NDA 215887

CORRECTED ACCELERATED APPROVAL

Biogen Inc.
Attention: Priya Singhal, MD, MPH
Executive Vice President, Global Safety and Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Dr. Singhal:

Please refer to your new drug application (NDA) dated May 25, 2022, received May 25, 2022, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDCA) for Qalsody (tofersen) injection.

We acknowledge receipt of your submissions dated October 5, 2022, and October 7, 2022, which constituted a major amendment to this application, and extended the goal date by three months.

We also refer to our Accelerated Approval letter dated April 25, 2023, which contained the following error: incorrect final report submission date listed for PMC 4436-6.

Letter Location	Incorrect Date for the PMC 4436-6 Final Report Submission Date	Correct Date for the PMC 4436-6 Final Report Submission Date
Page 6	03/2024	03/2026

This corrected action letter incorporates the correction of the error. The effective action date will remain April 25, 2023, the date of the original letter.

This NDA provides for the use of Qalsody (tofersen) injection for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

APPROVAL & LABELING

We have completed our review of this application. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the container labeling submitted on April 13, 2023, and the carton labeling submitted on April 20, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215887**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Qalsody (tofersen) injection shall be 18 months from the date of manufacture when stored at 2°C to 8°C.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 13, 2023. This requirement, along with required completion dates, is listed below.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4436-1 In order to verify the clinical benefit of tofersen, complete Study 233AS303 (ATLAS), “A Phase 3 Randomized, Placebo-Controlled Trial With a Longitudinal Natural History Run-In and Open-Label Extension to Evaluate BIIB067 Initiated in Clinically Presymptomatic Adults With a Confirmed Superoxide Dismutase 1 Mutation”. The study will enroll presymptomatic adults who have a confirmed superoxide dismutase 1 mutation into a natural history run-in period, followed by a randomized, double-blind, placebo-controlled period. Subjects will remain in the double-blind, placebo-controlled study until they develop clinically manifest ALS or the end of the study. The primary endpoint is the proportion of subjects with emergence of clinically manifested ALS. The study should be of sufficient duration to observe changes on the endpoint in the patient population enrolled in the study.

Draft Protocol Submission:	02/2021 (submitted)
Final Protocol Submission:	07/2021 (submitted)
Trial Completion:	12/2027
Final Report Submission:	06/2028

Submit clinical protocols to your IND 124264 for this product.

You must submit reports of the progress of the clinical trial listed above to the NDA not later than 180 days after the date of approval of this NDA and every 180 days thereafter (per section 506B(a)(2) of the FDCA). The report should include expected trial completion and final report submission dates, any changes in plans since the last report with rationale for any changes, and, the current number of subjects entered into the trial.

Reports submitted 180 days after the date of approval of this NDA and on such date each year thereafter must be clearly designated “**180-Day AA PMR Progress Report**.”

Reports submitted one year after the date of approval of this NDA and on such date each year thereafter may be submitted as part of your annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). FDA will consider the submission of your annual status report under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval and on such date each year thereafter, to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s)**.”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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 an unexpected serious risk of carcinogenicity after exposure to tofersen.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

4436-2 Conduct a 2-year carcinogenicity study of tofersen in rat.

The timetable you submitted on April 24, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2024
Final Protocol Submission: 09/2024
Study Completion: 11/2027
Final Report Submission: 02/2028

4436-3 Conduct a carcinogenicity study of tofersen in mouse.

The timetable you submitted on April 24, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2023
Final Protocol Submission: 12/2023

Study Completion: 12/2026
Final Report Submission: 06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND124264 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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(a)(1) 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(a)(1) 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B(a)(1)

We remind you of your postmarketing commitments:

4436-4 Conduct population pharmacokinetics analysis to evaluate the relationship between tofersen systemic exposure and renal function characteristics using existing data. In addition, collect urine samples following intrathecal administration of tofersen 100 mg from an ongoing clinical study to evaluate the recovery of tofersen in the urine.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on April 19, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2021 (submitted)
Final Protocol Submission: 07/2021 (submitted)
Trial Completion: 12/2027
Final Report Submission: 06/2028

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4436-5 Conduct an extractable study for the rubber stopper. The aqueous extractions should use pH adjusted waters that bracket the pH of tofersen drug product as extracting solvents. The extraction should be conducted by heating at reflux conditions to ensure they represent worst-case scenarios for extractable impurities. Full extractable reports, including analytical method qualification, should be submitted to the Agency.

The timetable you submitted on January 24, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

4436-6 Conduct a leachable study using at least three batches of tofersen drug product. The leachables should be tested at multiple time points on stability storage - from release through the proposed shelf-life. Full study reports, including analytical method validation, should be submitted to the Agency.

The timetable you submitted on January 24, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/2024
Final Report Submission: 03/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 124264 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report

submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

REQUESTED ENHANCED PHARMACOVIGILANCE

We request that you perform postmarketing pharmacovigilance to characterize the risk for myelitis and the risk of radiculitis associated with the use of Qalsody. Please provide biannual reports of myelitis and of radiculitis. Provide a synthesized summary and analysis, including incidence of clinical trial cases, postmarketing cases, and total cases. Include information about management, including treatment required, if any, and interruption and/or discontinuation of Qalsody because of these events. Also provide information about the extent of symptom resolution. The summary should provide an analysis for all subjects and a separate analysis for patients in the United States and for those in the rest of the world.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

[4] https://www.fda.gov/media/128163/download.

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

If you have any questions, contact Michelle Mathers, Regulatory Project Manager, at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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