-	-	0.150	0.005	3.0	3	SD	0.020	0.053	2.8
	Val-42	0.183	0.197	0.166	0.178	0.169	0.188	0.180	0.012	6.5	6	CV (%)	11.9	0.047	3.8
	Val-43	0.195	0.210	0.196	-	-	-	0.200	0.008	4.2	3	N	8	0.052	3.9
	Val-44	0.161	0.180	0.187	-	-	-	0.176	0.013	7.6	3			0.051	3.5
	Val-45	0.171	0.190	0.165	-	-	-	0.175	0.013	7.4	3			0.052	3.4
	Val-48	0.164	0.160	0.188	-	-	-	0.171	0.015	8.9	3			0.070	2.4
	Val-51	0.155	0.143	0.143	-	-	-	0.147	0.007	4.7	3			0.053	2.8
														Mean	3.2
														N	8.0
														SD	0.5
														LPC Upper Limit ^a	5.0
														LPC Lower Limit ^b	1.3

Table 17 Intra- and Inter-assay Precision of Positive Controls Results for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

PC Level	Assay ID	Mean A _{450nm}												Inter-assay Precision	Mean NC	Ratio ^c
		Mean Duplicates						Intra-assay Precision								
		1	2	3	4	5	6	Mean	SD	CV (%)	N					
HPC (6250 ng/mL)	Val-40	2.427	2.353	2.401	2.380	2.324	2.324	2.368	0.042	1.8	6	Global Mean	2.553	0.051	46.4	
	Val-41	2.591	2.445	2.468	-	-	-	2.501	0.079	3.1	3	SD	0.128	0.053	47.2	
	Val-42	2.675	2.519	2.586	2.594	2.464	2.638	2.579	0.077	3.0	6	CV (%)	5.0	0.047	54.9	
	Val-43	2.756	2.812	2.740	-	-	-	2.769	0.038	1.4	3	N	8	0.052	53.3	
	Val-44	2.418	2.513	2.500	-	-	-	2.477	0.052	2.1	3			0.051	48.6	
	Val-45	2.621	2.731	2.737	-	-	-	2.696	0.065	2.4	3			0.052	51.9	
	Val-48	2.656	2.402	2.593	-	-	-	2.550	0.132	5.2	3			0.070	36.4	
	Val-51	2.597	2.431	2.427	-	-	-	2.485	0.097	3.9	3			0.053	46.9	
													Mean		48.2	
													N		8.0	
													SD		5.7	
													HPC Upper Limit ^a		68.2	
													HPC Lower Limit ^b		28.2	

Reviewer comment:

The % CV range for intra-assay precision was within 9% at LPC and HPC levels, and within 27% at the LLPC level. Notably, the 27% CV value was observed for a single assay (see highlight in Table 17 above) whereas the remaining values ranged from 2.4-12.9%. The % CV range for inter-assay precision was within 13.8% at all concentrations. Although the sponsor's acceptance criteria for precision is wider than the recommended 20% CV, the actual precision of the assay is well within this margin. Therefore, the level of precision is acceptable.

2.4.6 Selectivity

Selectivity is defined as the ability of the assay to detect product-specific ADA in the presence of matrix that may contain interfering components. The sponsor evaluated assay selectivity in presence of normal and disease state plasma matrix, and in the presence of hemolysis components.

Matrix selectivity

To assess selectivity and potential matrix interference, 10 individual lots of normal human plasma and 10 individual lots of disease state plasma were analyzed spike and unspiked with low (LPC, 150 ng/ml) and high (HPC, 6250 ng/ml) concentrations of anti-ISIS 396443. Blocking buffer spiked with LPC and HPC levels of anti-ISIS 396443 were analyzed to serve as reference for calculating recovery (i.e. % difference).

Acceptance criteria:

- At least 80% spiked plasma lots within $\pm 25\%$ difference compared to reference.
- At least 80% unspiked plasma lots < PSCP.

Acceptance criteria were met for both normal plasma and disease state plasma matrices. Table 18 below provides results from the matrix selectivity validation exercise (*highlights added by reviewer*).

Table 18 Matrix Selectivity Assessment Results for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

Serum ID	Matrix Designation	Mean A _{450nm}	Val-49 PSCP: 0.102	LPC (PSCP: 0.097)				HPC (PSCP: 0.098)			
				Assay ID	Spiked in Individual Lot	Spiked in Blocking Buffer	% Difference ^a	Assay ID	Spiked in Individual Lot	Spiked in Blocking Buffer	% Difference
Blocking Buffer (Control)		-	-			0.150	-			2.310	-
BRH775270	Normal	0.057	< PSCP	Val-48	0.156		4.0	Val-47	2.418		4.7
BRH775271	Normal	0.062	< PSCP		0.219		46.0		2.559		10.8
BRH775272	Normal	0.063	< PSCP		0.171		14.0		2.401		3.9
BRH775273	Normal	0.087	< PSCP		0.172		14.7		2.508		8.6
BRH775274	Normal	0.056	< PSCP		0.141		-6.0		2.383		3.2
BRH775310	Normal	0.086	< PSCP		0.150		0.0		2.288		-1.0
BRH775311	Normal	0.068	< PSCP		0.142		-5.3		2.326		0.7
BRH775312	Normal	0.047 c	< PSCP		0.150		0.0		2.554		10.6
BRH775313	Normal	0.055	< PSCP		0.148		-1.3		2.371		2.6
BRH775314	Normal	0.067	< PSCP		0.226		50.7		2.490		7.8
4006 Day 1 Predose	Disease	0.057	< PSCP		0.169		12.7		2.387		3.3
2006 Day 1 Predose	Disease	0.070	< PSCP		0.155		3.3		2.492		7.9
4008 Day 1 Predose	Disease	0.064	< PSCP		0.140		-6.7		2.241		-3.0
4009 Day 1 Predose ^b	Disease	0.126	≥ PSCP		0.147		-2.0		2.411		4.4
4010 Day 1 Predose	Disease	0.070	< PSCP		0.152		1.3		2.402		4.0
4001 Day 1 Predose	Disease	0.077	< PSCP		0.147		-2.0		2.365		2.4
2001 Day 1 Predose	Disease	0.057	< PSCP		0.152		1.3		2.263		-2.0
1005 Day 1 Predose	Disease	0.088	< PSCP		0.282		88.0		2.437		5.5
3001 Day 1 Predose	Disease	0.075	< PSCP		0.162		8.0		2.338		1.2
3006 Day 1 Predose	Disease	0.061	< PSCP		0.137		-8.7		2.179		-5.7

Reviewer comment:

The assay is sufficiently selective for ADA in the presence of normal and disease state plasma matrices. For spiked normal plasma, 8/10 and 10/10 samples exhibited ADA signal values within 15% of the spiked blocking buffer reference with a range of -6.0% to 14.7%. For disease state plasma, 9/10 and 10/10 samples exhibited ADA signal values within 15% of the reference with a range of -6.7% to 12.7%. These ranges support similar detection of ADA in presence of plasma compared to buffer alone. Of the 3 samples that failed to meet acceptance criteria, all exhibited higher values than the reference (see highlighted values in Table 18). This indicates matrices are free from components that could inhibit positive ADA signals. This is acceptable.

Hemolysis selectivity

To evaluate assay selectivity in the presence of potential interfering substances due to hemolysis, human plasma samples with NC, LPC, and HPC ADA levels were evaluated unspiked and spiked with hemoglobin. Three concentrations of hemoglobin were tested to approximate slight hemolysis (0.25 mg/ml), intermediate hemolysis (1.0 mg/ml), and severe hemolysis (5 mg/ml).

Acceptance criteria:

- NC values < PSCP
- 75-125% recovery of PC samples

Results are provided in the submission. Acceptance criteria were met. The % recovery values ranged from 89.9% to 110.4% across PC concentrations and hemoglobin concentrations.

Reviewer comment:

No interference and no trends in % recovery with increasing hemoglobin concentrations were observed. These results support maintained assay selectivity in the event of hemolysis.

2.4.7 Drug tolerance

Drug tolerance is the sensitivity of the assay to detect ADA in the presence of the ISIS 396443. To assess tolerance, human plasma with low (LPC, 150 ng/ml), intermediate (PC, 250 ng/ml), and high (HPC, 6250 ng/ml) levels of anti-ISIS 396443 were spiked with 7 different concentrations of drug. The following final concentrations of ISIS 396443 were tested: 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 µg/ml. The highest drug concentration that allowed a mean ADA signal above cut-point was defined as the drug tolerance for each concentration of PC. Raw data are provided in the submission. The below table provides a summary of drug tolerance at each PC level.

Anti-ISIS 396443 concentration	Highest tolerated level of drug
LPC, 150 ng/ml	4.0 µg/ml
PC, 250 ng/ml	8.0 µg/ml
HPC, 6250 ng/ml	≥ 16.0 µg/ml

Table prepared by reviewer

Reviewer comment:

The data support a drug tolerance of 4.0 µg/ml when relatively low levels of ADA are present. This level of tolerance is well above the expected levels of drug in patient plasma at the times of clinical immunogenicity sampling. For example, in pivotal study CS3B, levels of ISIS 396443 in patient plasma ranged from below LOQ to 2.33 ± 0.93 ng/ml at immunogenicity sampling times (pre-dose, D64, D183, and D302).⁵ In this study, C_{max} is reported as 1103 ± 854 ng/ml and median T_{max} is 2.00 hours (1-24 hour range). Thus, the assay is capable of detecting ADA even in the presence of C_{max} levels of ISIS 396443. The sponsor states that “after reaching the peak level, plasma concentrations of ISIS 396443 decline rapidly...the rapid decline in plasma concentrations is likely due to extensive distribution to systemic tissues.”⁶ Multiple doses of ISIS 396443 did not promote further accumulation in the plasma. Notably, drug tolerance levels are dependent on the affinity of the positive control and may not reflect tolerance of ADA in patient samples. However, collectively these data indicate the assay has good tolerance to drug.

2.4.8 Specificity

The sponsor tested specificity of the positive control antibody by immunodepletion analysis against ISIS 396443 and ISIS 489192. The two drugs have the same sequence, but ISIS 396443 has different backbone chemistry and MOE modifications. High (HPC, 6250 ng/ml) and low (LPC, 150 ng/ml) concentrations of anti-ISIS 396443 were

⁵ Refer to NDA 209531, Section 2.7.2—Summary of Clinical Pharmacology Studies, Table 20.

⁶ Refer to NDA 209531, Section 2.7.2—Summary of Clinical Pharmacology Studies, Section 1.2.

evaluated for inhibition of signal in the presence of 50 µg/ml ISIS 396443 or ISIS 489192. Results are provided in the submission.

Reviewer comment:

Review of the data provided in the submission found that ISIS 489192 did not inhibit ADA signal in positive control samples. Percent signal inhibitions ranged from 0.7% to 6.2% for LPC, and -1.9% to 7.1% for HPC in the presence of ISIS 489192. In contrast, the same PC samples were inhibited by 76.3% to 72.2% (LPC) and 98.2% to 98.5% (HPC) in the presence of ISIS 396443. These data indicate that the anti-ISIS 396443 positive control antibody recognizes the phosphorothioate backbone and MOE-modified sugars.

2.4.9 Precision of confirmatory cut-point

Inter-assay precision of the CCP was evaluated by testing % signal inhibition in plasma samples of LLPC (50 ng/ml), LPC (150 ng/ml), and HPC (6250 ng/ml) levels spiked or unspiked with 50 µg/ml ISIS 396443. Samples were tested in duplicate on six occasions by two analysts using a balanced design.

Acceptance criteria:

- %CV less than 25% for global values
- OD of spiked LLPC samples < PSCP, or % inhibition values ≥ CCP

Table 24 below provides the results from the CCP precision experiment.

Table 24 Summary of the Inter-assay Precision of the Confirmatory Cut-point (CCP) for the Detection of Anti-ISIS 396443 Antibodies in Human Plasma

Assay ID	PSCP	LLPC (50 ng/mL)			Assay ID	LPC (150 ng/mL)			Mean A _{450nm} HPC (6250 ng/mL)			Negative Control		
		Unspkd	Spiked	% Sig		Unspkd	Spiked	% Sig	Unspkd	Spiked	% Sig	Unspkd	Spiked	% Sig
		Mean A _{450nm}	Inhib ^a			Mean A _{450nm}	Inhib ^a		Mean A _{450nm}	Inhib ^a		Mean A _{450nm}	Inhib ^a	
Val-54	0.093	0.079	0.053	32.5	Val-40	0.135	0.045	66.8	2.348	0.051	97.8	0.056	0.044	21.0
		0.107b	0.051	52.2		0.135	0.046	65.5	2.389	0.054	97.7	0.051	0.047	6.6
		0.101	0.092b	8.8		0.160	0.051	68.0	2.428	0.060	97.5	0.075b	0.052	30.5
Val-54	0.093	0.089	0.070	22.2	Val-42	0.172	0.044	74.4	2.716	0.057b	97.9	0.049	0.045	9.3
		0.092	0.052	42.9		0.192	0.046	76.3	2.667	0.065b	97.6	0.048	0.051	-6.0
		0.088	0.049	44.2		0.205	0.050	75.8	3.021	0.050	98.3	0.061	0.048	21.2
Val-54	0.093	0.071	0.066	6.5	Val-44	0.166	0.043	74.3	2.292	0.051	97.8	0.046	0.045	2.3
		0.068	0.059	13.4		0.184	0.049	73.5	2.386	0.048	98.0	0.049	0.049	0.1
		0.084	0.054	35.8		0.194	0.048	75.4	2.352	0.046	98.0	0.060b	0.043	28.1
Val-59	0.066	0.092	0.045	50.8	Val-46	0.190	0.044	76.7	2.709	0.050	98.2	0.053	0.051	4.2
		0.095	0.049	48.0		0.188	0.056	70.4	2.693	0.050	98.2	0.053	0.046	13.8
		0.086	0.047	45.4		0.201	0.047	76.5	2.764	0.050	98.2	0.053	0.049	8.7
Val-59	0.066	0.085	0.050	41.3	Val-50	0.149	0.049	67.0	2.468	0.055	97.8	0.049	0.055	-10.9
		0.091	0.045	51.0		0.148	0.051	65.6	2.482	0.052	97.9	0.054	0.083b	-53.8
		0.080	0.045	43.7		0.177	0.052	71.0	2.681	0.045	98.3	0.072b	0.050	30.3
Val-59	0.066	0.084	0.047	43.9	Val-51	0.155	0.046	70.4	2.427	0.052	97.9	0.051	0.052	-0.8
		0.088	0.047	46.4		0.157	0.051	67.6	2.586	0.049	98.1	0.054	0.048	11.9
		0.084	0.045	46.0		0.170	0.051	69.8	2.554	0.058	97.7	0.051	0.050	2.9
Mean		0.087	0.054		Mean	0.171	0.048		2.554	0.052		0.055	0.050	
SD		0.009	0.012		SD	0.022	0.003		0.190	0.005		0.008	0.009	
N		18	18		N	18	18		18	18		18	18	
CV(%)		10.8	22.2		CV(%)	12.8	7.1		7.4	9.6		14.4	17.3	

Reviewer comment:

The %CV values are well within recommended limits. The data therefore support a suitable precision for the confirmatory assay.

2.4.10 Precision of titration

Precision of titration was evaluated in serial 2-fold dilutions of HPC (6250 ng/ml) antibody in pooled human plasma. Nine dilution steps were analyzed, which included the following dilution factors: 1, 2, 4, 8, 16, 32, 64, 128, and 256. Dilution series were analyzed in one replicate on three occasions (inter-assay precision) and in three replicates on one occasion (intra-assay precision). Final titers were reported as the highest dilution factor to allow mean A_{450nm} value above the cut-point. A minimum significant ratio (MSR) was also calculated in this exercise.

Acceptance criteria:

- No more than three 2-fold dilutions between highest and lowest PC titers

Data from this analysis are provided in the submission. Intra- and inter-assay acceptance criteria were met with an HPC titer range of 64 to 128 for all occasions. An MSR of 1.719 was calculated.

2.4.11 Stability: antibody

The positive control antibody at the LPC (150 ng/ml) and HPC (6250 ng/ml) levels was tested for stability under short term stability conditions at 4°C and up to six freeze-thaw cycles. For freeze-thaw cycles, stability samples were cycled between -80°C and room temperature for three and six times. For short term stability, samples were thawed at room temperature and then stored at 4°C for approximately 24 hours. Stability samples were also tested after storage at room temperature for approximately 24 hours.

Acceptance criteria for positive control antibody stability:

- Value of stability samples $\geq$ PSCP
- Titer of HPC within range defined in precision exercise (64 to 128)
- %Difference in ratios is within $\pm 25\%$ of one another at each PC level

Results are provided in the submission. All acceptance criteria were met. The LPC and HPC stability samples measured above cut-point after 3 and 6 freeze thaw cycles, and after short term storage at room temperature and 4°C. The HPC samples exhibited a titer range of 128 under all conditions, which is within the range described in titration precision exercises.

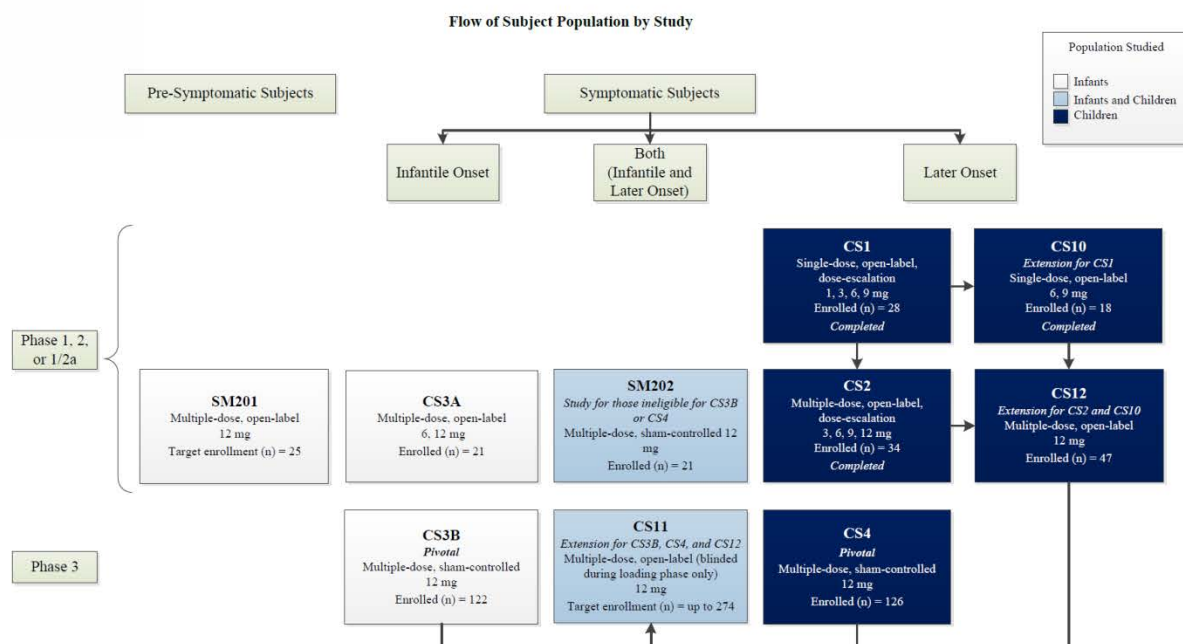
Reviewer comment:

The data support antibody stability under short term storage conditions and up to 6 cycles of freeze-thaw. Long term storage conditions were not tested directly; however, the sponsor references literature to support storage of antisera at -20°C for more than 1 year. Plasma samples are stored under deep freeze conditions at -80°C. Collectively, the provided information is reasonable to support stability of the PC antibody under long term storage conditions.

APPENDIX 1: Clinical studies overview

Figure 1⁷ below provides an overview of completed and ongoing clinical studies for development of ISIS 396443 at the time of submission.

Figure 1: Clinical Development Plan for ISIS 396443



- **Symptomatic SMA**

- Infantile-onset SMA
 - **ISIS 396443-CS3B (CS3B):** pivotal, multicenter, randomized, Phase 3, sham-controlled study in symptomatic subjects with infantile-onset SMA

⁷ Refer to NDA 209531, Section 2.5—Clinical Overview.

- **ISIS 396443-CS3A (CS3A)**: supportive, multicenter, Phase 2, open-label (uncontrolled) study in symptomatic subjects with infantile-onset SMA
- Later-onset SMA
 - **ISIS 396443-CS4 (CS4)**: pivotal, Phase 3, sham-controlled study in subjects with later-onset SMA
 - **ISIS 396443-CS1 (CS1)**: completed, Phase 1, first-in-human, single-dose, open-label dose-escalation study
 - **ISIS 396443-C10 (CS10)**: completed, multicenter, Phase 1, single-dose, open-label extension study for subjects who participated in Study CS1
 - **ISIS 396443-CS2 (CS2)**: completed, multicenter, Phase 1/2a, open-label, dose-escalation study, could include subjects who participated in CS1.
 - **ISIS 36443-CS12 (CS12)**: multicenter, Phase 1, open-label extension study in subjects who completed Studies CS2 or CS10
- Infantile- or later-onset SMA
 - **232SM202 (SM202)**: Phase 2, sham-controlled study in subjects with SMA not eligible to participate in Studies CS3B or CS4
 - **ISIS 396443-CS11 (CS11)**: open-label extension study for subjects with SMA who previously participated in investigational studies of ISIS 396443, including Studies CS12, CS3B, and CS4.
- **Presymptomatic SMA**
 - **232SM201 (SM201)**: supportive, multicenter, Phase 2, open-label study in subjects with genetically diagnosed, presymptomatic SMA

APPENDIX 2: Anti-ISIS 396443 antibody status

Table 1: Listing of Anti-ISIS396443 Antibody Status - Subject Treated with ISIS396443 or Sham Procedure Who had Confirmed ADA

Positive Results (1% False Positive Rate)
Page 1 of 3

Unique Subject ID	Time on Study (Day)	Study Sequence	Study	Dosing Cohort	Study Visit	Date/Time of Collection (Study Day)	Antibody Status	Titer
396443-CS2/1776-3201	1096	CS2-CS12	CS2	9 mg	Day 1	2013-04-08/8:35 (1)	NEGATIVE	1
					Day 8	2013-04-15/11:45 (8)	NEGATIVE	
					Day 85	2013-07-01/8:31 (85)	NEGATIVE	
					Day 169	2013-09-20/15:05 (166)	NEGATIVE	
			CS12	12 mg	Screening	2014-05-30/11:50 (418)	NEGATIVE	
					Day 85	2014-09-09/15:15 (520)	NEGATIVE	
					Day 169	2014-12-05/8:40 (607)	Positive	
					Day 351	2015-06-01/8:17 (785)	NEGATIVE	
			CS2	12 mg	Day 1	2014-03-26/8:40 (1)	NEGATIVE	
					Day 8	2014-04-02/10:07 (8)	NEGATIVE	
					Day 85	2014-06-17/9:55 (84)	NEGATIVE	
					Day 169	2014-09-17/11:32 (176)	NEGATIVE	
			CS12	12 mg	Screening	2015-02-04/12:01 (316)	Positive	4
					Day 85	2015-05-05/11:20 (406)	Positive	4

Note 1: Study day is in reference to the date of first ever dose.

2: Time on study (i.e., duration of exposure) is the number of days between the date of first ever dose and date of end of study (or for ongoing subjects the dataset cut-off date).

SOURCE: ISIS396443/ISS/FDA-REQ-21-NOV-2016/L-ANTIBODY-1PER.SAS

DATE: 28NOV2016

Listing of Anti-ISIS396443 Antibody Status - Subject Treated with ISIS396443 or Sham Procedure Who had Confirmed ADA
Positive Results (1% False Positive Rate)
Page 2 of 3

Unique Subject ID	Time on Study (Day)	Study Sequence	Study	Dosing Cohort	Study Visit	Date/Time of Collection (Study Day)	Antibody Status	Titer
396443-CS3A/1834-1301	994	CS3A	CS3A	6 mg	Day 1	2013-05-08/9:00 (1)	Negative	NA
					Day 85	2013-07-24/10:53 (78)	Negative	NA
					Day 169	2013-10-23/15:10 (169)	Negative	NA
					Day 253	2014-02-12/11:35 (281)	Positive	16
					Day 337	2014-04-11/12:35 (339)	Negative	NA

Note 1: Study day is in reference to the date of first ever dose.

2: Time on study (i.e., duration of exposure) is the number of days between the date of first ever dose and date of end of study (or for ongoing subjects the dataset cut-off date).

SOURCE: ISIS396443/ISS/FDA-REQ-21-NOV-2016/L-ANTIBODY-1PER.SAS

DATE: 28NOV2016

Listing of Anti-ISIS396443 Antibody Status – Subject Treated with ISIS396443 or Sham Procedure Who had Confirmed ADA Positive Results (1% False Positive Rate)
Page 3 of 3

Unique Subject ID	Time on Study (Day)	Study Sequence	Study	Dosing Cohort	Study Visit	Date/Time of Collection (Study Day)	Antibody Status	Titer
396443-CS3B/1778-5332	23	CS3B	CS3B	12 mg	DAY 1	2016-05-24/8:15 (1)	Positive	1
396443-CS3B/2000-5203	388	CS3B	CS3B	12 mg	DAY 1	2014-09-15/8:33 (1)	Negative	NA
					DAY 64	2014-12-16/8:08 (93)	Negative	NA
					DAY 183	2015-03-16/8:45 (183)	Positive	NA
					DAY 302	2015-07-13/10:47 (302)	Negative	NA
					DAY 394	2015-10-07/17:24 (388)	Negative	NA
396443-CS3B/2003-5201	235	CS3B	CS3B	0 mg	DAY 1	2015-06-17/9:30 (1)	Negative	NA
					DAY 64	2015-08-19/10:30 (64)	Negative	NA
					DAY 183	2015-12-16/12:42 (183)	Positive	NA
396443-CS3B/2006-5071	343	CS3B	CS3B	12 mg	DAY 1	2015-07-09/10:45 (1)	Negative	NA
					DAY 64	2015-09-10/11:35 (64)	Positive	8
					DAY 183	2016-01-28/11:45 (204)	Negative	NA
396443-CS3B/2007-5185	30	CS3B	CS3B	0 mg	DAY 1	2016-05-17/11:00 (1)	Positive	1

Note 1: Study day is in reference to the date of first ever dose.

2: Time on study (i.e., duration of exposure) is the number of days between the date of first ever dose and date of end of study (or for ongoing subjects the dataset cut-off date).

SOURCE: ISIS396443/ISS/FDA-REQ-21-NOV-2016/L-ANTIBODY-1PER.SAS

DATE: 28NOV2016

APPENDIX 3: ISIS 396443 levels in ADA positive patients

Table 6 Comparison of CSF and Plasma Concentrations of ISIS 396443 in Anti-ISIS396443 Antibody-Positive Patients to Group Mean CSF and Plasma ISIS 396443 Concentrations

Study	Patient	Dose	Day of Collection	Patient ISIS 396443 Concentration (ng/mL)	N	Group Mean $\pm$ SD ISIS 396443 Concentration (ng/mL) ^f
CSF						
ISIS 396443-CS12	1433	12 mg	169	2.57	38	2.85 $\pm$ 1.22 ^c
ISIS 396443-CS12	1447	12 mg	Predose	2.20	44	2.00 $\pm$ 1.83 ^d
ISIS 396443-CS3A	1301	6 mg eq. ^b	253	1.14	16	4.25 $\pm$ 3.87
Plasma						
ISIS 396443-CS12	1433	12 mg	169	0.154	41	0.205 $\pm$ 0.479
ISIS 396443-CS12	1447 ^a	12 mg	Predose	24.7	46	0.0512 $\pm$ 0.0956
ISIS 396443-CS12	1447	12 mg	85	25.4	46	0.519 $\pm$ 2.00
ISIS 396443-CS3A	1301	6 mg eq. ^b	253	BLQ ^e	16	0.377 $\pm$ 0.247

SD = Standard Deviation

^a CSF was not collected on Day 85 per protocol

^b Actual dose was adjusted based on patients age to be equivalent to 6 mg to account for differences in CSF volume. Dose level administered beginning on Day 253 and all subsequent days was 12 mg equivalent adjusted for patient's age to account for differences in CSF volume. See clinical study protocol for additional details (protocol ISIS 396443-CS3A)

^c Concentrations for Patients 1402 and 1404 removed from summary statistics as outliers

^d Concentrations for Patients 1404 and 1406 removed from summary statistics as outliers

^e Below the lower limit of quantification (0.05 ng/mL)

^f Concentrations for IM-positive patients were excluded from group mean calculations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICK J LYNCH
12/02/2016

Clinical Inspection Summary

Date	12/1/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, OSI, DCCE, GCPAB Susan Thompson, M.D., Team Leader, OSI, DCCE, GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI, DCCE, GCPAB
To	Fannie Choy, Regulatory Project Manager, DNP Rainer Paine, M.D., Medical Officer, DNP
NDA #	209531
Applicant	Biogen Inc.
Drug	Nusinersen
NME	Yes
Therapeutic Classification	Antisense oligonucleotide
Proposed Indication(s)	Treatment of spinal muscular atrophy
Consultation Request Date	10/13/2016
Summary Goal Date	12/5/2016
Action Goal Date	12/23/2016
PDUFA Date	5/23/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 209531, three clinical investigator sites were inspected. These inspections did not reveal significant regulatory violations. No Form FDA 483s were issued. Based on results of these clinical investigator inspections, it appears that the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies appear to have been conducted adequately.

All three of the clinical investigator inspections are preliminarily classified as No Action Indicated (NAI). Information contained in this summary is based on the Establishment Inspection Report (EIR) for one clinical investigator inspection (Chiriboga) and communication with the field investigators.

An addendum to this clinical inspection summary will be generated if conclusions change upon receipt and review of the EIRs.

II. BACKGROUND

Nusinersen (NDA 209531) is being developed for the treatment of spinal muscular atrophy (SMA). The sponsor has submitted results from two ongoing studies to support the safety and efficacy of nusinersen for the treatment of SMA. ISIS 396443 CS3A is a Phase 2, open-label supportive study in subjects with infantile-onset SMA. The pivotal study, ISIS 396443 CS3B, is a Phase 3, randomized, double-blind, sham-controlled study in subjects with infantile onset SMA.

Protocol ISIS 396443-CS3A

Title: A study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of nusinersen (ISIS 396443) delivered intrathecally to patients with infantile-onset spinal muscular atrophy

Subjects/Sites: 21 enrolled subjects in the United States (3 sites) and Canada (1 site)

Study Initiation: 5/8/2013 (date of first treatment)

Study Completion: 1/26/2016 (date of data cutoff)

This is an ongoing Phase 2 open-label study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of nusinersen administered as intrathecal injections by lumbar puncture to subjects with infantile-onset SMA. The primary efficacy endpoint was the proportion of subjects who achieved improvement in motor milestones based on Section 2 of the Hammersmith Infant Neurological Examination (HINE) at their last visit. Overall, thirteen out of twenty subjects (65%) met the primary efficacy endpoint as of the last evaluable study visit.

Protocol ISIS 396443-CS3B

Title: A Phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset spinal muscular atrophy

Subjects/Sites: 122 randomized subjects in North America (14 sites; 12 in United States and 2 in Canada), Western Europe (12 sites), Australia (2 sites), Middle East/Central Asia (1 site), Asia/Pacific (2 sites)

Study Initiation: 8/21/2014 (date of first treatment)

Study Completion: 6/15/2016 (date of data cut-off)

This is an ongoing Phase 3, multicenter, double-blind, randomized, sham-procedure controlled study. Primary efficacy endpoints were proportion of motor milestone responders (Section 2 of the HINE) and time to death or permanent ventilation. At a planned interim analysis, the sponsor reported a statistically significantly greater percentage of patients achieved a motor milestone response in nusinersen (41%) compared to the sham-control patients (0%, $p < 0.0001$). The sponsor decided to terminate the study early on the ground that conducting a sham-controlled study was no longer deemed ethical based on the interim analysis results.

Inspections of clinical sites were considered essential to verify the data submitted for this application. The review division targeted an action date of three months after receipt of the last part of this rolling NDA, the clinical module. Due to this timeline, clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site and were limited to domestic sites. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events, maintenance of the study blind, and verification of the primary and key secondary efficacy endpoints.

III. RESULTS (by site)

Site #, Name of CI, Address	Protocol # and # of Subjects	Inspection Date	Classification
Site #1776 Claudia Chiriboga, M.D. Columbia University Medical Center 180 Fort Washington Avenue Suite 552 New York, NY 10032-3791	ISIS 396443-CS3A Subjects: 4 ISIS 396443-CS3B Subjects: 9	11/1/2016 to 11/4/2016	No Action Indicated (NAI)*
Site #1833 Richard Finkel, M.D. Nemours Children's Hospital 13535 Nemours Parkway Orlando, FL 32827	ISIS 396443-CS3A Subjects: 9 ISIS 396443-CS3B Subjects: 4	11/9/2016 to 11/16/2016 (5 days)	No Action Indicated (NAI)*
Site #2000 Nancy Kuntz, M.D. Lurie Children's Hospital of Chicago 225 E. Chicago Avenue Chicago, IL 60611	ISIS 396443-CS3B Subjects: 12	10/28/2016 to 11/17/2016	No Action Indicated (NAI)*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Clinical Investigator: Claudia Chiriboga, M.D.; Site #1776; New York, NY

For Protocol ISIS 396443-CS3A, five subjects were screened, four subjects were enrolled, and no subjects have completed this ongoing study. For Protocol ISIS 396443-CS3B, nine subjects were screened, nine subjects were enrolled, two subjects discontinued due to death, and seven subjects completed the study. The two subjects who died during the study were included in the data listings. The two subjects who died during the study were included in the data listings with fatal adverse events noted as respiratory failure. For this inspection, a total of thirteen subject records were reviewed.

A Form FDA 483 was not issued. The field investigator noted three SAEs that were reported later than the protocol required. Per protocol, SAEs were to be reported to the sponsor within 24 hours of the center's first knowledge of the event. Three SAEs were reported days to weeks after the event:

For Subject 2301 (Protocol ISIS 396443-CS3A), the site was aware of the SAE "possible viral respiratory infection" on 11/26/2013 but the report was submitted on 12/3/2013, eight days after the event. The site stated that the subject was going to the ER and it therefore was considered an SAE on 12/3/2016.

For Subject 5042 (Protocol ISIS 396443-CS3B), the site was notified of the SAE "coronavirus" on 2/28/2016 and the report was submitted on 3/1/2016. The site stated that the subject had been admitted on 3/1/2016.

For Subject 5140 (Protocol ISIS 396443-CS3B), the site was notified of the SAE "brief oxygen desaturation" on 6/8/2015 and the report was submitted on 6/21/2016. The site explained that this event was originally reported as an AE but the monitor later requested that it be reported as an SAE.

The field noted one adverse event that was noted in the source document and eCRF, but not in the data listing. Restricted neck range of motion was noted on 6/13/16 for Subject #5202 (Protocol ISIS 396443-CS3B).

The primary efficacy endpoint data was verified for both protocols. There was no evidence of under reporting of adverse events at this site.

Reviewer comments: The site appeared to notify the sponsor more than 24 hours after the occurrence of an SAE in three of thirteen subjects. The late reporting occurred infrequently and, in the case of the brief oxygen desaturation event, the investigator did not think that the event was a SAE. All of these SAEs were reported to the sponsor and were included in the data listings. One adverse event (restricted neck range of motion) was noted in the source document and eCRF but was not included in data line listings. The sponsor did note "worsened plagiocephaly" occurring on the same date (6/13/16) which may be related to the event of restricted neck range of motion.

Based upon the summary data available, the study at Dr. Chiriboga's site appears to have

been conducted adequately and the data generated by this site appear acceptable in support of the indication.

2. Clinical Investigator: Richard Finkel, M.D.; Site #1833; Orlando, FL

For Protocol ISIS 396443-CS3A, ten subjects were screened, nine subjects were enrolled, four subjects discontinued due to death, and five subjects continue to participate in this ongoing study. The four subjects who died during the study were included in the data listings with fatal adverse events noted as cardiopulmonary arrest from accidental asphyxiation, respiratory failure (two subjects), and lower respiratory tract viral infection. For Protocol ISIS 396443-CS3B, five subjects were screened, four subjects were enrolled, and four subjects continue to participate in this ongoing study. For this inspection, all fifteen subject records were reviewed.

A Form FDA 483 was not issued. The field investigator noted one SAE that was reported later than required by protocol. Subject 5305, participating in ISIS 396443-CS3B, was hospitalized for acute respiratory distress. The subject was hospitalized for approximately two months. The clinical site received hospital records for this subject, but did not review them until approximately five months after they were received. During the hospitalization, the subject had experienced the SAE cardiac arrest, recovering the same day as this event, which was later reported to the sponsor.

The primary efficacy endpoint data was verified for both protocols. There was no evidence of under reporting of adverse events at this site.

Reviewer comments: Although reported late, all SAEs were reported to the sponsor and there was no evidence of under-reporting of AEs or SAEs. The finding was isolated.

Based upon the summary data available, the study at Dr. Finkel's site appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

3. Clinical Investigator: Nancy Kuntz, M.D.; Site #2000; Chicago, IL

For Protocol ISIS 396443-CS3B, thirteen subjects were screened, twelve subjects were enrolled, and seven subjects completed the study. For this inspection, all thirteen subject records were reviewed.

A Form FDA 483 was not issued. The primary efficacy endpoint data was verified for Protocol ISIS 396443-CS3B. There was no evidence of under reporting of adverse events at this site.

Based upon the summary data available, the study at Dr. Kuntz's site appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

CC:

Central Document Room/NDA #209531
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Nicholas Kozauer
DNP/Medical Officer/Rainer Paine
DNP /Project Manager/Fannie Choy
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/ Susan Thompson
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARA L ALFARO
12/01/2016

SUSAN D THOMPSON
12/01/2016

KASSA AYALEW
12/01/2016



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 30, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 209531** Nusinersen (Spiraza)
Indication: Treatment of Spinal Muscular Atrophy
Dosage: Intrathecal 12 mg; 4 Loading Doses followed by Maintenance
Doses every 4 Months
Applicant: (b) (4)
PDUFA Goal Date: December 23, 2016

Materials Reviewed:

NDA 209531
Global Submit Review 9/23/2016
Common Technical Document Summaries 2.2, 2.3, 2.4, 2.5, 2.6, 2.7
Clinical Study Reports 5.2, 5.3.5

Table of Contents

<u>I. SUMMARY</u>	3
<u>1. Background</u>	3
<u>2. Conclusions</u>	4
<u>3. Recommendations</u>	4
<u>II. DISCUSSION</u>	4
<u>1. Chemistry</u>	4
<u>1.1 Substance Information</u>	4
<u>2. Nonclinical Pharmacology</u>	5
<u>3. Clinical Pharmacology</u>	5
<u>3.1 Absorption, Distribution, Metabolism, Elimination (ADME)</u>	5
<u>4. Clinical Studies</u>	6
<u>4.1 Human Abuse Potential Studies</u>	6
<u>4.2 Safety Profile, Adverse Events</u>	6
<u>4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials</u>	8
<u>5. Regulatory Issues and Assessment</u>	8

I. SUMMARY

1. Background

Spinal muscular atrophy (SMA) results in atrophy of the voluntary muscles of the limbs and trunk. In most cases the cause of SMA is a deletion or mutation in the SMN1 gene located on chromosome 5q that result in a deficiency of survival motor neuron (SMN) protein and degeneration of the motor neurons in the anterior horn of the spinal cord. Although rare (prevalence ranging from 8.5 to 10.3 per 100,000 live births), SMA is the most common genetic cause of death in infants. A second gene, SMN2, located near SMN1, is responsible for a small amount of SMN protein production. The number of SMN2 copies that a patient has is the best known predictor of clinical phenotype. Infants with the worst form of SMA die within a few weeks of birth. Patients with all other forms of SMA are asymptomatic at birth. This asymptomatic phase lasts for a variable length of time, but is usually correlated with disease severity, with more severe disease associated with earlier symptom onset and less SMN protein production. Once patients develop symptoms of SMA they maintain or lose whatever motor function they may have developed. (The clinical phenotype of patients with SMA can vary significantly between patients who die soon after birth to patients who live into adulthood without symptoms.) Changes in the levels of SMN protein are not known to be involved in any other disease states.

Prior to the development of molecular medicine techniques which allow genotyping of both SMN1 and SMN2, SMA was diagnosed based on clinical presentation and categorized phenotypically based on the maximal motor milestone achieved and the age at symptom onset. This phenotypic classification requires subjects to be followed for enough time to determine whether a milestone will be achieved or not. A classification system based on age of symptom onset was used.

Type I SMA is the most common form of SMA and represents 58% of the birth prevalence.

Type II SMA represents approximately 29% of the birth prevalence.

Type III SMA represents approximately 13% of the birth prevalence.

Type IV SMA is the mildest form of SMA and represents <5% of the birth prevalence.

Antisense oligonucleotides (ASOs), including nusinersen, are short synthetic stretches of nucleotides designed to alter the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein. The therapeutic approach to treat SMA patients is based on increasing the protein produced from the SMN2 gene by modulating its mRNA splicing pattern. Nusinersen has been designed to bind to a specific sequence in the intron downstream of exon 7 in the SMN2 pre-mRNA, thus promoting the inclusion of exon 7 in the SMN2 mRNA transcript and thereby increasing the amount of full-length protein produced from the SMN2 gene.

Patients with only 1 copy of the SMN2 gene generally have the most severe form of SMA and generally do not survive long after birth; therefore, this population was not included in this clinical development program nor were patients with more than 4 copies of the SMN2 gene who have the least severe form of the disease and may not present with SMA symptoms until later in life.

The Applicant contends that no member of the ASO class is known to exhibit abuse potential and none are controlled substances or subject to special instructions for use, handling or disposal. The intrathecal (IT) route of administration is not likely to have a potential for abuse. The Applicant did address abuse potential related to the intravenous (IV) or subcutaneous (SC) routes of administration.

The clinical development program for nusinersen was designed after obtaining advice from the Division of Neurology Products (DNP). It is rolling submission and has been granted Orphan and Fast Track Designations.

2. Conclusions

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

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

3. Recommendations

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

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

II. Discussion

1. Chemistry

1.1 Substance Information

Nusinersen is a synthetic 2-*O*-(2-methoxyethyl) phosphorothioate antisense oligonucleotide, isolated as the heptadecasodium salt. The drug product is provided for IT administration as a

single use, sterile, isotonic solution containing no preservatives. It is a clear and colorless solution with sufficient fill to deliver a 5.0 mL volume.

2. Nonclinical Pharmacology

Genetic evidence suggests that SMA patients could benefit from increased SMN protein expression. Nusinersen increases the proportion of SMN2 mRNA that includes exon 7. Since ASOs can be used to alter the amount of exon inclusion, an extensive screen of hundreds of ASOs designed to bind around exon 7 of human SMN2 was completed. These studies identified a site in intron 7 approximately 10 nucleotides downstream from the intron/exon junction that promotes inclusion of exon 7 in SMN2 transcripts when targeted by ASOs.

In safety pharmacology studies, there were no pulmonary or cardiovascular effects in rats using continuous IT infusion for 25 days, or effects on ECG in the repeat-dose IT toxicology studies in monkeys. The only safety pharmacology effects observed were transient post-dose effects on lower spinal reflexes that were observed at the highest doses tested in monkeys (i.e., ≥ 3 mg). These effects did not progress with treatment. When given via the IV or SQ route in monkeys, nusinersen did not cross the BBB. Based on its specificity of binding to mRNA to modulate splicing of the SMN2 gene, the Applicant asserts that nusinersen will not bind to receptors known to be involved in drug abuse. In repeat-dose toxicology studies in monkeys there were no neurobehavioral changes and the animals appeared normal.

3. Clinical Pharmacology

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

IT injection of nusinersen into the cerebrospinal fluid (CSF) allows the drug to be fully available to the target CNS tissues without an initial absorption process and without crossing the BBB. It rapidly distributes throughout the CSF space with uptake into CNS tissues with little metabolic clearance in the CNS prior to eventual transfer into the systemic circulation via physiological CSF turnover. Plasma concentrations were relatively low compared to CSF concentrations (at least 100-fold less than CSF concentrations at every time point). Plasma C_{max} occurred 2 to 5 hours after IT dose administration. Distribution to the CNS was diffuse and included both spinal cord and brain. The highest CNS concentrations were observed in the lumbar spinal cord, consistent with the site of IT dose administration. CNS tissue half-lives of the drug (116 days) were much longer than in systemic tissues such as the liver (12 days).

4. Clinical Studies

4.1 Human Abuse Potential Studies

None were conducted.

4.2 Safety Profile, Adverse Events

The clinical safety of nusinersen has been studied in a randomized, controlled study and in open-label studies in a total of 173 subjects with presymptomatic infantile-onset and later-onset SMA. The overall exposure across the different clinical trials approximates 250 subject-years of exposure. Limited data are available in patients >18 years of age and data on long-term exposure are also limited.

There are no marketed IT-delivered ASOs, and no known class effects associated with this route of administration. Other ASOs, delivered by the SC or IV route that are on the market or in late-phase development are administered at higher doses and frequencies, have been associated with thrombocytopenia; this has not been seen with IT administration of nusinersen.

No acute toxicities and no treatment-limiting adverse drug reactions were observed. There were no treatment-related SAEs. In symptomatic infants and children with SMA, across different dosing regimens, the most common AEs reported were respiratory in nature. All reported events were consistent with those seen in the context of SMA. Presymptomatic infants had fewer AEs than symptomatic infants, suggesting that they had a healthier baseline condition. While no deaths were reported in subjects with presymptomatic SMA and later-onset SMA, there were several deaths during the studies in subjects with infantile-onset SMA. The causes of death in these infants were mostly respiratory in nature, considered to be consistent with the causes of death observed in infants diagnosed with Type I SMA.

AEs potentially associated with drugs of abuse are of limited value in these clinical trials as they involve infants and children with SMA. For this reason, AEs potentially associated with abuse potential were evaluated in patients with later-onset SMA and not in infants diagnosed with early-onset SMA. No abuse-related AEs were found in the reviewed clinical trials detailed in Table 1. Common AEs included headache, upper respiratory tract infections, post lumbar puncture syndrome, back pain, nasopharyngitis, fever, and vomiting.

Table 1: Clinical Studies Included in this Review

Study Type	Study ID	Objective	Design	Dosage	Pts. Enrolled, Completed	Patient Population	Duration Treatment
Safety, PK	ISIS 396443-CS1	Safety and tolerability of a single dose	Phase 1, open-label, single ascending dose; Uncontrolled	Cohort 1: 1 mg Cohort 2: 3 mg Cohort 3: 6 mg Cohort 4: 9 mg;	28 enrolled, completed Cohort 1: 6 Cohort 2: 6 Cohort 3: 6 Cohort 4: 10	2- to 14-year-old subjects with later-onset SMA	Single dose
Safety, PK	ISIS 396443-CS2	Safety and tolerability of multiple doses	Phase 1/2a, open-label, multiple ascending dose; Uncontrolled	Cohort 1: 3 mg Cohort 2: 6 mg Cohort 3: 9 mg Cohort 4: 12 mg Days 1, 29, and 85: Cohorts 1, 2 and 4 Days 1 and 85: Cohort 3 only	34 enrolled Cohort 1: 8 Cohort 2: 8 Cohort 3: 9 Cohort 4: 9 33 completed	2- to 15-year-old subjects with later-onset SMA	12 weeks
Safety, PK	ISIS 396443-CS10	Safety and tolerability of a single dose in subjects previously in Study CS1	Phase 1, open-label, single dose; extension study; Uncontrolled	6 or 9 mg	18 enrolled and completed 6 mg: 4 9 mg: 14	2- to 14-year-old subjects with later-onset SMA who completed Study CS1	Single dose
Safety, PK	ISIS 396443-CS12	Safety and tolerability of a single dose in subjects previously in Study CS2 or CS10.	Phase 1, open-label, multiple dose; extension study; Uncontrolled	12 mg Days 1, 169, 351, and 533	52 eligible; 47 enrolled and 23 completed as of 07 April 2016	3- to 17-year-old subjects with later-onset SMA who completed Study CS2 or CS10	18 months

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no drug accountability issues reported and no findings of abuse, misuse, or diversion in any clinical trial.

5. Regulatory Issues and Assessment

There is no nonclinical or clinical evidence to suggest that nusinersen (Spiraza) has abuse potential. Therefore, it should not be recommended for scheduling under the Controlled Substances Act.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN S RUSINOWITZ
11/30/2016

MICHAEL KLEIN
11/30/2016

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher**. **An application that does not meet all of these criteria is not eligible for a voucher.**

NDA 209531 Nusinersen	Review Division: DNP
Requirement	Meets? (yes/no)
For prevention or treatment of a <i>rare pediatric disease</i> ? (<i>OOPD makes determination</i>)	Yes – 10/21/2016
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	NME - Yes
FDA deems eligible for priority review?	Yes – Filing Meeting 10/24/2016
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	Yes
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	Yes
Does not seek approval for a different adult indication in the original rare pediatric disease product application?	Yes

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALTHEA CUFF
11/29/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 16, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209531
Product Name and Strength:	Spinraza (Nusinersen) Injection 2.4 mg/mL
Submission Date:	November 11, 2016
Applicant/Sponsor Name:	Biogen, Inc.
OSE RCM #:	2016-2354-1
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

On November 9, 2016, The Division of Neurology Products (DNP) submitted an information request (IR) to the Sponsor Biogen, Inc. on behalf of The Division of Medication Error Prevention and Analysis (DMEPA). Based on recommendations that we made during a previous label and labeling review^a, our request was for the Sponsor to consider using an expiration date format for their proposed Spinraza (nusinersen) injection carton labeling and container label in alignment with our current thinking^b or to alternatively clarify the intent to use a two digit number to identify the expiration month. On November 11, 2016, the Sponsor submitted a response the IR and DNP requested that we review their response and the revised carton

^a Morris, C. Container and Carton Labels and Labeling Review for Spinraza (nusinersen) (NDA 209531). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); November 14, 2016. 11 p. OSE RCM No.: 2016-2534.

^b Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. April 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf> Page 13. Lines 493-507.

labeling and container label for Spinraza (nusinersen) injection to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The revised carton labeling and container label for Spinraza (nusinersen) injection are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
11/16/2016

LOLITA G WHITE
11/16/2016

PRESCRIBING INFORMATION LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 14, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209531
Product Name and Strength:	Spinraza (Nusinersen) Injection 12 mg /5 ml (2.4 mg /ml)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biogen, Inc.
Submission Date:	September 23, 2016
OSE RCM #:	2016-2354
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

On September 23, 2016, Biogen, Inc. submitted Prescribing Information (PI) for Spinraza (nusinersen) sterile solution for intrathecal injection under NDA 209531. The Division of Neurology Products (DNP) requested that we review the submitted Prescribing Information (PI) labeling for areas of vulnerability that could lead to medication errors. Carton and container labeling and labels were previously submitted to the Agency for review; therefore, our review of the carton and container labeling and labels will be submitted under separate cover.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Spinraza (nusinersen) is a SMN2-directed antisense oligonucleotide pending approval for the treatment of spinal muscular atrophy (SMA). Spinraza (nusinersen) is a sterile, clear and colorless solution for intrathecal injection supplied as a 12 mg/5 mL (2.4 mg/mL) solution in a single-dose glass vial free of preservatives. Treatment should be initiated as early as possible after diagnosis of SMA as 4 loading doses on approximately (b) (4) followed by a maintenance dose once every 4 months. In patients (b) (4) the recommended dose is 12 mg (5 mL). (b) (4)

We reviewed the proposed PI as submitted by Biogen, Inc. on September 23, 2016 and noted the following sections of the PI that can be improved to reduce the risk for medication errors:

- A. Table 1 in the Full PI section 2.1 Dosing Information lacks clarity regarding the recommended dosing frequency. The column titles should clearly state the unit of time along with each corresponding value. In addition, the time to start maintenance dosing can be improved upon to decrease risk of dosing errors.

- B. The preparation statement in section 2.2 Important Administration Instructions lacks clarity for how to return the product to room temperature after the product has been refrigerated. The information can be clarified and key points can be more prominent to decrease risk of deteriorated drug.
- C. The administration statement 3 in section 2.2 Important Administration Instructions is inconsistently stated when compared to the carton labeling. To decrease confusion relating to proper storage of the product once the product is removed from the vial, we recommend these statements are in alignment.

We note the PI uses the terminology (b) (4) which is inconsistent with the Agency's current thinking. Additionally, we note the PI contains the statement (b) (4) " As presented, this statement is not prominently placed within the PI and inconsistent with the carton labeling. This information may be presently more prominently and improved upon to align with the recommended handling of this product. We defer to the Office of Pharmaceutical Quality (OPQ) to address these issues in their review.

We provide recommendations regarding these areas below in Section 4.1 in order to help minimize the potential for medication errors to occur with the use of the product.

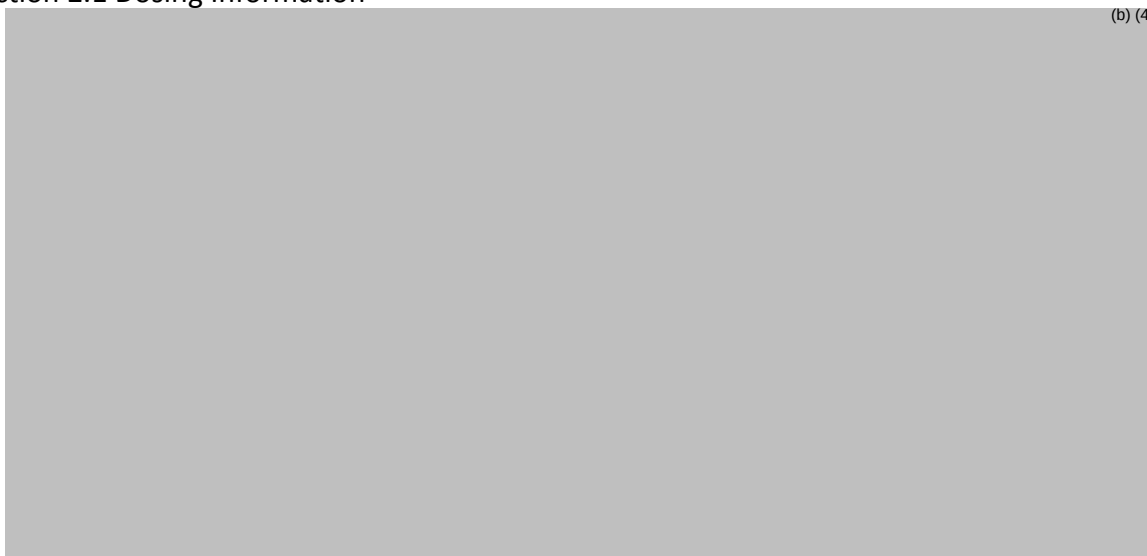
4 CONCLUSION & RECOMMENDATIONS

We identified areas of the PI labeling where additional important information should be added or information should be revised in order to help ensure the safe use of the product. We provide recommendations below in Section 4.1 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

We recommend the following are implemented prior to approval of this NDA:

- A. Section 2.1 Dosing Information



- B. Section 2.2 Important Administration Instructions

a. Preparation

- i. The storage of the product requires refrigeration and must be returned to room temperature prior to administration; however, the instructions are not clearly communicated and can be improved upon. As presented, Statement 1, (b) (4)

. We recommend the following:

1. The product should be stored under refrigeration in the carton and protected from light prior to use. Consider changing instructions to indicate this, such as “remove carton from fridge then remove the Spinraza vial and...” to decrease product deterioration or improper storage.
2. The PI states that the product should be returned to room temperature prior to use, however, the instructions do not indicate a timeframe. If it is known, clarify and add data suggesting how long it may take the solution to reach 25° C/77° F.
3. The product should not be warmed using an external heat source based on information in the PI, however, this statement is not prominently placed and may lead to deterioration of the drug product. To increase prominence of this statement. Consider making this statement its own bullet such as, “Do not use external heat sources to warm Spinraza vial.”

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION

Table 2 presents relevant product information for Spinraza (nusinersen) that Biogen, Inc. submitted on September 23, 2016.

Table 2. Relevant Product Information for Spinraza (nusinersen)									
Initial Approval Date	N/A								
Active Ingredient	Nusinersen (ISIS 396443)								
Indication	Treatment of patients with spinal muscular atrophy (SMA)								
Route of Administration	Intrathecal								
Dosage Form	Sterile Solution for Injection								
Strength	12 mg/5 ml (2.4 mg/ml)								
Dose and Frequency	(b) (4)								
How Supplied	SPINRAZA is a sterile, clear and colorless solution for intrathecal injection supplied as a 12mg/5mL (2.4mg/mL) solution in a (b) (4) glass vial free of preservatives								
Storage	- Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. - SPINRAZA should be protected from light and kept in the original carton until time of use. - If no refrigeration is available, SPINRAZA may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days. - Prior to administration, unopened vials of SPINRAZA can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours, at a temperature that does not exceed 25°C (77°F).								
Container Closure	<table> <tr> <th>Packaging Component</th><th>Description</th></tr> <tr> <td>Vial</td><td>(b) (4) Type I, clear glass</td></tr> <tr> <td>Stopper</td><td>20-mm, gray (b) (4) rubber stopper, (b) (4)</td></tr> <tr> <td>Overseal</td><td>20-mm, aluminum overseal with plastic cap (b) (4)</td></tr> </table>	Packaging Component	Description	Vial	(b) (4) Type I, clear glass	Stopper	20-mm, gray (b) (4) rubber stopper, (b) (4)	Overseal	20-mm, aluminum overseal with plastic cap (b) (4)
Packaging Component	Description								
Vial	(b) (4) Type I, clear glass								
Stopper	20-mm, gray (b) (4) rubber stopper, (b) (4)								
Overseal	20-mm, aluminum overseal with plastic cap (b) (4)								

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with post-market medication error data, we reviewed the following Spinraza (nusinersen) labeling submitted by Biogen, Inc. on September 23, 2016.

- Prescribing Information - No image

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
11/14/2016

LOLITA G WHITE
11/14/2016

CONTAINER AND CARTON LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 14, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209531
Product Name and Strength:	Spinraza (Nusinersen) Injection 12 mg /5 mL (2.4 mg /mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biogen, Inc.
Submission Date:	August 9, 2016
OSE RCM #:	2016-2354
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1. REASON FOR REVIEW

On August 9 and August 16, 2016 respectively, Biogen, Inc. submitted the proposed container label and carton labeling for Spinraza (nusinersen) sterile solution for intrathecal injection under NDA 209531. This product has received Fast Track, Orphan Drug, and Priority Review (expedited) designations for treatment for patients with Spinal Muscular Atrophy (SMA) and the Division of Neurology Products (DNP) accepted the Sponsor request for Rolling Submission.

DNP requested that we review the submitted container and carton labels and labeling for areas of vulnerability that could lead to medication errors. The Prescribing Information (PI) was submitted to the division September 23, 2016 and our review of the PI will be submitted under separate cover.

2. REGULATORY HISTORY

On August 31, 2016, we evaluated the carton labeling and container label as submitted by Biogen, Inc. and noted areas of the label and labeling that can be improved to reduce the risk for medication errors. The recommendations include increasing prominence and clarity of key terms to improve product identification and important information (e.g. lot number, expiration date, storage statement); and using standard language throughout the label and labeling.

Additionally, we noted that the carton labeling and container label use the terminology (b) (4) which is inconsistent with the Agency's current thinking. Also, we noted the carton label contains the statement (b) (4) As presented, this statement is confusing and may be improved upon to align with the recommended handling of this product. We defer to the Office of Pharmaceutical Quality (OPQ) to address these issues in their review.

On September 23, 2016, DMEPA sent recommendations for the carton labeling and container label to the sponsor electronically to expedite the review of this priority application. (Appendix F). On October 25, 2016 the Sponsor submitted revised carton labeling and container labels based on those recommendations.

3. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

4. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

On October 25, 2016 Biogen, Inc. submitted revised carton labels and container labeling to the agency in response to our September 23, 2016 electronically communicated recommendations. We note that all of our recommendations (Appendix F) were addressed or considered with the exception of the following two recommendations:

1. The recommendation to move the numeric code “49158-01” from the left to the right of the barcode on the container label to mitigate the possible confusion between the LOT/EXP and numeric code “49158-01” was mitigated instead by changing the orientation of the LOT/EXP from horizontal to vertical. We find this provides an increase in the white space between the text and decreases the risk for confusion due to proximity of the numeric code to the lot number and expiration date. As such, we find this mitigation acceptable.
2. The Sponsor proposes to use an expiration date format MM/YYYY instead of the previously recommended format similar to either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017) on the carton labeling. We are concerned the use of a two character month may lead to medication errors if letters are used in the format instead of numbers to represent the calendar month (e.g. MA for March can be confused for May, JU for June can be confused with July). We do not find this mitigation acceptable without further clarification.

5. CONCLUSION & RECOMMENDATIONS

The revised carton labeling and container label is unacceptable from a medication error perspective. The proposed expiration date format lacks clarity and may lead to medication error. We provide recommendations for Biogen, Inc. in Section 4.1. to clarify the expiration date format on the carton labeling and container label.

5.1. RECOMMENDATIONS FOR BIOGEN, INC.

- A. We recommend the following be clarified prior to approval of NDA 209531:
 1. Carton Labeling and Container Label

- i. The proposed format for the expiration month submitted by the sponsor lacks clarity. The proposed date format MM/YYYY may lead to confusion of expiration date if using letters to represent the months. (e.g. JU/2017 for June 2017 vs. JU/2017 for July 2017). To help minimize confusion relating to the month of expiration and reduce the risk for “deteriorated drug” medication errors relating to using the proposed month format, we recommend the following:

Use a format similar to either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017) to identify the expiration date for your product or alternatively clarify if you intend to use a two digit number to identify the expiration month (i.e. 06/2017 for June 2017).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION

Table 2 presents relevant product information for Spinraza (nusinersen) that Biogen, Inc. submitted on August 16, 2016.

Table 2. Relevant Product Information for Spinraza (nusinersen)									
Initial Approval Date	N/A								
Active Ingredient	Nusinersen (ISIS 396443)								
Indication	Treatment of patients with spinal muscular atrophy (SMA)								
Route of Administration	Intrathecal								
Dosage Form	Sterile Solution for Injection								
Strength	12 mg/5 ml (2.4 mg/ml)								
Dose and Frequency	(b) (4)								
How Supplied	SPINRAZA is a sterile, clear and colorless solution for intrathecal injection supplied as a 12mg/5mL (2.4mg/mL) solution in a (b) (4) glass vial free of preservatives								
Storage	- Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. - SPINRAZA should be protected from light and kept in the original carton until time of use. - If no refrigeration is available, SPINRAZA may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days. - Prior to administration, unopened vials of SPINRAZA can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours, at a temperature that does not exceed 25°C (77°F).								
Container Closure	<table> <tr> <th>Packaging Component</th><th>Description</th></tr> <tr> <td>Vial</td><td>(b) (4) Type I, clear glass</td></tr> <tr> <td>Stopper</td><td>20-mm, gray (b) (4) rubber stopper. (b) (4)</td></tr> <tr> <td>Overseal</td><td>20-mm, aluminum overseal with plastic cap (b) (4)</td></tr> </table>	Packaging Component	Description	Vial	(b) (4) Type I, clear glass	Stopper	20-mm, gray (b) (4) rubber stopper. (b) (4)	Overseal	20-mm, aluminum overseal with plastic cap (b) (4)
Packaging Component	Description								
Vial	(b) (4) Type I, clear glass								
Stopper	20-mm, gray (b) (4) rubber stopper. (b) (4)								
Overseal	20-mm, aluminum overseal with plastic cap (b) (4)								

APPENDIX F. CARTON LABEL AND CONTAINER LABEL RECOMMENDATIONS SENT ELECTRONICALLY TO THE SPONSOR ON SEPTEMBER 23, 2016

A. Carton Label

1. Principal Display Panel

- i. The language used to identify the recommended route of administration is not consistently presented between the container label and carton labeling which may be confusing and lead to the medication error “wrong route of administration.” For consistency with language used on the container label, we recommend you change the route of administration statement on the carton label (b) (4) to “For intrathecal use only.”
- ii. The lot number and expiration date is not prominently displayed. To improve visual contrast, ensure the prominence of essential information, and reduce the risk for “deteriorated drug” medication errors, change font color for the text “EXP” and “LOT” and associated numbers from pink to another contrasting color.
- iii. The format for the expiration date lacks clarity. Please identify the format for expressing the expiration date. To help minimize confusion and reduce the risk for “deteriorated drug” medication errors, we recommend that you use a format similar to one of the following: MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN012013).

2. Second Flap

- i. The phrase used to direct patients and health care providers how to find dosing information is inconsistently stated. To eliminate confusion we recommend that these statements follow standard language. For consistency with the terminology used in 21 CFR 201.56 , change the statement of dosage (b) (4) to “See prescribing information for dosing and administration.”
- ii. The information regarding recommended handling and storage as presented lacks clarity and prominence. To reduce the risk for medication errors related to the safe storage of Spinraza (nusinersen):
 1. Delete the statement (b) (4)
 2. Increase the font size or bolden the statement (b) (4).

B. Container Label

1. The route of administration statement lacks prominence and may be overlooked and lead to the medication error “wrong route of administration.” If space permits, we recommend you increase the font size and bolden the statement, “For intrathecal Use only.”

2. The product identifier on the container label is placed such that it takes away from the prominence of essential product information. To ensure prominence of the essential product information (e.g. lot number and expiration date) and to reduce the risk for “deteriorated drug” medication errors, we recommend you move the numeric code “49158-01” from the left of the barcode to the right of the barcode.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with post-market medication error data, we reviewed the following Spinraza (nusinersen) labels and labeling submitted by Biogen, Inc. on August 16, 2016.

- Carton labeling
- Container label

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
11/14/2016

LOLITA G WHITE
11/14/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 14, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Nicholas Kozauer, M.D., Medical Officer, DNP

Fannie Choy, RPh, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP comments on proposed carton and container labeling for
SPINRAZA (nusinersen) injection
NDA 209531

On September 27, 2016, DNP consulted OPDP to review the draft prescribing information (PI) and carton and container labeling for SPINRAZA (nusinersen) injection (Spinraza).

OPDP has reviewed the attached proposed carton and container labeling submitted to the electronic document room on October 25, 2016, and we do not have any comments.

OPDP labeling comments on the draft PI will be provided under a separate cover when the substantially completed PI is available.

If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALINE M MOUKHTARA
11/14/2016

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209531

Application Type: New NDA

Drug Name(s)/Dosage Form(s): SPINRAZA (nusinersen) sterile solution for injection, 2.4 mg/mL

Applicant: Biogen Inc.

Receipt Date: September 23, 2016

Goal Date: May 23, 2016

1. Regulatory History and Applicant's Main Proposals

The applicant submitted this original new drug application (NDA) for nusinersen for the treatment of spinal muscular atrophy (SMA) under Rolling Review. Nusinersen (ISIS 396443) was developed under IND 110011. Nusinersen is an antisense oligonucleotide administered intrathecally that binds to pre-mRNA to increase production of normal SMN protein.

The Agency granted orphan drug designation and fast track designation for nusinersen for the treatment of SMA on April 18, 2011, and November 29, 2011, respectively.

A Type C meeting was held between the applicant and the Division on September 15, 2015. At the meeting, the applicant presented the results of Study CS3A, a Phase 2, open-label, historical control trial in infants with Type 1 SMA, as the potential basis for an NDA submission. The Division noted that a possible way to support the Phase 2 data would be to conduct an interim analysis (IA) of the ongoing Phase 3 trial in infants with Type 1 SMA (CS3B). Subsequently, the Division worked with the applicant to develop the IA plan. The result of the IA for Study CS3B was shared with the Division on July 30, 2016, and the applicant informed DNP of its intent to file an NDA.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review. ADL noted that the omission of sections 5 and 17 will be further discussed with the review team.

All SRPI format deficiencies of the PI has been conveyed to the applicant in an advice letter. The applicant has been asked to correct these deficiencies and the PI in Word format was received on October 21, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: *HL is not in two-column format (Word version).*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment:
- YES** 3. A horizontal line must separate:
• HL from the Table of Contents (TOC), **and**
• TOC from the Full Prescribing Information (FPI).
Comment:
- NO** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.
Comment: *Note that each horizontal line should extend over the entire width of the column when converted to the 2-column format.*
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.
Comment:
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment:
- NO** 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: The heading *Warnings and Precautions* is not required by regulation, but should be present. The heading *Patient Counseling Information Statement* is required.

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.
Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.
Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.
Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- NO** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment: Note that Patient Counseling Information Statement is required in HL. If your product does not have FDA-approved patient labeling, include the statement “See 17 for PATIENT COUNSELING INFORMATION”.

Revision Date in Highlights

- NO** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: The revision date should be right justified.

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Patient Counseling Information Section of Labeling is missing.*

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
10/24/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209531 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: SPINRAZA Established/Proper Name: Nusinersen Dosage Form: Sterile solution for intrathecal injection Strengths: 2.4 mg/mL		
Applicant: Biogen, Inc. Agent for Applicant (if applicable):		
Date of Application: September 23, 2016 Date of Receipt: September 23, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: May 23, 2017		Action Goal Date (if different): December 23, 2016
Filing Date: November 22, 2016		Date of Filing Meeting: October 17, 2016
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of spinal muscular atrophy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: <i>The application will be a priority review if:</i> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ No <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
---	--

Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): **IND 110011**

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☐	☒	
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐	☒	
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> N/A ☐ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>		☐	☒		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:																																			
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☐	✓																															
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☐	✓																															
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>		☐	☐	✓																															
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>		Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☐	✓															
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																																
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> <table border="1"> <thead> <tr> <th>Exclusivity</th> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</td> <td>☐</td> <td>☒</td> <td></td> <td></td> </tr> <tr> <td>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</td> <td>☐</td> <td>☐</td> <td>☒</td> <td></td> </tr> <tr> <td>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</td> <td>☒</td> <td>☐</td> <td>☐</td> <td></td> </tr> <tr> <td>If yes, # years requested: 5 years</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td colspan="5">Note: An applicant can receive exclusivity without requesting it;</td> </tr> </tbody> </table>						Exclusivity	YES	NO	NA	Comment	Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒			If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒		NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐		If yes , # years requested: 5 years					Note: An applicant can receive exclusivity without requesting it;				
Exclusivity	YES	NO	NA	Comment																															
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒																																	
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																																
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐																																
If yes , # years requested: 5 years																																			
Note: An applicant can receive exclusivity without requesting it;																																			

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible	☐	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <u>paper</u> forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	Electronic submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff: August 25, 2016</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	CSS consulted on Aug 25, 2016. Noted in Clinical Filing Review: Abuse studies are not clinically relevant for intrathecal treatment of SMA infants.
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☐	☒		Orphan designation – exempt from PREA

²

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMatern>

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☐	☒	☐	Request submitted on Oct 1, 2016.
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

alHealthStaff/ucm027829.htm

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	No data to inform the drug-associated risk.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	OPDP consult: 9/27/16
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☐	☒	None requested by the review team at this time.
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): Type B (Guidance/EOP2) 1/24/2013	☒	☐		Type C Guidance: 9/15/2015 CMC-Type C WRO: 4/17/15
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☒		
Any Special Protocol Assessments (SPAs)? Date(s): 6/12/2014	☒			ISIS 396443-CS3B

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 17, 2016

BACKGROUND: NDA 209531

SPINRAZA (nusinersen) sterile solution for intrathecal injection, 2.4 mg/mL

The applicant submitted this original new drug application (NDA) for nusinersen for the treatment of spinal muscular atrophy (SMA) under Rolling Review. Nusinersen (ISIS 396443) was developed under IND 110011. Nusinersen is an antisense oligonucleotide administered intrathecally that binds to pre-mRNA to increase production of normal SMN protein.

The Agency granted orphan drug designation and fast track designation for nusinersen for the treatment of SMA on April 18, 2011, and November 29, 2011, respectively.

A Type C meeting was held between the applicant and the Division on September 15, 2015. At the meeting, the applicant presented the results of Study CS3A, a Phase 2, open-label, historical control trial in infants with Type 1 SMA, as the potential basis for an NDA submission. The Division noted that a possible way to support the Phase 2 data would be to conduct an interim analysis (IA) of the ongoing Phase 3 trial in infants with Type 1 SMA (CS3B). Subsequently, the Division worked with the applicant to develop the IA plan. The result of the IA for Study CS3B was shared with the Division on July 30, 2016, and the applicant informed DNP of its intent to file an NDA. A teleconference was held on August 4, 2016, the Division indicated that the findings appeared sufficiently positive, on face, to support the filing of an NDA.

CMC Type C WRO was issued on April 17, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fannie (Yuet) Choy	Y
	CPMS/TL:	Jacqueline Ware	Y
Cross-Discipline Team Leader (CDTL)	Nicholas Kozauer		Y
Division Director/Deputy	Billy Dunn/ Deputy - Eric Bastings		Y / Y
Office Director/Deputy	Ellis Unger/ Deputy – Robert Temple		Y / Y
Clinical	Reviewer:	Rainer Paine	Y

	TL:	Nicholas Kozauer	Y
Clinical Safety	Reviewer:	Evelyn Mentari	Y
	TL:	Sally Yasuda	Y
Clinical Pharmacology	Reviewer:	Hobart Rogers	Y
	TL:	Sreedharan Sabarinath	Y
• Genomics	Reviewer:	Hobart Rogers	Y
	TL:	Christian Grimstein	Y
• Pharmacometrics	Reviewer:	Atul Bhattaram	Y
	TL:	Kevin Krudys	Y
Biostatistics	Reviewer:	Tristan Massie	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	J. Ed Fisher	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Product Quality (CMC) Review Team:	ATL:	Wendy Wilson	Y
	RBPM:	Dahlia Woody	Y
• Drug Substance	Reviewer:	Monica Cooper	N
• Drug Product	Reviewer:	Mariappan Chelliah	Y
• Process	Reviewer:	Erin Kim	N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Aditi Thakur	N
• Biopharmaceutics	Reviewer:	Gerlie Gieser	N
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Neuro Lead:	Martha Heimann	N
DNP / Labeling	ADL: Tracy Peters		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Aline Moukhtara	Y

	TL:	Mathilda Fienkeng	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Chad (John) Morris	Y
	TL:	Lolita White	Y
(REMS)	Reviewer:	Robert Pratt	Y
	TL:	Jamie Wilkins Parker	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	Martin Rusinowitz	Y
	TL:		
Other reviewers/disciplines			
OSE/DPV	Reviewer:	Charlene Flowers	Y
	TL:		
Other attendees	DNP / RPM: Laurie Kelley		Y
	OSE / Safety PM: Corwin Howard		Y
	OSE / Safety PM: Ruth Maduro		Y
	OSE / DEPI: Lockwood Taylor		Y
	OSE / DPV: David Croteau		Y
	COA: Elektra Papadopoulos		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
---	---

Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES Consult request: 10/13/16 ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: the clinical study design was acceptable. As noted in Clinical Filing Review, Phase 2 study CS3A and interim analysis of Phase 3 study CS3B previously agreed with FDA.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO

CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested?	☒ YES ☐ NO

If no, was a complete EA submitted? Comments:	☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	N/A ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) - Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? - If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO Did not hold a pre-submission meeting ☐ YES ☐ NO N/A
What late submission components, if any, arrived after 30 days?	N/A
Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger, M.D. Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Oct 27, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review (DNP is considering to act early on this application under expedited review)
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74

☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
10/24/2016