DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209531

NDA APPROVAL

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, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spinraza (nusinersen) injection, 2.4 mg/mL.

This new drug application provides for the use of Spinraza (nusinersen) injection for the treatment of spinal muscular atrophy in pediatric and adult patients.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on October 25, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209531**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We note your agreement dated December 9, 2016, to update the drug product carton label to include the expression of the active ingredient's strength and to update the drug product expiration period when stored refrigerated in the commercial packaging to 30 months. We also note your agreement to submit the updated draft label as a CBE labeling supplement.

PRODUCT QUALITY

We remind you of the following post-approval quality agreements:

A. To provide the nusinersen (ISIS 396443) [redacted] (b) (4) data [redacted] (b) (4) [redacted]

B. To provide the drug substance melting point (T_m) method validation data, numerical acceptance criteria with justification, and description of the analytical method [redacted] (b) (4) [redacted]

C. To re-examine the [redacted] (b) (4) impurity acceptance criteria after data are generated from a total of [redacted] (b) (4) commercial drug substance batches, including the [redacted] (b) (4) process validation batches in the filing. Biogen will tighten the specification limit to [redacted] (b) (4) %, if appropriate, based on the data. These results and a revised drug substance specification table, if warranted, should be submitted in a CBE-0 supplement.

D. To conduct stability testing of the [redacted] (b) (4) drug product process validation batches up to [redacted] (b) (4) months and report the results per post-marketing reporting requirements (21 CFR 314.70).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been

assigned a tracking number, PRV NDA 209531. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for nusinersen was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would have benefited from advisory committee discussion.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of carcinogenicity; reproductive and developmental toxicity; and development of anti-double stranded DNA antibodies that could lead to autoimmune disease in patients taking nusinersen.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3143-1 A two-year carcinogenicity study in one rodent species (CD-1 mice) with subcutaneous administration of nusinersen.

The timetable you submitted on December 13, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2017
Study Completion:	12/2020
Final Report Submission:	03/2021

The final protocol for PMR 3143-1 should reflect Agency agreement and be submitted prior to starting the studies.

3143-2 A pre-and postnatal development (including maternal function) study of nusinersen in rodent.

The timetable you submitted on December 13, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2017

3143-3 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.

The timetable you submitted on December 9, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2018

Submit the protocols to your IND 110011, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

ADDITONAL POSTMARKETING REPORTING

In addition to the aforementioned reporting requirements, we request that you:

1. Provide expedited reporting of each reported case of thrombocytopenia <20 x 10^9/L. For each case, provide the following information:
   - Case ID
   - Study (if applicable)
   - Age
   - Country
   - A table of platelet measurements sorted by date (baseline and all post-treatment)
   - Nadir platelet count
   - Time from first dose of nusinersen to thrombocytopenia start date
   - Listing of dates of nusinersen dosing
   - 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 patient was tested for anti-platelet antibodies (Y/N)
   - If tested for anti-platelet antibodies, whether the patient had a positive test result for anti-platelet antibodies (Y/N)
   - If the patient 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 patient experienced while he had thrombocytopenia
   - Whether the patient was hospitalized while he had thrombocytopenia
   - List the treatment(s) received for thrombocytopenia

2. Provide expedited reporting of all cases of glomerulonephritis.

3. Provide expedited reporting of all cases of nephrotic syndrome or nephrotic range proteinuria.

4. As a component of your periodic safety reporting (i.e., in your Periodic Safety Update Report [PSUR] or, if applicable, the Periodic Benefit-Risk Evaluation Report [PBRER]), provide a synthesized summary (clinical study cases and postmarketing cases) and analysis, including incidence of clinical study cases, postmarketing cases, and total cases, of the following:
   - Cases of thrombocytopenia (including a listing and discussion of all cases <20 x 10^9/L)

- Reported renal abnormalities (including a listing and discussion of all cases of glomerulonephritis, nephrotic syndrome, or nephrotic range proteinuria)
- Serious cases of lumbar puncture complications
- Serious cases of coagulation abnormality
- All reported cases of vasculitis or suspected vasculitis
- Serious cases of hyponatremia
- Serious hepatic disorders

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

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

/s/

ELLIS F UNGER
12/23/2016