APPLICATION NUMBER:

209531Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 209531 SUPPL # HFD #

Trade Name  SPINRAZA
Generic Name  Nusinersen
Applicant Name  Biogen, Inc.
Approval Date, If Known  December 23, 2016

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  YES ☒  NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety?  (If it required review only of bioavailability or bioequivalence data, answer "no.")  YES ☒  NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A
c) Did the applicant request exclusivity?  

YES ☑  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?  

YES ☐  NO ☑

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  

YES ☐  NO ☑

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐  NO ☑

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A – not a combination product

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference
to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES □   NO □

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES □   NO □

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES □   NO □

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES □   NO □

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?
If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no." )

Investigation #1 YES □ NO □
Investigation #2 YES □ NO □

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES □ NO □
If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES □ ! NO □ !

! Explain:

Investigation #2

IND #

YES □ ! NO □ !

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
Investigation #1

YES □ ! NO □
Explain: ! Explain:

Investigation #2

YES □ ! NO □
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES □ ! NO □

If yes, explain:
Name of person completing form: Fannie (Yuet) Choy
Title: Regulatory Project Manager, Division of Neurology Products
Date: December 23, 2016

Name of Division Director signing form: Billy Dunn, M.D.
Title: Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
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
12/23/2016

WILLIAM H Dunn
12/23/2016
### ACTION PACKAGE CHECKLIST

#### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
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<tbody>
<tr>
<td>209531</td>
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</table>

Proprietary Name: SPINRAZA  
Established/Proper Name: nusinersen  
Dosage Form: Injection for intrathecal use  
RPM: Fannie Choy  
Division: Neurology Products

<table>
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<tr>
<td>Efficacy Supplement:</td>
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<td>351(a)</td>
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</table>

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

- No changes
- New patent/exclusivity (notify CDER OND IO)
  Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

#### Actions

- Proposed action  
- User Fee Goal Date is May 23, 2017  
- Previous actions (specify type and date for each action taken)  

- If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?  
  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ________

- Received  
  N/A

#### Application Characteristics

1 The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

2 For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.
Review priority:  □ Standard  □ Priority  
Chemical classification (new NDAs only):  NME 
(confirm chemical classification at time of approval)

- □ Fast Track
- □ Rolling Review
- □ Orphan drug designation
- □ Breakthrough Therapy designation

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; 
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

NDAs: Subpart H
- □ Accelerated approval (21 CFR 314.510)
- □ Restricted distribution (21 CFR 314.520)
- □ Approval based on animal studies

- □ Submitted in response to a PMR
- □ Submitted in response to a PMC
- □ Submitted in response to a Pediatric Written Request

BLAs: Subpart E
- □ Accelerated approval (21 CFR 601.41)
- □ Restricted distribution (21 CFR 601.42)
- □ Approval based on animal studies

REMS: □ MedGuide
- □ Communication Plan
- □ ETASU
- □ MedGuide w/o REMS
- □ REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2  
(approvals only) □ Yes □ No □ N/A

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action □ Yes □ No
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? □ No □ Yes
  - If so, specify the type

- Patent Information (NDAs only)
  - Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.

- CONTENTS OF ACTION PACKAGE

  Officer/Employee List
  - List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) □ Included
  - Documentation of consent/non-consent by officers/employees □ Included
# Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  
  Action(s) and date(s)
  Approval: 12/23/16

## Labeling

- Package Insert *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included 9/23/16

- Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*
  - Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included - N/A
  - Original applicant-proposed labeling
    - Included - N/A

- Labels *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most-recent draft labeling
    - Included 10/25/16

- Proprietary Name
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
    - Conditionally Acceptable: 11/8/16
    - Review: 11/2/16

## Administrative / Regulatory Documents

- RPM Filing Review*/Memo of Filing Meeting *(indicate date of each review)*
  - RPM: #10/24/16
  - DMEPA: #1 & #2: 11/14/16
  - #3: 11/16/16
  - DMPP/PLT (DRISK):
    - None
  - OPDP: #1: 11/14/16
    - #2: 12/21/16
  - SEALD: None
  - CSS: None
  - Product Quality: None
  - Other: None

- NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Completed (not included)

- Application Integrity Policy (AIP) Status and Related Documents
  - Applicant is on the AIP
    - Yes
    - No

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4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- This application is on the AIP
  - If yes, Center Director’s Exception for Review memo (indicate date)
  - If yes, OC clearance for approval (indicate date of clearance communication)
  □ Yes  □ No
  □ Not an AP action

- Pediatrics (approvals only)
  - Date reviewed by PeRC: N/A
    - If PeRC review not necessary, explain:
      - Orphan Designation, Exempt from PREA requirements
    N/A

- Breakthrough Therapy Designation
  □ N/A

- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)

- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)

- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)
  (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

- Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)
  Included

- Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)
  Administrative Reviews

- Minutes of Meetings
  - If not the first review cycle, any end-of-review meeting (indicate date of mtg)
    □ N/A or no mtg
  - Pre-NDA/BLA meeting (indicate date of mtg)
    □ No mtg
  - EOP2 meeting (indicate date of mtg)
    □ No mtg
  - Mid-cycle Communication (indicate date of mtg)
    □ 10/31/16
  - Late-cycle Meeting (indicate date of mtg)
    □ 11/17/16
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)
    CMC Guidance: 4/17/15
    Guidance: 9/15/15
  - Advisory Committee Meeting(s)
    □ No AC meeting
  - Date(s) of Meeting(s)

**Decisional and Summary Memos**

- Office Director Decisional Memo (indicate date for each review)
  □ 12/23/16

- Division Director Summary Review (indicate date for each review)
  □ 12/23/16

- Cross-Discipline Team Leader Review (indicate date for each review)
  □ 12/12/16

- PMR/PMC Development Templates (indicate total number)
  □ 12/22/16

Clinical
<table>
<thead>
<tr>
<th>Clinical Reviews</th>
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<tbody>
<tr>
<td>- Clinical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>Clinical Safety TL 12/15/16</td>
<td>Clinical Efficacy: 12/14/16 Clinical Safety: 12/14/16</td>
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<tr>
<td>- Clinical review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td>- Social scientist review(s) *(if OTC drug) <em>(indicate date for each review)</em></td>
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<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>See Clinical Efficacy Review, Section 13.2</td>
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<tr>
<td>If no financial disclosure information was required, check here □ and include a review/memo explaining why not <em>(indicate date of review/memo)</em></td>
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<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers <em>(indicate date of each review)</em></td>
<td>Immunogenicity: 12/2/16 Q1-IRT: 12/8/16</td>
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<td>Controlled Substance Staff review(s) and Scheduling Recommendation <em>(indicate date of each review)</em></td>
<td>11/30/16</td>
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<tr>
<td>Risk Management</td>
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<td>- REMS Documents and REMS Supporting Document <em>(indicate date(s) of submission(s))</em></td>
<td>No REMS</td>
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<td>- REMS Memo(s) and letter(s) <em>(indicate date(s))</em></td>
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<td>- Risk management review(s) and recommendations (including those by OSE and CSS) <em>(indicate date of each review and indicate location/date if incorporated into another review)</em></td>
<td>DRISK review: 12/13/16</td>
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<tr>
<td>OSI Clinical Inspection Review Summary(ies) <em>(include copies of OSI letters to investigators)</em></td>
<td>12/1/16</td>
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**Clinical Microbiology**

| Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | No separate review *(See OPQ overall assessment)* |
| Clinical Microbiology Review(s) *(indicate date for each review)* | None |

**Biostatistics**

| Statistical Division Director Review(s) *(indicate date for each review)* | No separate review |
| Statistical Team Leader Review(s) *(indicate date for each review)* | No separate review |
| Statistical Review(s) *(indicate date for each review)* | 11/30/16 |

**Clinical Pharmacology**

| Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | No separate review |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | No separate review |
| Clinical Pharmacology review(s) *(indicate date for each review)* | 11/30/16 |
| OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | None requested |

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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive *(for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).*
### Nonclinical

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<thead>
<tr>
<th>Discipline/Review</th>
<th>Date/Details</th>
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<tr>
<td>ADP/T Review(s)</td>
<td>12/22/16</td>
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<tr>
<td>Supervisory Review(s)</td>
<td>12/20/16</td>
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<tr>
<td>Pharm/tox review(s), including referenced IND reviews</td>
<td>12/20/16</td>
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<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer</td>
<td>None</td>
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<td>Statistical review(s) of carcinogenicity studies</td>
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<td>ECAC/CAC report/memo of meeting</td>
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<tr>
<td>OSI Nonclinical Inspection Review Summary (include copies of OSI letters)</td>
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### Product Quality

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<th>Date/Details</th>
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<tr>
<td>Tertiary review</td>
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<td>Secondary review (e.g., Branch Chief)</td>
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<td>Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline)</td>
<td>Overall Assessment: 12/1/16 Final Memo: 12/15/16</td>
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<td>Reviews by other disciplines/divisions/Centers requested by product quality review team</td>
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<td>Environmental Assessment (check one) (original and supplemental applications)</td>
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<td>Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</td>
<td>11/23/16: See Quality assessment, Environmental Analysis section</td>
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<td>Review &amp; Environmental Impact Statement (indicate date of each review)</td>
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<td>Facilities Review/Inspection</td>
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<td>Re-evaluation date:</td>
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<td>Withhold recommendation</td>
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<tr>
<td>Not applicable</td>
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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
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<tbody>
<tr>
<td>✗ For all 505(b)(2) applications:</td>
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<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>□ No changes</td>
</tr>
<tr>
<td>□ New patent/exclusivity <em>(Notify CDER OND IO)</em></td>
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<tr>
<td>N/A</td>
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<tr>
<td>✗ Finalize 505(b)(2) assessment</td>
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<td>✗ For Breakthrough Therapy (BT) Designated drugs:</td>
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<tr>
<td>• Notify the CDER BT Program Manager</td>
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<tr>
<td>□ Done N/A</td>
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<td><em>(Send email to CDER OND IO)</em></td>
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<tr>
<td>✗ For products that need to be added to the flush list (generally opioids): Flush List</td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
</tr>
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<td>□ Done</td>
</tr>
<tr>
<td>N/A</td>
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<tr>
<td>✗ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
</tr>
<tr>
<td>✗ Done</td>
</tr>
<tr>
<td>✗ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
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<td>✗ Done</td>
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<tr>
<td>✗ Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
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<tr>
<td>✗ Done</td>
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<tr>
<td>✗ Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>✗ Done</td>
</tr>
<tr>
<td>✗ Send approval email within one business day to CDER-APPROVALS</td>
</tr>
<tr>
<td>✗ Done</td>
</tr>
</tbody>
</table>
Hi Fannie,

Attached are the proposed milestone dates for the PMRs. We plan to submit the identical response to the NDA via the Gateway tonight.

Thank you,

Heather

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

The Division has revised the language and milestone dates for the carcinogenicity postmarketing requirement (PMR). Additionally, we have identified an additional PMR.

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

<table>
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<tr>
<td>Final protocol submission</td>
<td>10/31/17</td>
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<tr>
<td>Study completion</td>
<td>12/28/19</td>
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<tr>
<td>Final report submission</td>
<td>5/31/20</td>
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A pre- and postnatal development (including maternal function) study of nusinersen in rodent.

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<td>DD/MM/YY</td>
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<tr>
<td>Final report submission</td>
<td>DD/MM/YY</td>
</tr>
</tbody>
</table>

We request this information by December 13, 2016.

-----------------------------------------------------------------------------------------------
Kindly confirm receipt of email and let me know if you have any questions.

Reference ID: 4033334
Regards,
Fannie

**Fannie Choy, RPh**
*Regulatory Project Manager*

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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December 13, 2016

William Dunn, M.D., Director
c/o: Fannie Choy, RPh. - Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE:  NDA 209531: PMR Milestone Dates
SPINRAZATM (nusinersen); ISIS 39443: Spinal Muscular Atrophy
Serial No.: 0049

Dear Dr. Dunn,

Reference is made to the PMRs received December 12, 2016. The requested milestone dates have been provided below.

- **PMR 1**: A two-year carcinogenicity study in one rodent species (CD-1 mice) with subcutaneous administration of nusinersen.
  
  Milestone dates:
  
  Final protocol submission: Oct 31, 2017
  Study completion: December 28, 2020
  Final report submission: March 31, 2021

- **PMR 2**: A pre- and postnatal development (including maternal function) study of nusinersen in rodent.
  
  Milestone dates:
  
  Final protocol submission: Study is complete
  Study completion: Study is complete
  Final report submission: 01/31/17

The study to assess pre- and postnatal development (including maternal function) of nusinersen via subcutaneous administration in CD-1 mice has recently completed. The final study report will be submitted by January 31, 2017.

If you have any questions regarding this submission, please do not hesitate to contact me or Heather Faulds, Senior Director, Regulatory Affairs at (617) 914-7775. The contact for technical aspects for this submission is Michelle Petty, Associate Director, Regulatory Affairs Operations at (617) 679-2893.

Sincerely yours,
Trevor Mill
Senior Vice President, Regulatory Affairs
Biogen
Telephone: 617-914-4143
Fax: 617-679-4459
Email: Regulatory@biogen.com
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/s/

YUET L CHOY
12/23/2016
Dear Tammy,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

In the proposed label revisions, there is a proposal to update the % of patients with Upper respiratory infection in Table 2 based on internal analyses. Please send datasets with:

1. Listings of each AE included in the internal analysis (using lines selected from Summary of Clinical Safety dataset ADAE)
2. A dataset (with the universal subject ID and treatment assignment) listing each patient counted as having an upper respiratory infection in the internal analyses

Please provide this information by 3:30 PM today.

Kindly confirm receipt of this request.

Regards,

Fannie
Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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Reference ID: 4033344
Dear Tammy,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016. We have the following comments in advance of today’s labeling discussion. The comments are intended to provide the context for what we included in the label.

The WARNINGS AND PRECAUTIONS section of the prescribing information (PI) is intended to convey potential safety hazards that are serious or otherwise clinically significant because they have implications for prescribing decisions and/or patient management. The selected events for the Spinraza PI fulfill these criteria and are therefore important to convey in Section 5.

The CLINICAL STUDIES section of the (PI) is intended to convey information from adequate and well-controlled trials that support the effectiveness of a product. With respect to Study CS3B, only the analysis of the primary endpoint at the interim analysis had any alpha allocated to it. The descriptive results from the analysis of the CHOP-INTEND were tentatively included in labeling, based largely on the size of the effect. We are still considering the appropriateness of this description. However, a description of survival benefit would need to be supported by a statistically significant finding.

The data from the additional uncontrolled trials included in the application were able to provide context for our review of your proposed claim for the treatment of all patients with SMA.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov
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/s/

YUET L CHOY
12/23/2016
at the request of Dr. Nick Kozauer, DNP Clinical TL
Dear Fannie,

We have accepted all of the changes and as agreed with Dr. Dunn changed the 23 to 26. No other additional changes were made.

Please confirm receipt.

Regards,
Tammy

Tammy Phinney  Vice President, US Regulatory Sciences
Biogen | 133 Boston Post Road, Weston MA 02493 | Email: tammy.phinney@biogen.com
Office: (781) 464 5687 | Cell: [redacted]
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/s/

YUET L CHOY
12/23/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

The Division has revised the language and milestone dates for the carcinogenicity postmarketing requirement (PMR). Additionally, we have identified an additional PMR.

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

- Final protocol submission: 10/31/17
- Study completion: 12/28/19
- Final report submission: 5/31/20

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

- Final protocol submission: DD/MM/YY
- Study completion: DD/MM/YY
- Final report submission: DD/MM/YY

We request this information by December 13, 2016.

-----------------------------------------------------------------------------------------------

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

Reference ID: 4026663
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/s/

YUET L CHOY
12/12/2016
Heather

The Division has the following comment regarding nusinersen:

To further characterize any effect of nusinersen on the QT interval, we request that you incorporate high quality 12-lead ECGS (replicate, digital ECGs) into ongoing and future studies. Any QTc measurement greater than 500 ms should be repeated.

Please confirm receipt.

Regards,
Laurie
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/s/

Laurie A Kelley
12/08/2016
Heather,

The Division has identified the following PMRs for NDA 209531. Please provide the milestone dates for each. Please provide your response by December 9, 2016.

Fannie is currently out of the office, but will return tomorrow. Please provide email your response to her (cc me).

Regards,
Laurie

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

Milestone dates:
- Final Protocol Submission
- Study Completion
- Final Report Submission

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.

Milestone dates:
- Final Report Submission
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/s/

LAURIE A KELLEY
12/08/2016
Hi Nicole,

As discussed, below are the comments we discussed on our call today.

1. The currently approved drug product carton label does not meet the USP salt policy requirement for the expression of the active ingredient's strength. Please refer to USP General Chapter <7> LABELING -- Amount of Active Moiety and/or Drug Substance per Dosage Unit. We ask that, before your next printing of the carton labels,

   You may submit your edited draft label as a CBE labeling supplement.

2. Based on the review of the data provided and in accordance with ICH Q1E, we grant a 4-month re-test period for the drug substance when stored and a 30-month drug product expiration period when stored refrigerated in the commercial packaging.

Thank you,
d.

Dahila A. Woody, M.S., PMP, FAC-P/PM
Sr. Regulatory Business Process Manager
Office of Program and Regulatory Operations | Office of Pharmaceutical Quality
Center for Drug Evaluation and Research | U.S. Food and Drug Administration
10903 New Hampshire Ave | Bldg 77 Rm. 4658 | Silver Spring, MD 20993
01301-796.0427 | dahila.woody@fda.hhs.gov
Hi Fannie,

I can confirm receipt.

Thanks,

Heather

Sent from my iPhone

On Dec 6, 2016, at 5:09 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016. We also refer to your December 5th email in response to our December 2nd request for information. We have the following request for clarification.

Please provide the current numbers of patients who died from Studies 201, CS3A, and CS3B, their ages of death, and nusinersen treatment duration. We request this information by COB on Wednesday 12/7/16.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

Hi Fannie,

Attached is the response to the IR described below. We plan to submit the identical
response to the NDA via the Gateway tonight.

Thanks,

Heather

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, December 02, 2016 3:22 PM
To: Heather Faulds
Cc: Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 209531
Importance: High

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

Please provide updated information on the current ages, or age at time of death, of patients enrolled in Studies 201, CS3A, and CS3B. This information can be presented by age-ranges (e.g., 0-6 months, 6-12 months, etc.). The duration of nusinersen treatment in these patients should also be provided in a similar manner. We ask for this response by the close of business on Monday, December 5th.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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Hi Fannie,

I can confirm receipt.

Thanks,

Heather

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, December 06, 2016 4:32 PM
To: Heather Faulds
Cc: Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 209531
Importance: High

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

We request this information by close of business on Wednesday December 7, 2016.

Please provide the age range at Baseline of subjects enrolled in the CS4 trial, including a rough breakdown of how they were distributed. Please also provide a similar presentation of the baseline height and weight information, if available.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

Reference ID: 4023761
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Reference ID: 4023761
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Please provide updated information on the current ages, or age at time of death, of patients enrolled in Studies 201, CS3A, and CS3B. This information can be presented by age-ranges (e.g., 0-6 months, 6-12 months, etc.). The duration of nusinersen treatment in these patients should also be provided in a similar manner. We ask for this response by the close of business on Monday, December 5th.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager
Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Please complete the attached ClinPharm and Cardiac Safety Table and return to us promptly, but no later than 12/5/16 Monday morning.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
12/06/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
Dear Heather,

Reference is made to your IND 110011 for nusinersen. The Division has the following comment regarding laboratory evaluation in the ongoing and future nusinersen clinical studies.

Nusinersen accumulation has been demonstrated in the proximal tubule of the kidney in animal studies. The urinary dipstick test used in the nusinersen clinical studies is relatively insensitive to proteins that are major constituents of tubular proteinuria. In ongoing studies and any future studies of nusinersen, instead of a urine dipstick test to measure protein, we recommend that you perform quantitative spot urine testing (preferably using a first morning urine specimen). For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation. We also suggest that you include serum bicarbonate routinely as part of the chemistry panel.

Because ALT and AST can be elevated in patients with SMA, we also recommend that hepatic tests include gamma-glutamyl transferase (GGT).

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
12/06/2016
at the request of Dr. S Yasuda, DNP safety TL
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by the close of business on 11/30/2016.

In Study CS3B, 4 of 80 (5%) of nusinersen subjects had had a QTc value above 500 milliseconds (ms) and an increase of >60 ms compared from baseline. For these subjects, provide the following information:

- Dates and times of nusinersen dosing
- Description of all ECG results (including but not limited to each QTc measurement and a description of any abnormal findings) with dates and times of testing
- Listing of adverse events with dates and times
- If the patient died, provide the date of death

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie
Fannie Choy, RPh
Regulatory Project Manager
Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
11/30/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by 11/29/2016.

1. Reference is made to p. 5 of the responses to information requests submitted in Section 1.11.4 of the 9/23/2016 submission to NDA 209531. Bicarbonate is listed as a parameter that was checked at Screening (Day -21 to -1), Days 64, 183, and 394. Provide the mean change in bicarbonate from baseline to the Day 64, Day 183, and Day 394 study visits (+/- 15 days) for Study CS3B subjects stratified by treatment group.

2. For each subject who had a ECG shift from normal or unknown at baseline to abnormal, clinically significant post-baseline, provide a narrative with the following information:
   - Study
   - Subject ID
   - Date and description of baseline ECG
   - Date and description of abnormal ECG.
   - Describe the clinical significance of each abnormal ECG and any related adverse events and vital signs.
   - If the ECG was done on the same day as nusinersen dosing, provide the timing of the ECG in relation to nusinersen dosing.
   - All dates of nusinersen treatment
   - Provide any concomitant medications that may have affected the ECG results.
   - Describe any treatment(s) provided for the abnormal ECG or related events.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
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/s/

YUET L CHOY
11/28/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by noon on 11/23/2016.

1. Study CS3B Subject 2007-5136 had a heart rate reported to be 32 beats per minute on 05/12/2016 at 12:30:00 PM, which was one hour after nusinersen dosing. Provide a narrative describing events surrounding this reported bradycardia. Describe any medications received on 5/12/2016, including any sedation or anesthesia. Describe all treatment received on 5/12/2016, including any treatment received for bradycardia.

2. For Study CS3B subjects, provide analyses of the median, interquartile range, and range of change from baseline heart rate to the lowest heart rate post-treatment. Stratify analyses by treatment group.

3. Analyze the frequency of decreases in heart rate in relation to nusinersen dosing. Did a decrease in heart rate ≥30 beats per minute from baseline occur more frequently post-dose on the same day of dosing, as compared to pre-dose measurements or measurements on days when no dosing occurred?

4. Did a decrease in heart rate occur on the same day as the use of sedation or anesthesia in any subject? Provide heart rate measurement, the subject number, date of decrease in heart rate, and a list of the anesthetic and sedation medications used.

5. Provide a listing of Study CS3B subjects who received sedation or anesthesia for lumbar puncture. Include which medications each subject received and dates of administration.

-----------------------------------------------------------------------------------------------

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016. Please see below for another request for information.

We request this information by 11/28/2016.

Reference is made to the FDA information request sent 11/21/2016 (copied below).

We have the following information requests. Please provide responses within 1 week of receiving this request.

1. You calculated a confirmatory cut point for anti-drug antibody (ADA) testing based on the 99.9\textsuperscript{th} percentile of percent inhibition data. We are concerned that a 0.1\% false-positive rate is too tight to ensure that all ADA-positive clinical samples are captured by the assay. Re-calculate your ADA confirmatory assay cut point for normal human plasma and disease state human plasma samples using a 1\% false positive rate. Use the re-calculated cut point to evaluate ADA samples that screened positive in clinical studies.

2. Please provide a table summarizing the number and percentage of patients from each clinical study with confirmed positive ADA results after applying the re-calculated confirmatory cutpoint based on a 1\% false positive rate. For patients with confirmed ADA positive results, provide available information on the study number, patient number, ISIS 396443 dose, duration of ADA (i.e. Day of positive samples), titer, and last sampling time with ADA testing results.

We have the following addendum to the 11/21/2016 FDA request:

1. Based on the updated set of subjects who were ADA positive, provide an analysis of median, interquartile range, and range of titers by duration of nusinersen exposure.

2. Based on the results of analyses requested by FDA on 11/21/2016, provide an updated assessment of the impact of immunogenicity on safety, including a description of adverse events seen in ADA positive subjects.

3. For each patient with one or more positive anti-ISIS 396443 antibody test results according to the revised calculations requested 11/21/2016, we request individual patient profiles.
containing all laboratory and other study results in a single place. Provide the date and results of each test for anti-ISIS 396443 antibodies as well as the following information:

- Age
- Sex
- Dates of screening, randomization and starting therapy
- Date(s) when treatment was received (specify which treatment and dose for each date).
- Whether the patient completed or did not complete the study, with dates and reason for withdrawal
- Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
- Prior medications and concomitant medications with dates of start and end
- Vital signs and laboratories, sorted by date, with reference ranges

Create a PDF file for each patient and a table of contents with links to each assessment for each patient. We acknowledge that patient profiles for 6 patients with positive anti-drug antibodies have already been submitted to NDA 209531 on 10/17/2016.

-----------------------------------------------------------------------------------------------
Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

Reference ID: 4018029
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016. Please see below for today’s Information Request #3.

We request a response by 5 PM on 11/23/2016.

For the laboratory parameters listed in the Summary of Clinical Safety Source Table 77, provide the mean change from baseline to the Day 64, Day 183, and Day 394 study visits (+/- 15 days) for Study CS3B subjects stratified by treatment group.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov
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/s/

YUET L CHoy
11/22/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by November 16, 2016.

1. Provide a table of adverse events for Study CS3B listing the number and percentage of patients stratified by treatment group. Include events that occurred in nusinersen subjects ≥5% more frequently than in control subjects, as well as events that occurred ≥2 times as frequently in nusinersen subjects compared to control subjects. Sort the events from most common to least common in the nusinersen group.

2. Reference is made to the response submitted to NDA 209531. Page 30 says that 2 subjects failed screening based on Exclusion Criterion 9. Pages 24-25 list the inclusion and exclusion criteria for Study CS3A, but no Exclusion Criterion 9 is listed. Please clarify the reason(s) for screening failures in Study CS3A.

3. Reference is made to Appendix A from the 11/10/2016 submission to NDA 209531. Provide a listing of subjects with an abnormal high or low shift. Include this information on each line:
   - Study
   - Subject ID
   - Treatment and dose
   - Lab parameter for the shift (i.e., aPTT, INR)
   - Type of shift: [i.e., (1). High to low (2). Normal to Low (3). Unknown to Low (4). Low to Low provided the post-baseline value is lower. (5). Low to High (6). Normal to High (7). Unknown to High (8). High to High provided the postbaseline value is higher.]
   - Date and test result for the baseline value
   - Date and test result for the posttreatment value

4. Provide a table reporting the number and percentage of subjects with a laboratory measurement who had treatment-emergent abnormalities in coagulation labs (aPTT and INR), stratified by treatment and dose, for all nusinersen clinical studies combined. Provide the median and interquartile range of time from first nusinersen treatment to the time of last aPTT or INR measurement.

Please confirm receipt of email and let me know if you have any questions.

Reference ID: 4014289
Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2699
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
11/16/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We have the following information requests. Please provide responses within 1 week of receiving this request.

1. You calculated a confirmatory cut point for anti-drug antibody (ADA) testing based on the 99.9th percentile of percent inhibition data. We are concerned that a 0.1% false-positive rate is too tight to ensure that all ADA-positive clinical samples are captured by the assay. Re-calculate your ADA confirmatory assay cut point for normal human plasma and disease state human plasma samples using a 1% false positive rate. Use the re-calculated cut point to evaluate ADA samples that screened positive in clinical studies.

2. Please provide a table summarizing the number and percentage of patients from each clinical study with confirmed positive ADA results after applying the re-calculated confirmatory cut-point based on a 1% false positive rate. For patients with confirmed ADA positive results, provide available information on the study number, patient number, ISIS 396443 dose, duration of ADA (i.e. Day of positive samples), titer, and last sampling time with ADA testing results.

-----------------------------------------------------------------------------------------------

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
11/21/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Please promptly respond to this request:

We are considering the prospect of dosing nusinersen in all subjects at a consistent 5 mL (12 mg) dose. Please provide any rationale you may have regarding your dose selection and why a 5 mL dose may be unwarranted.

__________________________________________________________________________________________

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
11/14/2016
w/ concurrence: Dr. Nick Kozauer, DNP clinical TL
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by November 10, 2016.

1. Provide a narrative for Study CS3A Subject 1776-2306 with an assessment of the possible causes for hyponatremia in this subject. Include an assessment of the subject’s intravascular volume status, as well as all related laboratory tests (e.g., blood and urine electrolyte and osmolality measurements) with dates and times of measurement. Describe the treatment received for hyponatremia (include dates of treatment).

2. Was syndrome of inappropriate antidiuretic hormone secretion (SIADH) considered as a possible diagnosis in any nusinersen study subject? Provide the name and subject number, a narrative if not already provided, and copies of related medical records.

--------------------------------------------------------------------------------------------
Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

Please see attached for our request for information. We request this information by November 10, 2016.

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov
We request this information by 11/10/2016.

1. Provide a narrative for Study CS3A Subject 1834-1304 (AE PT “Blood sodium decreased”) with an assessment of the possible causes for hyponatremia in this subject. Include an assessment of the subject’s intravascular volume status, as well as all related laboratory tests (e.g., blood and urine electrolyte and osmolality measurements) with dates and times of measurement. Describe the treatment received for hyponatremia.

2. Provide a narrative for Subject 396443-CS1/1780-1005 with an assessment of the possible causes of hyperkalemia (including serum potassium level 6.1 mmol/L on 6/18/2013). Provide a table with serum potassium levels and related laboratory measurements with dates and times of measurement.

3. Provide a narrative for Subject 396443-CS1/1780-2006 with an assessment of the possible causes of hypernatremia (including serum sodium 158 mmol/L on 2/5/2013). Provide a table with serum sodium levels and related laboratory measurements with dates and times of measurement.

4. Regarding CS3A Subject 1776-2305, describe any measures that were taken after August 2014 to maintain the subject’s sodium level. For any treatment used (including sodium chloride solution or sodium citrate-citric acid solution), include the dates and doses.

5. For each study in which post-treatment coagulation laboratory measurements were performed, provide a table reporting the number and percentage of subjects with a laboratory measurement who had treatment-emergent abnormalities in coagulation labs (aPTT and INR), stratified by treatment and dose, as well as for all nusinersen subject with a measurement in that study.

6. Perform a search of the nusinersen clinical development program for adverse events using the MedDRA Embolic and Thrombotic SMQ. Provide a summary of the adverse events found. Include a listing of these adverse events, including:
   - Universal subject ID
   - Study
   - Date of first nusinersen and dose received
   - Date of last nusinersen and dose received
   - Adverse event Preferred Term
   - Adverse event date

7. Perform a search of the nusinersen clinical development program for adverse events using the MedDRA Haemorrhages SMQ. Provide a summary of the adverse events found. Include a listing of these adverse events, including:
   - Universal subject ID
   - Study
   - Date of first nusinersen and dose received
   - Date of last nusinersen and dose received
   - Adverse event Preferred Term
   - Adverse event date
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/s/

YUET L CHOY
11/09/2016
NDA 209531

Biogen Inc.
225 Binney Street
Cambridge, MA  02142

ATTENTION: Trevor Mill, PhD
Senior Vice President, Regulatory Affairs

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) dated and received September 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nusinersen Injection, 2.4 mg/mL.

We also refer to your October 1, 2016, correspondence, received October 3, 2016, requesting review of your proposed proprietary name, Spinraza.

We have completed our review of the proposed proprietary name, Spinraza and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 1, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
  (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Corwin Howard, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-8654. For any other information regarding this application, contact Fannie (Yuet) Choy, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2899.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/08/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

Please see attached for our request for information. We request this information by November 7, 2016.

---------------------------------------------------------------

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

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Reference ID: 4010081
We request this information by November 7, 2016.

1. We request copies of any photographic documentation of the suspected vasculitis in Subject 2010-5026 with the date and the location on the body where the photo(s) were taken. Provide a description of the suspected vasculitis findings on physical exam.

2. Regarding subject 2002-5370, describe the location(s) of the painless acral lesions. Provide any photographic documentation that was obtained of the skin changes in this subject.

3. For each nusinersen clinical study subject with a hemorrhagic complication of lumbar puncture (successful or attempted), list the treatment(s) received for the hemorrhagic complication(s).

4. Provide a narrative for Study CS3B Subject 2010-5096 with an assessment of the possible causes for hyponatremia in this subject. Include an assessment of the subject’s intravascular volume status, as well as all related laboratory tests (e.g., blood and urine electrolyte and osmolality measurements) with dates and times of measurement. Describe the treatment received for hyponatremia.

5. Provide a narrative for Subject 396443-CS2/1778-4206, who had an AE coded to the Preferred Term “CSF white blood cell count increased.”

6. Provide a dataset with one line for each nusinersen-treated subject who, in any study, had: a) at least one treatment-emergent platelet count below the lower limit of normal; b) a thrombocytopenia adverse event; c) or had testing for anti-platelet antibodies. Include the following information:

- Subject ID
- Center ID
- Study
- Age
- Country
- Region
- Thrombocytopenia start date
- Thrombocytopenia end date (date after which platelet count remained ≥ lower limit of normal or ≥ baseline value)
- Thrombocytopenia duration (days from thrombocytopenia start date to the date after which platelet count remained ≥ lower limit of normal or ≥ baseline value)
- Date(s) on which platelet count was < lower limit of normal and corresponding values
- Whether thrombocytopenia is resolved (Y/N)
- Thrombocytopenia adverse event reported (Y/N)
- Nadir platelet count
- CTCAE grade of nadir platelet count
- Time (months) from first dose of nusinersen to thrombocytopenia start date
- Time (months) from last dose of nusinersen to thrombocytopenia start date
• Cumulative nusinersen dose at the thrombocytopenia start date
• Whether the thrombocytopenia was considered related to nusinersen (Y/N)
• If a cause for thrombocytopenia other than nusinersen treatment was found, list the alternate cause
• Whether the subject was tested for anti-platelet antibodies (Y/N)
• If tested for anti-platelet antibodies, whether the subject had a positive test result for anti-platelet antibodies (Y/N)
• If the subject had a positive test result for anti-platelet antibodies, describe the type of anti-platelet antibodies
• List any symptoms, bleeding, or other adverse events that the subject experienced while he had thrombocytopenia
• Whether the subject was hospitalized while he had thrombocytopenia
• List the treatment(s) received for thrombocytopenia
• Dates of nusinersen dosing after first treatment-emergent platelet count < lower limit of normal

7. Provide a dataset with one line for each nusinersen-treated subject who, in any study, had: a) at least one treatment-emergent neutrophil count below the lower limit of normal; b) an adverse event of neutropenia; c) or had testing for anti-neutrophil antibodies. Include the following information:

• Subject ID
• Center ID
• Study
• Study treatment
• Age
• Country
• Region
• Neutropenia start date
• Neutropenia end date (date after which neutrophil count remained ≥ lower limit of normal or ≥ baseline value)
• Neutropenia duration (days from neutropenia start date to the date after which neutrophil count remained ≥ lower limit of normal or ≥ baseline value)
• Date(s) on which neutrophil count was < lower limit of normal and corresponding values
• Whether neutropenia is resolved (Y/N)
• Neutropenia adverse event reported (Y/N)
• Nadir neutrophil count
• CTCAE grade of nadir neutrophil count
• Time (months) from first treatment to neutropenia start date
• Time (months) from last treatment to neutropenia start date
• Cumulative nusinersen dose at the neutropenia start date
• Whether the neutropenia was considered related to treatment (Y/N)
• If a cause for neutropenia other than study treatment was found, list the alternate cause
• Whether the subject was tested for anti-neutrophil antibodies (Y/N)
• If tested for anti-neutrophil antibodies, whether the subject had a positive test result for anti-neutrophil antibodies (Y/N)
• If the subject had a positive test result for anti-neutrophil antibodies, describe the type of anti-neutrophil antibodies
• List any symptoms or other adverse events that the subject experienced while he had neutropenia
• Whether the subject was hospitalized while he had neutropenia
• List the treatment(s) received for neutropenia
• Dates of nusinersen dosing after first treatment-emergent neutrophil count < lower limit of normal

8. Were there any cases of hemolytic anemia or autoimmune hemolytic anemia in nusinersen clinical studies? (Provide the search strategy and search terms that were used.) If yes, provide narratives for the related events.

9. In the Summary of Clinical Safety, which version of MedDRA was used to code adverse events for each subject pool A-F?

10. Provide a list of the inclusion and exclusion criteria for each of the nusinersen clinical studies, including those introduced as part of protocol amendments.

11. We request that you provide information on subjects who failed screening. We request a table in the format below for each study. For each study, we request the total number of subjects screened, total number of subjects who failed screening, and a list of inclusion and exclusion criteria that lead to screening failures (with the number of subjects that met each criterion).

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total screened</td>
<td></td>
</tr>
<tr>
<td>Total Number of Subjects</td>
<td></td>
</tr>
<tr>
<td>who Failed Screening</td>
<td></td>
</tr>
<tr>
<td>Exclusion criterion 1</td>
<td></td>
</tr>
<tr>
<td>Exclusion criterion 2</td>
<td></td>
</tr>
<tr>
<td>Inclusion criterion 1</td>
<td></td>
</tr>
<tr>
<td>Inclusion criterion 2</td>
<td></td>
</tr>
</tbody>
</table>
Hi Fannie,

I can confirm receipt.

Thanks,

Heather

Sent from my iPhone

On Nov 1, 2016, at 10:30 AM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

We request this information by November 4, 2016.

<![if !supportLists]>1.  ![if !endif]>
Please provide information regarding the diagnostic test(s) utilized in your clinical studies to confirm the diagnosis of SMA. Specifically, provide the approximate turnaround time of the assay results and the associated assay performance (i.e., % false positives/negatives, etc…). Please also comment on the anticipated turn-around time for diagnostic tests in clinical practice.

<![if !supportLists]>2.  ![if !endif]>
Where possible, please provide the number of screen failures (i.e., the number of subjects not diagnosed with SMA when SMA genotype was determined) for your clinical development program.

-----------------------------------------------------------------------------------------------

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov
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/s/

YUET L CHOY
11/07/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
NDA 209531

Biogen Inc.
Attention: Trevor Mill, Ph.D.
Sr. Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA 02142

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spinraza (nusinersen) sterile solution for injection, 2.4 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on October 31, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
MID-CYCLE COMMUNICATION

Meeting Date and Time: October 31, 2016, at 2:00 p.m.

Application Number: NDA 209531
Product Name: Spinraza (nusinersen)
Indication: Treatment of spinal muscular atrophy
Applicant Name: Biogen Inc.

Meeting Chair: Nick Kozauer, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

EASTERN RESEARCH GROUP

Independent Assessor
Independent Assessor

APPLICANT ATTENDEES

Biogen Inc.
Heather Faulds, Sr. Director, Regulatory Affairs
Stephanie Fradette, Sr. Manager, Regulatory Affairs
Tammy Phinney, VP, Regulatory Affairs
Nicole Del Canto, Associate Director, Regulatory Affairs
Wildon Farwell, Sr. Director, Clinical Development
Sarah Gheuens, Medical Director, Drug Safety
Adam Townsend, Asset Executive

Ionis Pharmaceuticals
Matt Buck, Executive Director, Regulatory Affairs

Reference ID: 4008923
1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

A Mid-Cycle Communication agenda was sent to Biogen on October 28, 2016.

2.0 SIGNIFICANT ISSUES

There are no specific issues requiring responses from the applicant at this time.

Meeting Discussion: There was no meeting discussion.

3.0 INFORMATION REQUESTS

Further requests for information are likely as the review is ongoing.

Meeting Discussion: There was no meeting discussion.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no plan for a REMS.

Meeting Discussion: There was no meeting discussion.

5.0 ADVISORY COMMITTEE MEETING

We are not currently planning to hold an advisory committee meeting to discuss this application.

Meeting Discussion: There was no meeting discussion.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As noted in the Filing Communication, if major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 23, 2017. The user fee goal date is May 23, 2017.
As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for November 17, 2016, 2:00 – 3:00 p.m. We intend to send the briefing package to you approximately two business days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

**Meeting Discussion:**

The applicant is currently planning to hold a face to face LCM with the review team.

Biogen asked if the Division can share the planned action date, in order for the applicant to prepare for launch if the application is approved. The Division noted that this application is high priority for the Agency, however, the Division cannot commit to a date as the review is ongoing. More information may be available at the LCM and the timeline for labeling comments will be communicated after the LCM.
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/s/

NICHOLAS A KOZAUER
11/04/2016
NDA 209531

INFORMATION REQUEST

Biogen
Attention: Nicole del Canto
Associate Director, Regulatory Affairs, CMC
225 Binney St
Cambridge, MA 02142

Dear Ms. Del Canto:

Please refer to your New Drug Application (NDA) dated 8 August 2016, received 23 September 2016 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Spinraza (nusinersen) ; ISIS 39443.

We are reviewing the Chemistry Manufacturing and Controls section(s) of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Friday, 4 November 2016.

Facility:
- During an inspection to support this NDA review at the testing site [Redacted]稳定性数据 was verified and discrepancies with the submission were observed. Please provide revised stability data in 3.2.P.8 accordingly for ISIS 396443 drug product batch CP396443-007 and batch CP396443-008 stored at 5 ± 3°C and include an explanation for this difference.

Pharm/Tox- CMC:
- In Section 3.2.S.3.2. of your NDA submission, you state that oligonucleotide impurity qualification was based on the results of the 1-year toxicology study in juvenile monkeys (396443-AS06) in which drug substance batch CA396443-001 was administered intrathecally at doses of 0.3, 1.0, or 4 mg to give total human equivalent doses (HED) of 39, 130, and 520 mg/53 weeks. By considering the high dose in that study a NOAEL, you state that the amounts of impurities present in the human equivalent dose of 520 mg/53 weeks may be considered qualified. However, since we consider the NOAEL in that study to be the low dose of 0.3 mg (total HED 39 mg), based on the findings of brain histopathology at the mid- and high doses, the actual qualified impurity levels determined according to this calculation should be [Redacted] times those shown in Table 1 on pages 6-7 of that section. Using this calculation the qualified levels for most of your specified...
impurities would be less than \( \frac{1}{2} \)%; therefore, revise your proposed limits for specified impurities (b) and (b) Impurities to the qualification threshold of NMT \( \frac{9}{8} \)%.

- In your response to Question 3 of the amendment dated Oct. 26, 2016, you stated that the drug substance sequence would be provided when the analysis was completed. Provide a commitment date for submitting the data to the NDA.

- In your response to Question 4a of the amendment dated Oct. 26, 2016, you agreed to tighten the drug substance acceptance criterion for purity to NLT \( \frac{1}{2} \)% for release. However, you proposed to maintain the NLT \( \frac{9}{8} \)% purity acceptance criterion for stability and retest samples. Having different acceptance criteria for release vs shelf life does not apply to the drug substance. The drug substance should meet one regulatory specification from release throughout its retest period before use in the manufacture of the drug product. Thus, revise the acceptance criterion for purity to NLT \( \frac{9}{8} \)% and the total oligonucleotide impurity limit to NMT \( \frac{9}{8} \)% as the drug substance regulatory specification to be applied from batch release throughout shelf-life.

- In your response to Question 4b of the amendment dated Oct. 26, 2016, regarding the identification test by (b) you proposed to provide the numerical difference between the standard and sample. Instead, please provide the numerical results for the standard and sample, as the difference between them can be readily determined.

- In your response to Question 4c of the amendment dated Oct. 26, 2016, you provided a rationale for why the [Please revise your drug substance specification accordingly, and provide the validation of the new method.]

- Harmonize the drug product specification to align with the proposed changes to the drug substance specification.
  - Revise the acceptance criterion of the [b]
o Revise the acceptance criterion for the [redacted] from NMT (4%) to NMT (6%)%

o Tighten the acceptance criterion for total degradation products.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

Dahlia A. Woody, M.S., PMP
Regulatory Business Process Manager
Division of Neurology Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hi Fannie,

I can confirm receipt.

Thanks,

Heather

Sent from my iPhone

On Oct 31, 2016, at 4:52 PM, Choy, Fannie (Yuet) wrote:

Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016

Please provide a table summarizing the incidence of serious adverse events (sorted by MedDRA System Organ Class and Preferred Term) using the format provided below. We request this information by the close of business 11/01/2016.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Study CS3B Nusinersen Subjects N=80</th>
<th>Study CS3B Control Subjects N=41</th>
<th>All Nusinersen Subjects (Pool F) N=173</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)

Reference ID: 4006878
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/s/

YUET L CHOY
10/31/2016
NDA 209531

NEW DRUG APPLICATION – Spinraza (nusinersen) sterile solution for injection, 2.4 mg/mL

Biogen Inc.
Attention: Trevor Mill, Ph.D.
Sr. Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA 02142

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) dated September 23, 2016, received September 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Spinraza (nusinersen) sterile solution for injection, 2.4 mg/mL.

We also refer to your amendments dated:

<table>
<thead>
<tr>
<th>Date</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 26, 2016</td>
<td>September 28, 2016</td>
<td>September 30, 2016</td>
</tr>
<tr>
<td>October 1, 2016</td>
<td>October 3, 2016</td>
<td>October 4, 2016</td>
</tr>
<tr>
<td>October 7, 2016</td>
<td>October 14, 2016</td>
<td>October 17, 2016</td>
</tr>
<tr>
<td>October 19, 2016</td>
<td>October 21, 2016</td>
<td></td>
</tr>
</tbody>
</table>

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 23, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If
major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 23, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is October 27, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266
Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
10/25/2016
Dear Heather,

We refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Please see attached for a request for information. We request this information by October 26, 2016.

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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Reference ID: 4003476
We request this information by October 26, 2016.

1. For Pools A-F (looking at nusinersen and control groups separately for Pool B), analyze all adverse events that occurred on the same day or within 5 days (up to 120 hours) of lumbar puncture. The analyses listed in Summary of Clinical Safety Source Tables 21 and 23 do not appear to list all adverse events occurring within 72 hours of lumbar puncture (e.g., AE PT spinal cord haematoma in Subject 232SM201/504-001 and AE PT Spinal subarachnoid haemorrhage in Subject 232SM201/511-002 are not listed). These events do not have an observation entered for ISS dataset ADAE variable AETMINTC. We request analyses up to 5 days, because onset of post-lumbar puncture adverse events were reported 120 hours and beyond in some studies of nusinersen.¹

2. For Pools A-F (looking at nusinersen and control groups separately for Pool B), provide a summary of successful and failed lumbar punctures, using the format of Table 76 in the Study 232SM201 study report. (A copy is attached.)

3. For Pools A-F (looking at nusinersen and control groups separately for Pool B), provide the number and percentage of subjects who, at least once, required endotracheal intubation for administration of treatment.

### Table 76: Summary of Successful and Failed LPs - ITT Set

Summary of successful and failed LPs - ITT Set  
Data cut-off date = 08JUN2016  
Page 1 of 2

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects dosed</td>
<td>17</td>
</tr>
<tr>
<td>Total number of days where LP ultimately successful or failed</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Number of days where LP successful</td>
<td>77 (95)</td>
</tr>
<tr>
<td>Number of days where LP attempted but not successful</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Number of days where successful at first LP attempt</td>
<td>56 (69)</td>
</tr>
<tr>
<td>Number of days where successful after more than one attempt</td>
<td>20 (25)</td>
</tr>
<tr>
<td>First attempted LP day</td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Number of successes</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Number of attempts made</td>
<td></td>
</tr>
<tr>
<td>Number of attempts made</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (71)</td>
</tr>
<tr>
<td>2</td>
<td>2 (12)</td>
</tr>
<tr>
<td>3</td>
<td>1 (6)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Number of failures</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Number of attempts made</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

**NOTE:** Numbers in parentheses are percentages.

**SOURCE:** ISIS396443/232SM201/INTERIM2/T-LP.SAS  
**DATE:** 31AUG2016
Summary of successful and failed LPs - ITT Set
Data cut-off date = 08JUN2016
Page 2 of 2

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of guidance</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Number of successes</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Number of successes with guidance</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>1 (100)</td>
</tr>
<tr>
<td>For successful LP number of attempts made</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1 (100)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>0</td>
</tr>
</tbody>
</table>

For unsuccessful LP number of attempts made

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>For unsuccessful LP number of attempts made</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;3</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Numbers in parentheses are percentages.

SOURCE: ISIS396443/232SM201/INTERIM2/T-LP.SAS
DATE: 31AUG2016
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/s/

----------------------------------------------------
YUET L CHOY
10/24/2016
w/ concurrence: Nick Kozauer, MD, DNP Clinical TL

Reference ID: 4003476
Dear Heather,

Please refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information promptly but no later than October 27, 2016. The datasets contain no Motor Milestones (primary endpoint) assessments after 2016-06-15 (interim cutoff) and no deaths or permanent ventilation events after 2016-05-16. Were there any data collected or submitted by investigators between the time the database was frozen for the interim analysis and the absolute stopping of the study? If so, please provide it.

It seems that there are 35 patients that were included in the interim analysis population who had not had the opportunity to have their Day 394 visits at the time of the interim analysis and were surviving at last assessment. Twenty of these were last seen at Day 183 and 14 were last assessed at day 302. Eleven of the 24 of these assigned to drug were Motor Milestone responders at their last assessment. Were the vital statuses of any of these patients followed up at study closeout?

The study report states that the randomization list is not being provided in this interim report but will be provided in the final report. Please identify the randomization block size and provide the randomization list generated by the IRXS vendor.

Please provide the study closeout plan and actual closeout timeline (the plan and procedures for terminating all follow-up due to stopping for early benefit), the DSMB meeting minutes and any formal correspondence from the DSMB to the study steering committee.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2890 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
10/21/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
Hi Fannie,

I can confirm receipt of this information request.

Thanks,

Heather

Sent from my iPhone

On Oct 19, 2016, at 6:55 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Heather,

Please refer to your pending NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by October 24, 2016.

1. Provide information regarding the experience of administering intrathecal injections in the nusinersen development program in the table shell below.

<table>
<thead>
<tr>
<th>Pool A</th>
<th>Pool B: Nusinersen</th>
<th>Pool B: Control</th>
<th>Pool C</th>
<th>Pool D</th>
<th>Pool E</th>
<th>Pool F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory at time of first dose, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of scoliosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal rods, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lumbar Puncture Procedural Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who received at least 1 intrathecal injection placed under</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients who received at least 1 intrathecal injection placed under fluoroscopy, the median (range) times that each patient had an intrathecal injection placed under fluoroscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who received at least 1 intrathecal injection placed using ultrasound guidance, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who received inhalational anesthesia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List which inhalational anesthetic drugs were used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who received intravenous sedation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List which intravenous sedation drugs were used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who received local anesthesia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List which local anesthetic drugs were used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients on assisted ventilation prior to nusinersen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients not on assisted ventilation prior to nusinersen administration who received assisted ventilation during at least 1 nusinersen administration, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients treated with epidural blood patch, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Provide a summary of how adverse events related to lumbar puncture can be minimized.

3. We request copies of reports for all tissue biopsies performed in clinical studies in the nusinersen development program. Please include reports from all skin biopsies, including the skin biopsy performed on CS3B Subject 2002-5370.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

**Fannie Choy, RPh.**
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215

Reference ID: 4001505
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
10/19/2016
METHOD VERIFICATION
MATERIALS RECEIVED

NDA 209531                                          October 14, 2016

Trevor Mill, Ph.D.
Sr. Vice President, Regulatory Affairs
regulatory@biogen.com
Biogen
225 Binney Street
Cambridge, MA 02142

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spinraza (Nusinersen) Injection 2.4 mg/mL and to our 8/24/2016, letter requesting sample materials for method verification testing.

We acknowledge receipt on September 21, 2016, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Digitally signed by Michael E. Hadwiger -S
DN: c=US, o=U.S. Government, ou=FDA, ou=People, 09.2342.19200300.100.1.1=1300384000. cn=Michael E. Hadwiger -S
Date: 2016.10.14 09:55:24 -05'00'  

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov

Phone  314.539.2135
FAX   314.539.2113
Hi Fannie,

I can confirm receipt of this e-mail request.

Thanks,

Heather

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, October 13, 2016 10:22 AM
To: Heather Faulds
Cc: Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 209531
Importance: High

Dear Heather,

Please refer to your NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Please provide sample informed consent documents for Studies ISIS 396443-CS3A and ISIS 396443-CS3B. Submit the information to the NDA by COB Friday.

It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
10/13/2016
with concurrence: Dr. Nick Kozauer, DNP Clinical TL
Heather

You are correct regarding the questions. I’ve removed 7-12 in the email below for clarification.

Laurie

Hi Laurie,

I can confirm receipt.

It looks like questions 7-12 are a duplicate of 1-6?

Thanks,

Heather

Dear Heather,

In reference to your NDA 209531, we have the following requests:

1. Please clarify why dataset ADSL includes 165 subjects, while Pool F (All treated subjects) is described as including 173 subjects. Advise us on how to reconcile this difference.

2. Provide the numbers for the duration of exposure table shell copied below.

**Nusinersen Safety Population. Duration of Exposure.**

<table>
<thead>
<tr>
<th>Number of patients exposed to nusinersen:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=6 months</td>
</tr>
</tbody>
</table>

Reference ID: 3997627
3. Summarize the neurologic examination and/or testing procedures for each study in the nusinersen clinical development program, including a schedule of when each assessment was performed. Provide a listing of information related to neurologic examination and/or testing procedures or results submitted to NDA 209531 with hyperlinks. Provide copies of the assessments that were performed.

4. Provide a narrative for each patient listed in the table below. Please the narrative format that has been previously used in NDA 209531. In addition provide the specific information requested for each subject listed in the table below.

<table>
<thead>
<tr>
<th>Preferred Term(s)</th>
<th>Universal Subject ID</th>
<th>Study ID</th>
<th>Specific Information Requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperreflexia</td>
<td>232SM201/511-002</td>
<td>232SM201</td>
<td>Symptoms and physical examination findings</td>
</tr>
<tr>
<td>Syncope</td>
<td>396443-CS1/1775-4002</td>
<td>396443-CS12</td>
<td>Assess the possible causes for syncope.</td>
</tr>
<tr>
<td>Tremor</td>
<td>396443-CS2/1776-3202</td>
<td>396443-CS12</td>
<td>Provide the symptoms and physical examination findings.</td>
</tr>
<tr>
<td>Dyslexia</td>
<td>396443-CS2/1776-4202</td>
<td>396443-CS2</td>
<td>Related findings in the subject’s history, physical, examination of hearing and vision, and psychoeducational testing. History of language and speech development.</td>
</tr>
<tr>
<td>Syncope/Lethargy</td>
<td>396443-CS3A/1776-2305</td>
<td>396443-CS3A</td>
<td>Assess the possible causes for syncope. Assess the possible causes for hyponatremia in this subject; include the following information related to the hyponatremia (adverse event verbatim term was “LETHARGY (SECONDARY TO HYPONATREMIA”) : Provide an assessment of the subject’s intravascular volume status, as well as all related laboratory tests (e.g., blood and urine electrolyte and osmolality measurements) with dates and times of measurement. Describe the treatment received for hyponatremia.</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>232SM201/511-001</td>
<td>232SM201</td>
<td>Symptoms and physical examination findings</td>
</tr>
<tr>
<td>Clonus</td>
<td>396443-CS3B/2111-5387</td>
<td>396443-CS3B</td>
<td>Symptoms and physical examination findings</td>
</tr>
</tbody>
</table>

*Study CS3B subjects*
5. Provide all biopsy reports (translated) relevant to the adverse event in Study CS3B subject 2010-5026, coded to PT Vasculitis. Provide the date and results of each test for anti-ISIS 396443 antibodies in this subject.

6. For each patient with one or more positive anti-ISIS 396443 antibody test results, we request individual patient profiles containing all laboratory and other study results in a single place. Provide the date and results of each test for anti-ISIS 396443 antibodies as well as the following information:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Date(s) when treatment was received (specify which treatment and dose for each date).
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

We request this information by October 14, 2016.

Please feel free to contact me if you have any questions.

Regards,

Laurie
(for Fannie Choy)

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Reference ID: 3997627
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/s/

Laurie A Kelley on behalf of Yuet L Choy
10/12/2016

Reference ID: 3997627
Dear Fannie,

I can confirm receipt of this information request. We will respond by 10/7, as requested.

Thank you,

Heather

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
To: Heather Faulds
Cc: Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 209531
Importance: High

Dear Heather,

Please refer to your NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

Information Request

Submit the datasets and analysis codes used in the exploratory exposure-response analyses as discussed in your report (is11-pop-pk-report.pdf). The datasets should be submitted as SAS transport files and analysis codes as TXT files. In addition, please also submit the NONMEM control files used in population PK analysis as TXT files. We would like to receive this information by 10/7/2016.

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002

Reference ID: 3992648
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/s/

YUET L CHOIY
09/29/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
IND 110011

MEETING MINUTES

Isis Pharmaceuticals, Inc.
Attention: Matt Buck, J.D.
Executive Director, Regulatory Affairs
2855 Gazelle Ct.
Carlsbad, CA 92010

Dear Mr. Buck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ISIS 396443.

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2015. The purpose of the meeting was to discuss your proposed submission of a New Drug Application for ISIS 396443 for [b] spinal muscular atrophy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: September 15, 2015, 3:00 – 4:30 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Room 1315

Application Number: IND 110011
Product Name: ISIS 396443
Indication: Treatment of spinal muscular atrophy
Sponsor/Applicant Name: Isis Pharmaceuticals, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of the Center Director
Robert Temple, MD, Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology
Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer

Office of Biostatistics
Kun Jin, PhD, Team Leader, Division of Biometrics I
Tristan Massie, PhD, Statistical Reviewer

SPONSOR ATTENDEES

Isis Pharmaceuticals
Eugene Schneider, M.D., Vice President, Clinical Development, Project Team Leader
1.0 BACKGROUND

Isis Pharmaceuticals Inc. (Isis) is developing ISIS 396443 for the treatment of spinal muscular atrophy (SMA). ISIS 396443 is an antisense oligonucleotide targeted to alter splicing of the Survival Motor Neuron 2 (SMN2) gene. The drug product is administered by intrathecal injection.

FDA has granted ISIS 396443 Fast Track and Orphan Drug designations for the treatment of SMA.

The sponsor has requested this Type C meeting to discuss the adequacy of data from the ongoing Phase 2 study (ISIS 396443-CS3A) in infantile-onset SMA patients, as compared to the natural history data from a matched subgroup of infants in the Pediatric Neuromuscular Clinical Research Network for SMA (PNCR) database, to support the submission and review of a New Drug Application (NDA) for ISIS 396443 for the treatment of SMA. The sponsor is also seeking Agency’s feedback on labeling considerations as well as on the adequacy of the proposed clinical and nonclinical database at the time of NDA submission.

FDA sent Preliminary Comments to Isis on September 14, 2015.
2.0 DISCUSSION

Question 1:

The data from the Phase 2 study ISIS 396443-CS3A in infantile-onset SMA patients demonstrate prolonged survival compared to natural history, improvements in muscle function from two different and independently assessed clinical measures (CHOP INTEND and motor milestones), evidence of improved neuronal function as demonstrated by robust increases in CMAP amplitude and compelling evidence of confirmation of the study drug’s mechanism of action based on comparison of the amount of full-length SMN2 mRNA and SMN protein in the CNS tissue of ISIS 396443 treated infants compared to untreated SMA infants and non-SMA infants. Does the Agency agree that the results of ISIS 396443-CS3A are acceptable for submission and Agency review of an NDA for ISIS 396443 for the treatment of SMA?

FDA Response to Question 1:

As communicated to you previously, even large apparent effects on the clinical endpoints you propose are not reliable in the context of a historically-controlled trial, and you should instead demonstrate that treated patients achieve a functional status that could not reasonably be due to factors such as more intensive supportive care or selection of patients with a more favorable prognosis. We note that you believe that at least one patient in your study has reached such a functional status; this appears to provide reassurance that such an endpoint is feasible.

We also note that you chose to initiate a placebo-controlled trial in SMA1. It is possible that an earlier analysis than you have planned may provide evidence of efficacy. Your placebo-controlled trial in SMA2/3 could also provide supportive evidence for effectiveness for SMA1.

It is possible that positive biomarker findings might play some supportive role, but are unlikely to address our concerns about bias for your proposed clinical endpoints. We also note that the improvement from baseline in CMAP amplitude is difficult to interpret because, as you state, there is no direct historical comparison for popliteal CMAP values. Also, there is limited and contradictory longitudinal data for the use of CMAP amplitude in assessing SMA patients, with a rapid and sustained age-dependent decline in SMA1 and SMA2 CMAP amplitudes in one study (Swoboda et al. 2005), but a stabilization of CMAP with spontaneous increase in motor unit number estimation (MUNE) in SMA2 patients in another study (Kang et al., 2014). The mRNA data is derived from the total cell population, not the specific cells affected by SMA1, and thus it is not clear if, or how large, the effect on SMN2 mRNA might have been in the target neurons. The peroxidase method used for immunohistochemical detection of SMN protein is poorly suited even for rough qualitative comparison of protein amount, and it is not clear that the images you presented are interpretable.
Meeting Discussion:

The sponsor began with a presentation about SMA type 1 and the results of the open-label Phase 2 study, (ISIS 396443-CS3A), including video of one patient to demonstrate developmental milestones including sitting and use of the arms. The sponsor stated that patients who received ISIS 396443 had achieved developmental milestones that are never reached in untreated SMA type 1 patients. The sponsor stated that although improvements in respiratory and other supportive care have prolonged survival in SMA type 1 patients, such supportive care has not enabled patients to reach motor milestones and, in fact, relentless loss of function continues to occur despite any intervention.

The sponsor then provided an update on the status of the Phase 3 randomized sham-procedure controlled trial (study ISIS 396443-CS3B), stating that 55-60 patients have been enrolled thus far, with less than 3 months of study drug exposure in most patients. The sponsor stated that an interim analysis based on survival was planned, but would not occur in the near future. Consequently, the sponsor proposed submitting an NDA based solely on the results of the Phase 2 study, ISIS 396443-CS3A, in December 2015.

The Agency responded that it appeared reasonable, based on the effect size suggested by the Phase 2 study, to revise the Phase 3 study (ISIS 396443-CS3B) to include an interim analysis based on function, not survival. Such an interim analysis might show a robust result with far fewer patients than originally estimated, and positive results from the interim analysis, combined with the results of the Phase 2 study (ISIS 396443-CS3A), might support an NDA filing.

The sponsor remained concerned that the time course of motor milestone development in ISIS 396443-CS3A was highly variable, and that it expects similar variability in ISIS 396443-CS3B. The sponsor was not certain that sufficient data would be available for an interim analysis by the intended December filing date, and suggested submitting interim analysis results after the NDA submission. The Agency responded that the interim analysis results of ISIS 396443-CS3B would be a crucial component of an application and would need to be submitted at the time of NDA filing.

The sponsor stated that it will consider and respond to the Agency’s advice.

There was additional discussion about the robustness of the Phase 2 study. The Agency recommended that the sponsor strengthen documentation of the functional status of the patients, potentially including video documentation and independent examination of the patients by blinded observers.

The meeting concluded with agreement that the sponsor and Agency should remain in contact as the sponsor considers the Agency’s advice to further discuss the issues raised during the meeting, as needed.
Question 2:

Of the two ISIS 396443 clinical studies in infantile-onset SMA, the dosing regimen in the ongoing Phase 3 study ISIS 396443-CS3B (i.e., 4 loading doses on Days 1, 15, 29 and 64 followed by maintenance doses every 4 months) is more frequent than the dosing regimen in the ongoing Phase 2 study ISIS 396443-CS3A (i.e., 3 loading doses on Days 1, 15 and 85 followed by a maintenance dose after 6 months and thereafter maintenance doses every 4 months). The change in dosing was employed based on available safety and PK/PD data and was considered appropriate given the severity and rapidly progressive nature of the disease in infantile-onset SMA.

Does the Agency agree that submission in the NDA of blinded safety data from the ongoing Phase 3 study ISIS 396443-CS3B will be sufficient to include the more frequent dosing regimen in the proposed product labeling? If yes, does the Agency agree that these data support inclusion of the more frequent dosing regimen as the “recommended” dosing regimen?

**FDA Response to Question 2:**

See response to question 1. Questions about the strength of evidence of efficacy from different dosing regimens are premature at this time, and would likely be a matter of NDA review, assuming an otherwise adequate application could be submitted.

**Meeting Discussion:** There was no meeting discussion.

Question 3:

At the time of the anticipated NDA submission for infantile-onset SMA, the nonclinical studies conducted with ISIS 396443 will include a single dose toxicology/pharmacokinetic study in adult cynomolgus monkey, two repeat-dose toxicology/pharmacokinetic studies in juvenile monkeys (14 and 53 weeks), a 1-year pharmacokinetic study in adult monkey, a pulmonary and cardiovascular safety assessment in rats, a Segment I/II reproductive toxicity study in mice, a Segment II reproductive toxicity study in rabbits, and *in vitro* genotoxicity assessments in the bacterial reverse mutation assay and the mammalian chromosome aberration test.

Nonclinical studies that will have been initiated but will be ongoing at the time of the NDA filing include a sub-chronic systemic toxicology study in mice and an *in vivo* mouse micronucleus test. Nonclinical studies that will not have been initiated include a radiolabeled mass balance/ADME study in rats and a Segment III reproductive toxicity study in mice.

A waiver for carcinogenicity studies based on (i) the IT route of administration, (ii) infrequent administration, (iii) results from the sub-chronic systemic toxicology study in mice, and (iv) the clinical indication will have been requested.
Does the Agency agree that the anticipated completed nonclinical studies are sufficient for filing the initial indication in SMA and that the studies that are ongoing at the time?

**FDA Response to Question 3:**

We do not agree with your proposal. The subchronic toxicity study and the in vivo micronucleus assay should be conducted concurrent with clinical development and completed prior to submission of the NDA.

**Meeting Discussion:** There was no meeting discussion.

**Question 4:**

Given the known pharmacokinetics of ISIS 396443 and the 2'-MOE ASO class, as well as the natural history of the target population, in vitro drug-drug interaction studies (CYP450 and P-gp transporter) are planned to initiate in 2016 (following the proposed NDA filing) and specific drug-drug interaction, thorough QT/QTc, and hepatic and renal impairment studies are not planned.

Does the Agency agree that these clinical pharmacology and special population studies are not required for the initial indication for ISIS 396443 for the treatment of SMA?

**FDA Response to Question 4:**

Your justification is acceptable for not conducting hepatic- or renal-impairment studies to support an indication in SMA.

*In vitro* drug-drug interaction (DDI) studies (including assessment of drug inhibition and induction effect on CYP isozymes, and transporter-mediated drug interaction potential) should be conducted before the late-phase clinical studies and the NDA submission in order to guide drug use with co-medications and to support the drug label. *In vivo* DDI studies may be needed based on the results of *in vitro* studies. If you believe these DDI studies are not applicable to your product, you will need to provide an adequate justification in your NDA. We recommend that you refer to the Agency’s Draft Guidance for drug interaction studies for detailed recommendations: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.

A thorough QT/QTc study would not be required before NDA filing, but you must ensure that patients are adequately monitored during drug development, and the possible need for such a study post-approval would remain a review issue.

**Meeting Discussion:** There was no meeting discussion.
Question 5:
Based on the serious and life-threatening nature of SMA and the ISIS 396443 data demonstrating the potential to address an unmet medical need, ISIS 396443 was granted Fast Track designation upon initiation of IND 110,011 in October 2010.

Does the Agency agree that a rolling submission for the NDA may be utilized?

**FDA Response to Question 5:**
Yes.

**Meeting Discussion:** There was no meeting discussion.

Question 6:
Given the different natural histories of type I and type II SMA, the Sponsor intends to analyze safety data separately for these two populations. Does the Agency agree with the proposed approach to integrate safety data in the NDA?

The Sponsor plans to locate the Integrated Summary of Safety (ISS) in Module 5 of the eCTD (Section 5.3.5.3). Section 2.7.4 will refer the reader to Section 5.3.5.3 for the appendices and datasets. Section 5.3.5.3 will refer the reader to Section 2.7.4 for the text portion of the ISS. Does the Agency agree with the proposed approach to split the ISS?

**FDA Response to Question 6:**
The intent of the ISS is to present appropriate analyses at various levels of integration across studies, from all exposed individuals to narrower groupings of studies of similar duration in a single disease subtype. Therefore, it would not be acceptable only to analyze safety data separately for type I and type II SMA patients, although such separate analyses should be conducted.

It is important that a common data format be followed to allow for analyses at various levels of integration, as discussed in more detail in the response to question 7.

The proposed approach to split the ISS is consistent with an acceptable format for a small ISS split between Module 2 and Module 5, as described in the FDA Guidance for Industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

**Meeting Discussion:** There was no meeting discussion.

Question 7:
Does the Agency agree that it is acceptable to submit datasets in the following formats?
- **Legacy format**: datasets for studies ISIS 396443-CS1, -CS2, -CS3A, -CS10, and -CS12, as well as the ISS and Summary of Clinical Efficacy (SCE)
- **Clinical Data Interchange Standards Consortium (CDISC) format**: datasets for studies ISIS 396443-CS3B and ISIS 396443-CS4

**FDA Response to Question 7:**

Legacy format datasets may be problematic and an obstacle to the review process. Any decisions regarding the filing of an NDA will follow a substantial review of the submission and a detailed examination of the reviewability of datasets. All data must be in a format that can be readily reviewed: transparent, reproducible, and traceable to study documents such as narratives and case report forms.

The Center for Drug Evaluation and Research (CDER) is currently accepting non-standard study data. The PDUFA V negotiated agreement includes a phase-in period such that the submission of standard data will not be absolutely required until after that phase-in period is completed.

If you so choose (and we ask that you do so), for a future NDA, you may submit both the original (legacy) and the converted (SDTM) data. In this case, the converted data should be viewed as a reviewer aid since it may support the use of newer review tools. You should be aware that when submitting non-standard data, there is less certainty as to its ability to support the review process. If non-standard data are submitted, the Reviewer’s Guide and the Define file become especially important in assisting the reviewer to locate where the data reside within the dataset and in understanding its format. It is helpful to have active links from the Define file to the domains and variable names preferably constructed using XML because PDF or XLS file formats may not be functional in this regard.

It is important that you are consistent in the use of the Unique Subject Identifier so that patients who participated in both efficacy trials and subsequent extension trials can be appropriately accounted for; for example, in terms of adverse events and overall drug exposure.

Technical assistance is available to ensure the compatibility of your datasets with FDA data systems and software review tools (eData team of the OBI Division of Data Management Services and Solutions, eData@fda.hhs.gov). In addition, please refer to the Industry Study Data Standards Resources webpage http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.

CDISC is an acceptable format, as described in the FDA Standardized Study Data Guidance and in the FDA Data Standards Catalog.

**Meeting Discussion**: There was no meeting discussion.
3.0 ADDITIONAL COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor’s slides titled, “ISIS 396443-CS3A Data in Support of the FDA Filing | FDA Meeting | 15 September 2015”.

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/s/

WILLIAM H Dunn
09/28/2015
Dear Heather,

Please refer to your NDA 209531 for nusinersen (ISIS 396443) submitted on September 23, 2016.

We request this information by September 29, 2016.

Provide a table listing each of the narratives provided in the 9/23/2016 NDA submission. Provide a hyperlink to each narrative, and include columns with the following information:

- Unique Subject Identifier
- Study Identifier
- Subject Identifier for the Study
- Study Treatment
- Actual Sequence of Treatments (corresponding to ADAE variable TRTSEQA)
- Reason for narrative (i.e., list each of the following that apply to events described in the narrative: death, life-threatening event, event requiring inpatient hospitalization or prolongation of existing hospitalization, event resulting in persistent disability/incapacity)

Please confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
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fannie.choy@fda.hhs.gov

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/s/

YUET L CHOI
09/27/2016
w/ concurrence: Sally Jo Yasuda, DNP safety TL

Reference ID: 3991352
NDA 209531

Biogen Inc.
Attention: Trevor Mill, Ph.D.
Sr. Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA  02142

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spinraza (nusinersen).

We also refer to your August 9, 2016, submission, containing your request to waive the 120-day safety update for NDA 209531 because all available safety data from the nusinersen development program will be included with original NDA.

We have reviewed your request and agree to waive the requirement for the 120-day safety update requirement for NDA 209531.

If you have any questions, please contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

[See appended electronic signature page]

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
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/s/

WILLIAM H Dunn
09/11/2016
Dear Heather,

We refer to your NDA 209531 presubmission dated August 8, 2016 for nusinersen (ISIS 396443). Reference is also made to your July 29, 2016, submission to IND 110011.

Your July 29, 2016, submission to IND 110011 states that when evaluating the primary endpoint in a population inclusive of all subjects who die or withdraw after baseline (regardless of whether or not they have had the opportunity to be assessed at their Day 183, Day 301 or Day 394 visit), as suggested by the Agency, a statistically significant greater proportion of responders was also observed in the ISIS 396443 group (21; 40%) compared to the sham control group (0; 0%) (p<0.0001). It will be important that you provide these analyses in your NDA submission and provide all available functional and mortality data for the ITT population, specifically including those not included in the interim efficacy analysis and any assessments that may have been taken between the time of freezing the database for the interim analysis and the actual stopping of the double blind part of the study.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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Reference ID: 3981829
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/s/

YUET L CHoy
09/06/2016
at the request of Dr. Nick Kozauer, DNP Clinical TL
Dear Heather,

We refer to your NDA 209531 presubmission dated August 8, 2016 for nusinersen. We also refer to the safety summary plan received via email on August 25, 2016.

Thank you very much for the safety summary plan for nusinersen. In that summary you mention that no adverse reactions were identified. We just want to be sure that you have included all adverse events, whether or not the investigator or Biogen consider them to be adverse reactions. Please also note the following request for analyses and presentation of laboratory measurements and vital signs in the presentation of safety data for NDA 209531.

**Request for Analyses of Laboratory Measurements and Vital Signs:**

1. Provide a table summarizing the frequency of each laboratory test routinely measured during each study in the clinical development program.
2. Provide the normal reference ranges for every laboratory value, as well as the thresholds for analysis of outliers.
3. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: [SI Units](#)
4. Using integrated data from sham-controlled studies, we request analyses of routinely measured laboratory parameters at baseline, as well as post-treatment change from baseline (median, interquartile range, and range), for each treatment group by visit. Provide the number of subjects included in each analysis.
5. Using integrated data from sham-controlled studies, provide shift analyses for all routinely measured laboratory parameters. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses. For laboratory parameters with no available CTCAE toxicity grades, provide shift analyses with clearly defined criteria for mild, moderate, and severe post-baseline changes.
6. Ensure that analyses shift analyses of blood sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, and platelets in placebo-controlled studies are provided. If any of these laboratory tests were not measured, please specifically state that they were not measured.
7. Please provide outlier analyses of laboratory measures.
8. For each treatment group and age range as appropriate, report the number and percentage of subjects with at least one post-treatment vital sign measurement (high or low) outside of the range of normal for the age and disease for systolic and diastolic blood pressure, pulse rate, body weight, temperature, and respiratory rate. Please provide justification for the normal ranges that you reference for vital signs.
9. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   1) Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   2) Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   3) Pulse Rate: <60 bpm, >100 bpm
   4) Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   5) Temperature: >38.0 °C, <36.0 °C
   6) Respiratory rate: <12 breaths/min, > 20 breaths/min
10. For each treatment group, please provide outlier analyses of the number of subjects with post-treatment vital sign changes compared to baseline listed below:
    - Systolic blood pressure (SBP) increment > 20 mm Hg
    - SBP increment > 40 mm Hg
    - SBP decrement > 20 mm Hg
    - SBP decrement > 40 mm Hg
    - Diastolic (DBP) increment > 10 mm Hg
    - DBP increment > 20 mm Hg
    - DBP decrement > 10 mm Hg
    - DBP decrement > 20 mm Hg
    - Heart rate increment > 15 bpm
    - Heart rate increment > 30 bpm
    - Heart rate decrement > 15 bpm
    - Heart rate decrement > 30 bpm
    - Treatment-emergent body temperature > 38.0 °C
11. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc intervals outside the range of normal for age and for disease.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
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fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
08/30/2016
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL
REQUEST FOR METHODS VALIDATION MATERIALS

Biogen
Attention: Trevor Mill, PhD
Sr. Vice President, Regulatory Affairs
225 Binney Street, Cambridge, MA 02142

Telephone: 617-914-4143
Email: regulatory@biogen.com

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spinraza (Nusinersen) Injection 2.4 mg/mL.

We will be performing methods validation studies on Spinraza (Nusinersen) Injection 2.4 mg/mL, as described in NDA 209531.

Please include the MSDSs and the Certificates of Analysis for the reagents, sample and reference materials.

In order to perform the necessary testing, we request the following sample materials and equipment:

Note: The sample volume for preparation of standards and samples is not specified, to achieve good accuracy and precision we assume a sample volume of 100 mL.

Method(s) for evaluation

<table>
<thead>
<tr>
<th>NDA Volume / Page</th>
<th>Method ID</th>
<th>Method Title</th>
<th>Analyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.S.4.2</td>
<td>IP-HPLC-UV-MS</td>
<td>Assay, Identity, and Impurity Profile by Ion-Pair-HPLC-UV-Mass Spec</td>
<td>Drug Substance</td>
</tr>
<tr>
<td>3.2.P.5</td>
<td>IP-HPLC-UV-MS</td>
<td>Identification, Assay (%Label Claim), Purity and Degradation</td>
<td>Drug Product</td>
</tr>
</tbody>
</table>
Samples and Reference Standards

<table>
<thead>
<tr>
<th>Method</th>
<th>Item</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.S.4.2 Assay, Identity, and Impurity Profile by Ion-Pair-HPLC-UV-Mass Spec</td>
<td>ISIS 396443 Drug Substance Sample (Any lot)</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>ISIS 396443 Reference Standard (Any Lot)</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>ISIS 396443 Drug Product Sample (Any lot)</td>
<td>5 vials (5 mL, 2.4 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>ISIS 396443 Reference Standard (Any Lot)</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per the procedure instructions: “A pre-prepared working solution standard of ISIS 396443 at a concentration of approximately 0.1 mg/mL in water...”</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

Because the grade (e.g. HPLC grade, spectroscopic grade, etc.), salt type (mono-, di-, tri-sodium, etc.) and/or concentration of some of the mobile phase reagents are not specified in the procedure(s) we also require.

Additional Reagents:

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient mass or volume to prepare 2 L of mobile phase</td>
<td></td>
</tr>
<tr>
<td>Sufficient mass or volume to prepare 2 L of mobile phase</td>
<td></td>
</tr>
</tbody>
</table>

Equipment:

Two C18 columns (μm particle size)
Miscellaneous
In section 2.4.3 of the IP-HPLC procedure described in 3.2.S.4 for the analysis of the drug substance, the following instructions for the preparation of sample and reference standard are given:

“Samples for analysis are prepared by dissolving ISIS 396443, which is allowed to equilibrate to ambient conditions prior to weighing, to a concentration of approximately 0.1 mg/mL in water.”

and

“ISIS 396443 is hygroscopic and therefore difficult to weigh accurately and precisely in its native form. Prior equilibration to ambient conditions ensures stable sample weights during the weighing operation.”

Please provide a description of this process (e.g. leave powder in a covered glass dish on bench for 24 hrs prior to weighing).

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Brian Noakes MVP Sample Custodian
Re: NDA 209531
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this document. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Digitally signed by Michael E. Hadwiger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300384000, cn=Michael E. Hadwiger -S
Date: 2016.08.23 14:16:51 -05'00'

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
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/s/

MICHAEL E HADWIGER
08/23/2016
MVP request for materials for NDA 209531
MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 4, 2016, 1:00 p.m. EDT
Application Number: IND 110011
Product Name: ISIS 396443 (nusinersen)
Sponsor/Applicant Name: Biogen Inc.

Subject: Planned NDA submission for nusinersen

FDA Participants:
Billy Dunn, Wendy Wilson, Martha Heimann, Teresa Buracchio, Natalie Getzoff, Fannie Choy

Sponsor Participants:
Paula Sandler, Heather Faulds, Nicole del Canto

1.0 BACKGROUND:

On July 29, 2016, the previous sponsor (Ionis) notified DNP via email that topline data from the interim analysis of Study CS3B, Phase 3 controlled study in patients with infantile-onset spinal muscular atrophy (SMA), have revealed positive topline data. On August 1, 2016, the sponsor formally submitted the information to its IND. In addition, Ionis notified the FDA that sponsorship of IND 110011 has been transferred from Ionis Therapeutics to Biogen Inc. on August 1, 2016. Biogen plans to submit an NDA under rolling submission. The Division requested this informal teleconference to discuss the anticipated submission plan for nusinersen.

2.0 DISCUSSION:

a. Manufacturing and scale-up commercial production
   - Discussed whether the sponsor is ready for scale-up manufacturing for commercial production
   - DNP requested that the sponsor to provide information on manufacturing sites as soon as possible, via email prior to formal submission
   - Biogen stated that the product is “launch-ready”

b. Expanded Access Program (EAP)
   - Biogen discussed its plan for EAP

c. Rolling Submission Strategies
   - The sponsor’s plan to submit partial CMC module is acceptable to OPQ
   - Planned submission dates: Part 1 on 8/15/16, Part 2 around 3rd-4th week of September
   - Safety data analyses (Refer to Q6 in the 9/15/15 Type C meeting minutes)
     The Division asked the integrated summary to include both type 1 and type 2 pts, in addition to safety data separately for type 1 and type 2 pts
d. 120-day Safety Update – DNP requested the sponsor to submit safety update by Day 60-75.

e. Breakthrough Designation (BTD) Request
   - Discussed sponsor’s interest in BTD

f. Review Classification
   - Determination will be at the time of filing

g. Electronic courtesy copies prior to Part 1 submission
   - FDA requested courtesy copies of the CMC module, proposed draft labeling and carton/container labeling as soon as possible

h. Clinical Sites Inspection
   - FDA will engage internal discussion with OSI

3.0 ACTION ITEMS:

a. Manufacturing and scale-up commercial production
   - Sponsor to send list of manufacturing sites as discussed
   - Sponsor to send list of sites that have recent Form 483 and corrective actions taken
   - OPQ requested extrapolation information related to the proposed 18-month expiry

b. Expanded Access Program
   - Sponsor will be submitting the EAP protocol

c. Rolling Submission Strategies
   - Sponsor will inform DNP when the 2nd/final portion of the NDA will be submitted

d. 120-day Safety Update
   - Sponsor will inform DNP whether they can submit the update by Day 60 or 75

e. Breakthrough Designation Request (BTDR) - none

f. Review Classification - none

g. Electronic courtesy copies prior to Part 1 submission
   - Sponsor will respond back to the Division whether and when they can send courtesy copies of the priority items

h. Clinical Sites Inspection
   - Sponsor will send courtesy copy of list of clinical sites as soon as possible
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/s/

YUET L CHOY
08/19/2016
IND 110011

ISIS Pharmaceuticals
Attention: Matt Buck, J.D., Executive Director, Regulatory Affairs
2855 Gazelle Ct.
Carlsbad, CA 92010

Dear Mr. Buck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ISIS 396443.

We also refer to your submission dated January 29, 2015 containing an IND/Type C Meeting request. The purpose of the requested meeting is to discuss and gain Agency agreement on the development and registration strategy for the Chemistry, Manufacturing and Control (CMC) module for the NDA.

Further reference is made to our Meeting Granted letter dated February 27, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 29, 2015, background package.

If you have any questions, call Dahlia A. Woody Regulatory Business Process Manager at (301) 796-8427.

Sincerely,

{See appended electronic signature page}

Wendy I. Wilson-Lee, PhD
Branch Chief, Branch 1 (Acting)
Division of New Drug Products 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Written Responses
WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Pre-IND

Application Number: 110011
Product Name: ISIS 396443
Indication: Treatment of spinal muscular atrophy
Sponsor/Applicant Name: ISIS Pharmaceuticals
Regulatory Pathway: 505(i)

1.0 BACKGROUND

The purpose of the meeting is to discuss development plans for chemistry, manufacturing and controls for IND 110011.

QUESTIONS AND RESPONSES

Question 1:
Does the Agency agree that, as part of our control strategy for drug substance specifications, the use of platform data from similar oligonucleotides is appropriate for the design of quality control acceptance criteria?

FDA’s Response:
On the basis of the data provided in the briefing package, we agree that the use of platform data from similar oligonucleotides for the design of quality control acceptance criterion for content is an acceptable approach. Similar approach may be used for other residual solvents, elemental impurities, content if adequate data are submitted to support the request. However, the acceptability of any acceptance criterion will ultimately depend on the potential for impact to patient safety based on proposed daily intake and duration of treatment. The final determination of the adequacy of any proposed control strategy will be evaluated at the time of NDA submission based on the justification and data included in the NDA.

Question 2:
Does the Agency agree with the use of [REDACTED] to establish limits for bacterial endotoxins?

FDA’s Response:
No, we do not agree. [REDACTED] was based on is the limit for the intrathecal delivery of radiopharmaceuticals. As this drug product is not a radiopharmaceutical, it must meet the USP endotoxin limit of 0.2 EU/kg/hour. The average neonate weight is 7.5...
pounds (3.4 kg), therefore the endotoxin limit should be \( \text{EU/dose (NMT } \leq \text{ EU/mL for a 4 mL dose)} \) or less.

**Question 3:**
Does the Agency agree that the tests, methods and specification limits for the commercial drug substance are adequate for the proposed product and its route of administration?

FDA’s Response: We agree that the proposed drug substance specification includes adequate tests, however, acceptability of the analytical methods and specification limits will be determined after complete review of the data submitted in the NDA. In addition, we have the following suggestions:

1) In the case of small molecules, if the API is contaminated with a process related impurity that has similar structure and biological activity, that impurity is not be included in the assay and purity calculations. Similarly, we suggest that you do not include [ISI 396443] in the definition of the active ingredient and in the assay and purity calculations of the API. We recognize that you have done so in the past; however, we do not recommend that you continue following this approach.

2) Since the drug product is an intrathecal injection and will be given to neonates, infants, and little children, we suggest you to prepare the drug substance as pure as practicable. Therefore, during manufacture of the drug substance, [the required purity level should be maintained].
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/s/

DAHLIA A WOODY
04/17/2015

MARTHA R HEIMANN
04/17/2015
Signed for Wendy Wilson-Lee
LATE-CYCLE COMMUNICATION
DOCUMENTS
Dear Dr. Mill:

Please refer to your New Drug Application (NDA) dated September 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spinraza (nusinersen) sterile solution for injection, 2.4 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 17, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

Nick Kozauer, M.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 17, 2016, 3:00 – 4:00 p.m.
Meeting Location: Teleconference

Application Number: NDA 209531
Product Name: Spinraza (nusinersen)
Applicant Name: Biogen Inc.

Meeting Chair: Nick Kozauer, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director
Robert Temple, MD, Deputy Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Ed Fisher, PhD, Nonclinical Reviewer
Sally Jo Yasuda, MS, PharmD, Safety Team Leader
Evelyn Mentari, MD, Clinical Safety Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Products
Wendy Wilson-Lee, PhD, Branch Chief
Monica Cooper, PhD, Quality Reviewer
Dahlia Woody, MS, PMP, Regulatory Business Process Manager

Division of Biometrics I
Kun Jin, PhD, Biometrics Team Leader
Tristan Massie, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer
Kevin Krudys, PhD, Pharmacometrics Team Leader

Reference ID: 4029498
1.0 BACKGROUND

NDA 209531 was submitted on September 23, 2016, for nusinersen.

Proposed indication: Treatment of spinal muscular atrophy

PDUFA goal date: May 23, 2017

FDA issued a Background Package in preparation for this meeting on November 15, 2016.

2.0 DISCUSSION

1. Introductory Comments

Discussion: There was no meeting discussion.
2. Additional Applicant Data

**Discussion:**
The applicant does not anticipate submitting additional data at this time.

3. Information Request(s)

The Division requested that the applicant submit a summary of the results of the CS4 study to the NDA.

**Discussion:**
The applicant agreed to submit a summary of the results of Study CS4 to the NDA as requested by the Division.

4. Postmarketing Requirements/Postmarketing Commitments

There are no currently anticipated postmarketing requirements or commitments.

**Discussion:**
The Division will notify the applicant if there are any changes.

5. Major Labeling Issues

We are considering adding a discussion of the neurotoxicity findings observed in monkey to the appropriate section(s) of labeling.

**Discussion:**
The Division discussed the basis for considering the monkey neurohistopathology findings to be evidence of neurotoxicity that should be described in the label and agreed to work with the applicant to develop strategies for further investigating the mechanism and clinical implications of these findings.

We are considering adding the following to Warnings and Precautions and note that these issues are still under review:

- Thrombocytopenia

**Discussion:**
The Division noted that these considerations are based on findings in the nusinersen NDA as well as on issues associated with antisense oligonucleotides.
6. Review Plans

The Division plans to continue with the ongoing reviews and begin labeling negotiations in early December.

**Discussion:** There was no meeting discussion.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

**Action Item:**

The applicant will submit a summary of the results of Study CS4 to the NDA as requested by the Division.

**Post Meeting Note:**

On November 18, 2016, the applicant submitted the topline summary of the data from interim analysis of Study CS4 for later-onset spinal muscular atrophy (SMA) as well as an additional overview on the extrapolation of safety and efficacy data across SMA phenotypes.
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/s/

NICHOLAS A KOZAUER
12/16/2016
Biogen Inc.
Attention: Trevor Mill, Ph.D.
Sr. Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA 02142

Dear Dr. Mill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spinraza (nusinersen) sterile solution for injection, 2.4 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 17, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 17, 2016, 3:00 – 4:00 p.m.
Meeting Location: FDA White Oak Campus, Building 22, Room 1309

Application Number: NDA 209531
Product Name: Spinraza (nusinersen)
Proposed Indication: Treatment of spinal muscular atrophy
Applicant Name: Biogen Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

   No Discipline Review letters have been issued to date.

2. Substantive Review Issues

   No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.
LCM AGENDA

1. Introductory Comments – 5 minutes (Nick Kozauer, MD, CDTL/Fannie Choy, RPM)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Additional Applicant Data – 5 minutes (Applicant)

3. Information Requests
   There are no pending information requests at this time. The Division requests that the
   applicant submit a summary of the results of the CS4 study to the NDA.

4. Postmarketing Requirements/Postmarketing Commitments
   There are no currently anticipated postmarketing requirements or commitments.

5. Major labeling issues – 10 minutes
   We are considering adding a discussion of the neurotoxicity findings observed in monkey to
   the appropriate section(s) of labeling.
   We are considering adding the following to Warnings and Precautions and note that these
   issues are still under review:
   - (b) (4)
   - (b) (4)
   - Thrombocytopenia
   - (b) (4)

6. Review Plans – 5 minutes
   The Division plans to continue with the ongoing reviews and begin labeling negotiations in
   early December.

7. Wrap-up and Action Items – 5 minutes
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/s/

WILLIAM H Dunn
11/15/2016