CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215887Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 19, 2023

To: Rainer Paine, M.D., Clinical Reviewer,
Division of Neurology (DN1)

Michelle Mathers, Regulatory Project Manager, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Qalsody (tofersen) injection, for intrathecal use

NDA: 215887

In response to DN1's consult request dated July 01, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for Qalsody (tofersen) injection, for intrathecal use.

PI: OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP by DN1 on April 05, 2023, and our comments are provided below.

Carton and Container Labeling: OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the Sponsor to the electronic document room on April 13, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 14, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 215887
Product Name, Dosage Form, and Strength:	Qalsody (tofersen) injection, 100 mg/15 mL (6.7 mg/mL)
Applicant/Sponsor Name:	Biogen MA Inc.
OSE RCM #:	2022-1035-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 13, 2023 for Qalsody. Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Qalsody (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant responded to our request to specify the expiration date format, implemented our usual dose statement recommendation, and proposed an alternative option to our request to include alternate storage information, all of which we find acceptable.

Additionally, the Applicant made additional revisions to the carton labeling and container label that included changes in font style, font color, letter casing, bolding, and administrative information. We determine theses additional revisions do not increase the risk for medication errors; therefore, we find them acceptable.

We have no further recommendations at this time.

[a] Morris, C. Label and Labeling Review for Qalsody (NDA 215887). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 SEP 13. OSE RCM No.: 2022-1035.

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JOHN C MORRIS
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STEPHANIE L DEGRAW
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IMMUNOGENICITY CONSULT AND ASSESSMENT

Application Type	NDA
Application Number	215887
Submit Date	05/25/2022
Received Date	05/25/2022
PDUFA Goal Date	10/07/2022 Mid cycle review 08/30/2022
Division/Office	ON/DNI
Review Completion Date	1/27/2023
Proposed Proper Name[1]	Tofersen
Proposed Proprietary Name[1]	qalsody
Pharmacologic Class	Anti-sense Oligonucleotide
Applicant	Biogen Idec Inc
Route of administration	Intrathecally
Applicant Proposed Indication(s)	treatment of amyotrophic lateral sclerosis (ALS) associated with a mutation in the SOD1 gene.

Immunogenicity Assessors

Primary Assessor(s)	Seth Thacker, PhD
Secondary Assessor (s)	Daniela Verthelyi, PhD MD
Tertiary Assessor (s)	

Consult request:

Please review validity of assay (validation # TS067-018VR) and sample analysis reports used to support the immunogenicity assessment of tofersen in ALS patients from studies 233AS101 Part C and 233AS102

Assessor Comments:

The sponsor submitted an ELISA assay to detect the presence of ADA against tofersen in ALS patients. The assay is acceptable and will allow detection of IgG/A against tofersen in serum. The cut points established during assay validation have been demonstrated to be appropriate for this patient population. Based on the product class of this drug (ASO) and the route of administration (intrathecal) the immunogenicity risk of the product was expected to be low. However, the sponsor has observed high levels of ADA in serum in both of their clinical trials. In Study AS102 51% of subjects (71 of 138) had at least 1 ADA+ result with titers as high as 102,400. 63 subjects had a persistent ADA response. The majority of subjects (52) had lower titers (25-800)

[1] The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

with 11 subjects having titers 1600-102,400. There was an observed association between ADA and decrease in serum clearance time. ADA decreased clearance time by 42.9%. No association was observed with drug concentrations in the CSF or the ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale). Of note, ADA to oligonucleotides with 2'-O-(2-methoxyethyl)-D-ribose MOE modifications have been previously reported for other products. Lastly, the absence of an apparent impact of ADA on product safety or efficacy could be due to the inability of the ADA to no cross the blood brain barrier.

2. Review

Document Reviewed	Submission Date
ISI	05/22/2022
Final Validation Report 5.3.1.4	05/22/2022
Clinical-overview	
Summary- clin-pharm	

2.1 Immunogenicity Risk Assessment

Tofersen is an antisense oligonucleotide that targets the mRNA for SOD1. Tofersen is 20 bp in length and has a mixed backbone. Five residues at each end have a 2'-O-(2-methoxyethyl)-D-ribose MOE modification, and 15 residues have a phosphonothioate diester linkage. The DP is administered intrathecally and is rapidly taken up by cells following injection. The sponsor states that in order to develop a positive control antibody tofersen had to be conjugated to an immunogenic carrier protein.

The following factors lower the concern for the immunogenicity risk of this product:

1) Route of administration
2) Rapid uptake/turnover
3) General low immunogenicity of ASO
4) Non inflammatory immune status of the intended patient population

These factors are of concern for this product

1) Risk of thrombocytopenia related to ASO
2) Wide expression of SOD1 multiple tissues

A multi-tiered ADA assays has been developed to monitor the develop of ADA in serum of treated individuals by [redacted] (b) (4). The ADA assay has been used to analyses studies 233AS101 and 233AS102. Biogen has results from 166 tofersen treated participants. Sampling dates for ADA testing are shown in the following table

Study Name	Collection time	Results
233AS101 (completed)		
Part A (phase 1/2) - Single IT dose: 10, 20, or 40 mg	Study Days 1 (pre-dose), 8, 29 and 57.	1/15 (6.7%) Treatment 1/5 (20%) Placebo

		Titer = 25 (MRD)
Part B (phase 1/2) - Multiple IT dose: 20, 40, 60, or 100 mg on days 1, 15, 29, 57, and 85.	Study Days 1 (pre-dose), 8, 22, 36, 64, 92, 106 and 169.	10/38 (26.3%) 1 positive at baseline. Placebo 0% Titer = 25-400
Part C (phase 3) - Multiple IT dose: 100 mg on days 1, 15 and 29 and then every 4 weeks up to day 169.	Pre-dose on Study Days 1, 15, 29 and every 4 weeks (pre-dose) up to Day 169, as well as on Day 197.	22/72 (30.6%) Treatment 2/36 (5.6%) placebo Titer = 25-400
		33 of 125 (26.4%) 5 (4.0%) had transient responses 28 (22.4%) had persistent responses
233AS102 (phase 3) (on going)		
100 mg IT dose every 4 weeks for 236 weeks following loading doses on Days 1, 15 and 29	Pre-dose only on Days 1, 15 and 29 and every 8 weeks (pre-dose) thereafter, as well as on the last visit (Day 248)	71 of 138 (51.4%) Titer 25-102,400

2.2 Validation of Anti-Drug Antibody Assay

2.2.1 Method Principle

The assay was developed by Biogen and then transferred to (b) (4) for validation and analysis of samples from clinical study 233AS-101 and -102

The assay is a sandwich ELISA. Free Amine Torfersen is bound to an immobilizer amino plate. Plasma is added to the plate and detection occurs with protein A/G-HRP (Will bind to all human IgG subclasses). Confirmatory assay uses spiked tofersen. Each plate had the following controls HPC, LPC, Confirm positive controls (HPC, LPC, NC), and NC.

See Table 2.1 for summary of key assay parameters.

2.2.2 Validation Exercises

The cut point of the assay was established using Thirty lots of normal plasma (15 male and 15 female) and 30 lots of diseases plasma. The MRD is 25. The samples were measured in duplicate over three runs by two analysist. There was a significant effect observed due to analysist and plate number (Figure 1 TS067-018VR). Each plate that was ran had 8 wells of the negative control (pooled human plasma) to allow for transformation of S/NC of the data. Following transformation, the data was not normally distributed so the "robust parametric approach" described by Devanarayan et al, in 2017 was used to select cut points; this is acceptable. Outliers were identified using the Tukey method (Q1–1.5*(Q3-Q1) or above Q3+1.5*(Q3-Q1)). At baseline 17 analytical outliers and 4 biological outliers (22 values) were identified. This resulted in a total of 39

of 360 values being excluded. For the CCP 22 analytical and 4 biological outliers were identified for a total of 51 of 360 values being excluded. See Table 2.1 for details of key assay parameters

Acceptance criteria for the assay validation can be found in the ISI Table 3 in appendix A and in Assay validation document. These criteria included system suitability criteria such as PSCP < LLPC < HPC, % CV <20%, and 3 of 4 PC on the plate have to meet the previous criteria.

Assessor Comment:
An IR was issued for clarification of the outlier methodology used in the outlier determination. The sponsor supplied more details and the raw data that was used to identify outliers. Outlier identification is acceptable. Acceptance criteria are reasonable and acceptable to assure assay performance.

Table 2.1: Validation Results and Assessor Analysis for ADA assays used in Phase 3 Safety (Validation Report TS067-018VR)

Validation Parameter	Clin Study 233A101 and 102 Validation Report: TS067-018VR	Assessor Comment
Contract Research Org	(b) (4)	
Assay principle	ELISA (HRP)	
Sample Pretreatment (Acid dissociation)	No sample pretreatment	*Acceptable. Generally concentration of the DP in plasma was less than 100ng/mL. Only 1 measured value was greater than the drug tolerance of the assay.*
Positive control (PC)	Affinity Purified Rabbit Polyclonal Ab	The detection reagent used in the assay is protein A/G conjugated to HRP. Will recognize human IgG/A.
PC Dose Curve and Hook Effect	PC dose curve 0.4-200,000ng/mL No hook effect observed up to 200,000ng/mL	
LLPC	160ng/mL	
HPC	20,000ng/mL	
Matrix and NC	Pooled Normal Human Plasma. Plasma from disease population	
MRD	25	
NC system suitability range	0.072 - 0.111 (OD)	*Details related to suitable range for clinical samples can be found here in Appendix A Table3 of the ISI.*
LPC system suitability range	0.166 – 0.387 (OD) 1.824 – 4.427 (S/NC)	

HPC system suitability range	3.101 – 4 (OD) 30.1662 – 46.301 (S/NC)	
Screening cut- point (SCP) Floating CP: Mean NC response × normalization factor [1.15]	1.7342	95% calculated using LCL Robust Parametric method.
Confirmatory cut-point (CCP) Floating	*24.263%*	*Determined using both LPC and HPC*
Titer Cut Point (TCP)	2.8917	99.9% calculated using LCL Robust Parametric method.
Assay Drug tolerance	500ng/mL	*Acceptable*
Sensitivity	121.64 ng/mL	*The sensitivity of the assay is acceptable for IgG*
Repeatability/Intra-assay variability	NC not reported %CV LLPC 14.9%CV HPC 11.1%CV	*Precision is acceptable*
Intermediate Precision (IP)/inter-assay variability	NC 8.9%CV LLPC 16.7%CV HPC 10.0%CV	*Precision is acceptable*
Selectivity	Demonstrated with irrelevant ASO	*Assay is specific for Tofersen*
Stability	Freeze Thaw - 7 cycles Benchtop - Stable for up to 50 hours.	*Stability is acceptable*
Lipemia	Tolerant	*10 lots of lipemic samples were tested and 9 of 10 showed no interference in either screening or confirmatory assay.*
Hemolysis	Tolerant	*Shown to be tolerant in both the screening and confirmatory.*
ADA Assay Assessment	**Suitable**	

Additional Reviewer Comments:

Assay is suitable to detect ADA against tofersen in serum of patients. The assay has suitable controls to demonstrate assay performance.

2.3 Assessment of Assay performance in Clinical Studies

The sponsor has confirmed the cut point (based on 1:1 mixture of normal serum and patient serum) in 15 treatment naïve patient samples. The FPR in the smaller cohort was 8.7%.

Assessor Comment:
The Cut point has been demonstrated to be appropriate for the intended patient population.

All the studies that have reported vales show significant levels of ADA in patients ranging from 26.4% (Study 101) to 51.4% (Study 102). The majority of these responses were persistent, and titers ranged from 25-1,600. There was a correlation between ADA and a decreased clearance time in serum by 42.9%. No correlation was noted with AE and ADA levels. Additionally no association with ADA status and efficacy were noted.

Assessor Comment:
No association of ADA levels and drug efficacy or safety have been observed to date even with the high prevalence of ADA in these patients. The levels of ADA are notable as most ASO do not generate ADA, but high levels of ADA to modified ASO have been reported before (Mipomersen). The data from the clinical studies does not indicate that the ADA are affecting safety or efficacy.

2.4 Information Requests Sent During Review

(b) (4)

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2022

TO: Teresa Buracchio, MD
Deputy Director
Division of Neurology I (DN-I)
Office of neuroscience (ON)
Office of New Drug (OND)

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Yi-Ying Chen, M.S.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDSI, OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4)

1. RRA Summary

OSIS conducted a remote regulatory assessment (RRA)[1] of the analytical portion of Studies 233AS101 Part C and 233AS102 (NDA 215887, Toferson) conducted at (b) (4) (b) (4)

We observed the following objectionable condition during the RRA: (b) (4) (b) (4)

Based on our review of the RRA observation, we conclude that NfL concentration data (pg/mL) from the audited studies (see Section 3) are not reliable because the method hasn't been

[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote record reviews" and "remote interactive evaluations."

shown to be accurate. However, the reported percent-change-from-baseline NfL data are reliable because the method is precise.

2. Reviewed Studies

Study 233AS101 Part C (NDA 215887)
"Quantitative Determination of NfL (Neurofilament Light) in Human EDTA Plasma for Clinical Study 233AS101"

Sample Analysis Period: (b) (4) (Plasma)

"Quantitative Determination of NfL (Neurofilament Light) in Human Cerebrospinal Fluid for Clinical Study 233AS101"

Sample Analysis Period: (b) (4) (CSF)

Study 233AS102 (NDA 215887)
"Quantitative Determination of NfL (Neurofilament Light) in Human EDTA Plasma and Cerebrospinal Fluid for Clinical Study 233AS102 - Interim Report"

Sample Analysis Period: (b) (4) (Plasma)
Sample Analysis Period: (CSF)

3. Scope of RRA

OSIS Chemists (b) (6) reviewed the analytical portion of the above studies conducted at (b) (4) (b) (4)

The RRA included an examination of records and processes for method validation of NfL assay, and study sample analysis. The RRA also included interviews with the firm's management and staff.

4. RRA Observations

During the RRA, we observed objectionable conditions that were discussed with the firm's management during the RRA close-out meeting.

Our evaluation of the observation and the firm's response is presented below.

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ECMS: CDER_OTS/Office of Study Integrity and Surveillance/ INSPECTIONS/BE Program/ANALYTICAL/ (b) (4)
(b) (4) RRA FYXX: First Day of Inspection/Post-Inspection Folder

http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f88910d0eb

OSIS File #: (b) (4)

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CHARLES R BONAPACE
12/19/2022 09:26:20 PM

Clinical Inspection Summary

Date	12/09/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Michelle Mathers, Regulatory Project Manager Rainer Paine, M.D., Medical Officer Kevin Krudys, Ph.D., Clinical Reviewer Emily Freilich, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	215887
Applicant	Biogen Inc.
Drug	Tofersen
NME	Yes
Proposed Indication	Treatment of amyotrophic lateral sclerosis with SOD1 mutation
Consultation Request Date	6/27/2022
Summary Goal Date	11/18/2022, extended to 12/16/2022
Priority/Standard Review	Priority
Action Goal Date	4/25/2023
PDUFA Date	1/25/2023, extended to 4/25/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Babu, Bucelli, and Genge as well as the sponsor, Biogen Inc., were inspected in support of this NDA, covering Protocol 233AS101 (Part C). The study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Tofersen injection for intrathecal use is being developed under NDA 215887 (IND 124264) for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

The sponsor has submitted the results of a Phase 3 study, Protocol 233AS101 (Part C), to support efficacy and safety in the treatment of ALS associated with a mutation SOD1 gene. The sponsor is seeking approval under the accelerated approval pathway based on a biological

endpoint, reduction in plasma neurofilament light chain (NfL), and not on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) score.

Protocol 233AS101 (Part C)

Title: "A study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of BIIB067 administered to adult subjects with amyotrophic lateral sclerosis and confirmed superoxide dismutase 1 mutation"
[Note: BIIB067 is tofersen]

Subjects: 108

Sites: 32 sites; North America (21; United States [18]), Western Europe (7), Asia/Pacific (4)

Study Initiation and Completion Dates: 3/27/2019 to 7/16/2021

Database Lock Date: 8/16/2021

This was a Phase 3, randomized, double-blind, placebo-controlled study in subjects with amyotrophic lateral sclerosis (ALS). This study was conducted in three parts: a single-ascending dose (Part A), a multiple-ascending dose (Part B), and a pivotal efficacy study (Part C).

Main eligibility criteria included ≥18 years of age; weakness attributable to ALS and a confirmed superoxide dismutase I (SOD1) mutation (confirmed by central reader, screening visit sample); with or without rapid disease progression (see below); concomitant riluzole was permitted if dose stable for 30 days prior to Day 1; concomitant edaravone was permitted if started >60 days prior to Day 1 and continue with same dose regimen during study.

Subjects with and without rapid disease progression were enrolled.
Subjects *with* rapid disease progression had to meet the following criteria:

- Protocol-specified mutations and a prerandomization Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) slope decline of ≥0.2 per month *or* SOD1 mutation other than those listed in the protocol and a prerandomization ALSFRS-R slope decline of ≥0.9 per month.
- Sitting slow vital capacity (SVC) ≥65% of predicted value

Subjects *without* rapid disease progression had to meet the following criteria:

- Must have a SOD1 mutation other than those listed in the protocol and no ALSFRS-R slope decline criteria.
- Sitting SVC ≥50% of predicted value

The study was comprised of three phases: screening, double-blind treatment, and follow-up phase.

Screening Phase (Day -28 to Day -1)
Study procedures to determine subject eligibility including, but not limited to: ALSFRS-R, SVC, ECG, labs, blood sampling for DNA analysis (genetic testing and confirmation).

Double-Blind Treatment Phase (Day 1 to Day 169)
Subjects were randomized (2:1) to one of two investigational product (IP) arms:

- Tofersen
    - 100 mg once every 2 weeks for 3 doses (loading dose) followed by 100 mg every 4 weeks for 5 doses (maintenance dose) by intrathecal bolus injection over one to three minutes
- Placebo
    - Administered by intrathecal bolus injection over one to three minutes following the same dosing regimen

Randomization was stratified by three factors: rapid or non-rapid disease progression, concomitant use of edaravone at baseline, and concomitant use of riluzole at baseline.

Study visits occurred on Day 1 (Baseline) and Days 15, 29, 57, 85, 113, 141, 169, and 197 (End of Study Visit/4 weeks after last IP dose). Subjects completing the End of Study visit were considered study completers and could enroll in a separate long-term extension study.

Follow-up Phase (Day 225)
Subjects who did not enroll in the separate long-term extension study had a safety follow-up visit 8 weeks after the last IP dose.

The primary efficacy endpoint was the change from baseline to Week 28 in the ALSFRS-R total score. The biological efficacy endpoint on which accelerated approval is being sought was the change from baseline to Week 28 in plasma neurofilament light chain (NfL).

Rationale for Site Selection

Sites were chosen for BIMO inspections based on risk ranking in Clinical Investigator Site Selection Tool, numbers of enrolled subjects for verification of biological endpoint for accelerated approval, SAEs, and prior inspection history.

III. RESULTS

1. Suma Babu, M.D
Site #101
Massachusetts General Hospital
Healey Center for ALS
165 Cambridge Street
Suite 600
Boston, MA 02114-2781
Inspection Dates: 8/9/2022 – 8/12/2022

At this site for Protocol 233AS101 (Part C), 11 subjects were screened, 10 subjects were randomized, and 8 subjects completed the study. Two subjects discontinued the study due to disease progression (Subjects # (b) (6) /placebo, # (b) (6) /tofersen).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised [ALSFRS-R]).

The primary efficacy data, ALSFRS-R scores recorded on paper source, were verified against sponsor data line listings. No discrepancies were identified. Plasma neurofilament light chain (NfL) concentrations, the biological efficacy data, were not available at the site. The sponsor stated that these data were not sent to clinical sites in order to maintain the study blind. Therefore, NfL concentration data was verified during the sponsor inspection (see inspection summary below). There was no evidence of under-reporting of adverse events.

2. Robert Bucelli, M.D.
Site #108
Washington University School of Medicine
Human Research Protection Office
660 South Euclid Avenue
St. Louis, MO 63110-1010
Inspection Dates: 8/9/2022 – 8/12/2022

At this site for Protocol 233AS101 (Part C), 15 subjects were screened, 10 subjects were randomized, and 10 subjects completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all

subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (ALSFRS-R).

The primary efficacy data, ALSFRS-R scores recorded on paper source, were verified against sponsor data line listings. No discrepancies were identified. Plasma NfL data, the biological efficacy data, was not available at the site. The sponsor stated that these data were not sent to clinical sites in order to maintain the study blind. Therefore, NfL concentration data was verified during the sponsor inspection (see inspection summary below). There was no evidence of under-reporting of adverse events.

3. Angela Genge, M.D.
Site #130
Montreal Neurological Institute & Hospital
3801 University Street, Room 207
Montréal, PQ, Canada
Inspection Dates: 9/19/2022 – 9/23/2022

At this site for Protocol 233AS101 (Part C), 21 subjects were screened, 15 subjects were randomized, and 14 subjects completed the study. One subject discontinued the study due to "withdrawal by subject".

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, Research Ethics Board/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (ALSFRS-R).

The primary efficacy data, ALSFRS-R scores recorded on paper source, were verified against sponsor data line listings. No discrepancies were identified. Plasma NfL data, the biological efficacy data, was not available at the site. The sponsor stated that these data were not sent to clinical sites in order to maintain the study blind. Therefore, NfL concentration data was verified during the sponsor inspection (see inspection summary below).

On four occasions in four of 15 randomized subjects, ALSFRS-R ratings were conducted by unblinded raters rather than the protocol-specified blinded raters. These ratings were conducted by unblinded raters due to staffing issues at the site and impact of COVID-19. These protocol deviations were included in the sponsor data line listings and impacted the following subjects:

- Subject # (b) (6) randomized to tofersen, Week 28
- Subject # randomized to tofersen, Week 2
- Subject # randomized to placebo, Week 28
- Subject # randomized to tofersen, Week 28

Reviewer's comment: In four subjects, ALSFRS-R ratings were conducted by unblinded raters; three of these ratings occurred at Week 28, a timepoint relevant to the efficacy analysis. However, the sponsor is seeking approval under the accelerated approval pathway based on a biological endpoint, reduction in plasma neurofilament light chain (NfL), and not on the ALSFRS-R ratings.

The inspection identified 6 unreported adverse events occurring in 3 of 15 randomized subjects. The majority of these adverse events were reported during the telephone visit contact the day after a lumbar puncture for intrathecal administration of study drug.

- Subject # (b) (6) randomized to tofersen, reported feeling tired (Day 15)
- Subject # randomized to placebo, reported feeling weak (Day 29), light-headed (Day 57), and tired (Day 113)
- Subject # (b) (6), randomized to tofersen, reported feeling tired (Day 85) and experiencing headache (Day 141)

Reviewer's comment: Most of the unreported adverse events were reported to the site during the telephone contact visit occurring 24-hours after the lumbar puncture/study drug administration. No further information is available regarding these adverse events. These unreported adverse events occurred in subjects randomized to placebo and tofersen; it is unlikely that this omission would impact the overall safety assessment.

4. Biogen Inc.
225 Binney St
Cambridge, MA 02142-1031
Inspection Dates: 11/1/2022 – 11/4/2022

The inspection covered sponsor practices related to Protocol 233AS101 (Part C) and focused on the three clinical investigator sites chosen for inspection.

Records reviewed during the inspection included, but were not limited to, SOPs, organizational charts, monitoring plan and reports, site selection/qualification, monitor qualification, vendor list, contracts, investigator agreements and 1572s, investigator compliance/corrective actions, IRB approvals, Independent Data Monitoring Committee charter and meeting minutes, Endpoint Adjudication Committee charter, eCRFs, data

management, financial disclosure forms, IP shipments/receipts/returns, pharmacovigilance procedures and documentation, and protocol deviations.

(b) (4) was contracted for data management, safety monitoring, site management, and site monitoring. No clinical sites enrolling subjects in Protocol 233AS101 were terminated. There were no serious non-compliance issues identified for any clinical investigators.

The vendor, (b) (4), was contracted as the central laboratory. (b) (4) provided the clinical sites with specimen kits for obtaining plasma and cerebrospinal fluid (CSF) neurofilament light chain (NfL) samples. Lab manuals describing how to collect, store, and ship samples were provided to the clinical sites. Plasma and CSF NfL samples were shipped from the clinical sites to (b) (4) packaged the samples and shipped them to (b) (4), the vendor contracted to assay the plasma and CSF NfL samples.

Plasma NfL concentration data is the primary basis for accelerated approval for this application. Both plasma and CSF NfL concentration data were verified during this inspection. For data verification, certified copies of the NfL plasma and CSF data as well as corresponding data line listings were requested from the sponsor. The sponsor did not send the certified copies to the clinical sites for data verification in order to maintain the study blind. The certified copies, obtained from (b) (4), were available at the sponsor site in addition to being submitted to the NDA. NfL plasma and CSF data were verified during the sponsor inspection for all randomized subjects at the three clinical sites selected for inspections. No discrepancies were identified.

A note-to-file written by the sponsor and dated 8/25/2022 stated that there were 6 sets of duplicate timepoint results in the certified copies obtained from (b) (4). Three of the duplicate results were for plasma NfL data and three were for CSF NfL data. Only one duplicate sample involved a timepoint of interest for the efficacy analysis. Subject # (b) (6), randomized to tofersen, had two plasma NfL aliquot vials for Day 197 (end of study). Both vials were tested with results of 19 pg/mL and <4.9 pg/mL. According to the sponsor, the two results were not within the 22% coefficient of variation (CV) of the assay and should have undergone reanalysis to confirm the results or to be reported as not determinable (ND). The sample with a value of 19 pg/mL was reported. The sponsor noted that this issue was investigated by (b) (4) and the root cause was not identified but thought to be site error.

Reviewer's comment: Only one of the duplicate plasma/CSF NfL samples were for a timepoint relevant to the efficacy analysis. For Subject # (b) (6), randomized to tofersen, the higher plasma NfL concentration of 19 pg/mL at Day 197 was included in the datasets. However,

according to the sponsor, these samples should have been reanalyzed to confirm the results. This isolated event is unlikely to affect the overall results of the study.

{See appended electronic signature page}

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MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 2, 2022

To: Teresa Buracchio, MD, Director, Division of Neurology I

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff
Chad Reissig, PhD, Supervisory Pharmacologist, Controlled Substance Staff

From: Neil Varshneya, PhD, Pharmacologist, Controlled Substance Staff

Subject: NDA 215887 for Tofersen (BIIB067) intrathecal (IT) injection
Indication: Amyotrophic Lateral Sclerosis (ALS)
Dosages: 10–100 mg, IT
Sponsor: Biogen, Inc.

Materials Reviewed: NDA 215887 (May 25, 2022)

I. Background

This memorandum is in response to a consult request from the Division of Neurology I (DNI) for NDA 215887 for tofersen (BIIB067) dated June 8, 2022. Tofersen is a novel superoxide dismutase (SOD1) antisense oligonucleotide in development by Biogen, Inc (Sponsor) for the treatment of amyotrophic lateral sclerosis (ALS). Tofersen received "Fast Track Designation" on November 24, 2015, to meet an unmet medical need for ALS treatment. The Applicant submitted an NDA for tofersen dated May 25, 2022 but did not include an abuse potential assessment for tofersen. However, CSS previously reviewed tofersen for abuse liability under IND 124264 in a memorandum dated February 24, 2022 and determined that tofersen was unlikely to have abuse potential given that no abuse-related AEs or SAEs were reported in clinical studies. Therefore, additional studies including nonclinical abuse potential assessments and a human abuse potential study were not needed.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by muscle atrophy driven by a selective loss of motor neurons. SOD1 is an enzyme encoded by the *SOD1* gene for which mutations have been implicated in the development of ALS. According to the Sponsor, tofersen selectively suppresses SOD1 RNA with a G93A mutation, and distributes broadly to CNS tissues following intrathecal (IT; intended clinical route) and intracerebroventricular (ICV) administration, but not following subcutaneous (SC) administration.

Overall, CSS has not identified any abuse- or dependence-related concerns with tofersen. A review of TEAEs in the clinical studies did not reveal any evidence to suggest that tofersen poses risks of addiction liability in humans. CSS concludes that tofersen is unlikely to be abused and therefore should

not be controlled under the Controlled Substance Act (CSA). The proposed drug product, if approved under this NDA, will not require Section 9 (Drug Abuse and Dependence section) in its label.

II. Conclusions

- Tofersen is an antisense oligonucleotide (ASO) that selectively suppresses SOD1 RNA.
- There are no ASO that selectively suppress SOD1 RNA scheduled under the Controlled Substances Act (CSA).
- A review of TEAEs in completed clinical studies did not reveal any evidence to suggest that Tofersen poses risks of addiction liability in humans.
- The proposed drug product, if approved under this NDA, will not require a Drug Abuse and Dependence section in its label.

III. Recommendations (to the Division)

- Tofersen does not appear to have a potential for abuse and does not require scheduling under the Controlled Substance Act.
- Tofersen does not require a section 9 (Drug Abuse and Dependence section) in its label.

IV. Discussion of Abuse and Dependence-Related Data

Chemistry

Drug Substance. The chemical structure of tofersen is shown in **Figure 1**. Tofersen has a molecular formula of $C_{230}H_{317}N_{72}O_{123}P_{19}S_{15}$ (free acid) and a molecular weight of 7127.86 g/mol. The chemical properties and structural identifiers of tofersen including the IUPAC Name, PubChem ID, CASRN, Molecular Formula, Molecular Weight are shown in **Table 1**.

Tofersen sequence is 5′-$^{Me}\underline{CA}_{P=O}\underline{GG}_{P=O}\underline{A}TA^{Me}CATTT^{Me}CTA^{Me}\underline{C}_{P=O}\underline{AG}_{P=O}{}^{Me}\underline{C}^{Me}\underline{U}$-3′ where the underlined residues are 2′-MOE nucleosides and P=O annotation reflects the location of phosphate diester linkages.

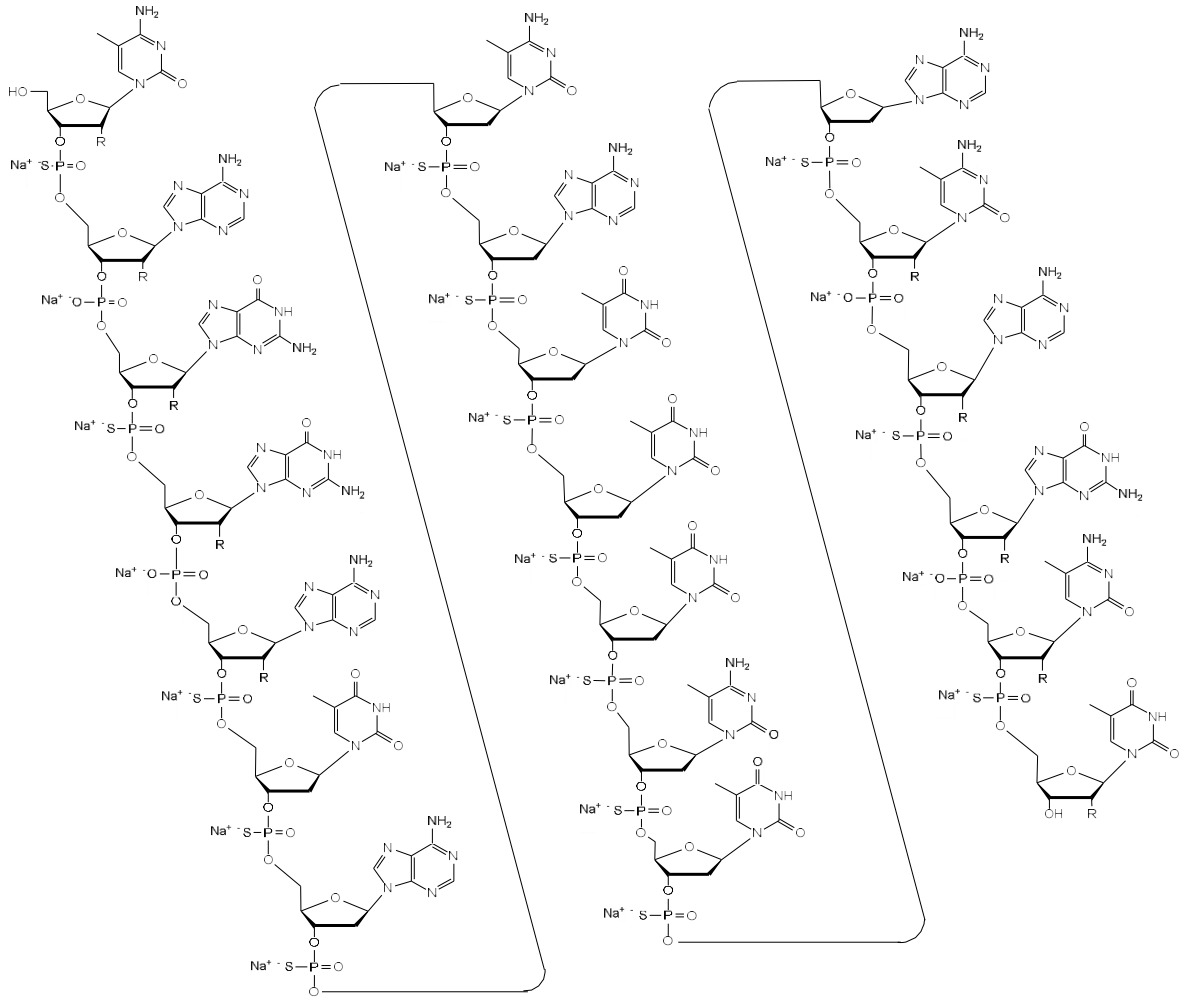

Fig. 1. Chemical structure (where R = $OCH_2CH_2OCH_3$) of Tofersen.

Table 1. Chemical Properties and Structural Identifiers of Tofersen	
Property or Identifier	**Value**
Common Name	Tofersen
IUPAC Name	Tofersen is named based on accepted oligonucleotide nomenclature, showing each 3′-O to 5′-O-linked phosphorothioate or phosphorodiester internucleotide linkage as follows: 2′-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-adenylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-P-thioguanylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-guanylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-P-thioadenylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O) -2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-deoxy-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O) -2′-deoxy-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O) -2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-5-methylcytidylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-P-thioadenylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-guanylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-5-methyluridine
PubChem SID	381128259
CASRN	2088232-70-4
Molecular Formula	$C_{230}H_{317}N_{72}O_{123}P_{19}S_{15}$ (free acid)
Molecular Weight	7127.86 g/mol
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number	

Drug Product. Tofersen ((b) (4) 100 mg) is prepared as a 15mL bolus for intrathecal administration. According to the Sponsor's NDA submission, provided under Module 2.3P (Drug Product; Description and Composition of the Drug Product, Pharmaceutical Development):

"The drug product is an aqueous solution for intrathecal injection. The drug product is supplied in a Type I glass vial closed with a rubber stopper and seal with a flip-off cap. Each vial of drug product contains a single dose of 100 mg tofersen at a concentration of 6.7 mg/mL in a formulation at pH 7.2."

<u>In Vitro Studies</u>

The Sponsor did not conduct nonclinical studies to evaluate the affinity, potency, efficacy, and functional selectivity of tofersen for biological targets other than SOD1 (e.g., receptors implicated in mediating the abuse-related effects of known drugs of abuse).

In Vivo Studies

The Sponsor did not conduct nonclinical studies to evaluate the abuse-related effects of tofersen (e.g., self-administration, drug discrimination, physical dependence). CSS determined that a nonclinical abuse potential assessments were not needed for tofersen.

Clinical Studies

The Sponsor did not conduct a clinical study to evaluate the human abuse potential of tofersen. However, no abuse-related AEs or SAEs were reported in clinical studies for tofersen. CSS determined that a HAP study was not needed for tofersen.

The following are excerpts from the Applicant's Nonclinical Overview and Clinical Overview documents. They are presented verbatim:

5.5. Abuse Liability

Given the route of administration (IT) and targeted mechanism of action, it is anticipated that tofersen would have a negligible potential for drug abuse; therefore, no studies were conducted to formally evaluate abuse potential. Tofersen is administered by IT lumbar injections in a hospital setting and thus there is low risk of drug abuse potential related to accidental administration.

Based on its specificity of binding to mRNA to lower SOD1 gene and protein expression, tofersen will not bind to receptors known to be involved in drug abuse. In repeat-dose toxicology studies in monkeys, neurobehavioral assessments were within normal limits, consistent with the lack of abuse potential. Thus, tofersen has a low potential for abuse and should not be considered a controlled substance.

6.10. Drug Abuse

No member of the ASO class, including tofersen, is known to exhibit abuse potential, and none are considered controlled substances or subject to special instructions for use, handling, or disposal.

Given the targeted mechanism of action and IT route of administration (necessitating in-clinic dosing), it is anticipated that tofersen would have a negligible potential for drug abuse. Tofersen does not cross the blood-brain barrier after administration peripherally, thus eliminating the possibility of drug abuse potential related to accidental intravenous or subcutaneous dose administration. Based on its specificity of binding to mRNA, tofersen is unlikely to bind to receptors known to be involved in drug abuse. In repeat-dose toxicology studies in monkeys, neurobehavioral assessments were within normal limits, consistent with the lack of abuse potential.

A pattern of AEs typical of drug abuse was not observed in the clinical studies of tofersen. Overall, tofersen has a low potential for abuse and should not be considered a controlled substance.

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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA215887
Submission Number	0001
Submission Date	6/8/2022
Date Consult Received	6/8/2022
Drug Name	Tofersen (BIIB067)
Indication	SOD1-ALS (Treatment of amyotrophic lateral sclerosis (ALS) in adults with a confirmed mutation of the superoxide dismutase 1 (SOD1) gene)
Therapeutic Dose	Three loading doses of 100 mg administered at 14-day intervals followed by maintenance doses once every 28 days
Clinical Division	DN1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 6/8/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Clinical Study Report (NDA215887/SDN1; link);
- Concentration-QTc Analysis report (NDA215887/SDN1; link);
- Sponsor's non-clinical hERG report (IND124264/SDN114; link);
- Proposed product labelling (NDA215887/SDN1; link);
- Previous IRT review dated 12/23/2020 in DARRTS (link);
- Previous IRT review dated 05/24/2019 in DARRTS (link);
- Investigator's brochure (IND (b) (4) / SDN193; link); and
- Highlights of clinical pharmacology and cardiac safety (IND124264/SDN01O7; link).

1 SUMMARY

Tofersen, an antisense oligonucleotide, did not prolong the QTcF interval in this clinical and integrated nonclinical risk assessment approach under ICH E14 S7B Q&A 5.1 (link) – see Table 1 for overall results.

The clinical study 233AS101 Part C was a randomized, double-blind, placebo-controlled study during which 108 patients were randomized to receive tofersen at the therapeutic dosing regimen or placebo in a 2:1 ratio. The high clinical exposure scenario was not

defined, but therapeutic exposures are not expected to be affected by intrinsic or extrinsic factors (section 3.1).

Table 1: Clinical and Integrated Nonclinical Risk Assessment

<table>
<tr><td>QT assessment pathway</td><td>☑ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>Therapeutic dosing regimen [100 mg intrathecal Q14 days x 3 (loading) followed by 100 mg intrathecal Q28 days x 5 (maintenance)]
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTc</td><td>Tofersen 100mg intrathecal</td><td>731 ng/mL</td><td>0.3</td><td>(-4.7 to 5.2)</td></tr>
<tr><td colspan="5">Concentration represents the largest geometric mean Cmax in Part C.</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td>
<table>
<tr><th></th><th>Safety Margin</th><th>Reference Drugs</th><th>Best Practice Deviations</th></tr>
<tr><td>Tofersen</td><td>>16576x (9% inhibition at 34 µM)</td><td>None</td><td>None that impacts interpretation of results</td></tr>
</table></td></tr>
<tr><td>In vivo findings</td><td>ECGs are not informative because concentration at 0 and 24 hours on day 84 are subtherapeutic. ECGs were not collected at Tmax. At exposure ratio of 48x with 35mg dose, tofersen was well tolerated and no adverse events were noted.</td></tr>
<tr><td>Conclusion</td><td>• Integrated nonclinical assessment showed low risk for QTc prolongation at exposures exceeding the therapeutic exposures.
• The clinical and nonclinical assessments can be used as a substitute for a TQT study.</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The Applicant did not propose QT labeling language in SDN 0001 (link). Our recommendations are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics *Cardiac Electrophysiology* *At the maximum approved recommended dosing regimen, QALSODY does not prolong the QTc interval to any clinically relevant extent.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Tofersen (BIIB067) is an antisense oligonucleotide (ASO) that contains 15 phosphorothioate diester and 4 phosphate diester linkages (MW: 7128 Da, free acid). It is under accelerated approval for the treatment of amyotrophic lateral sclerosis (ALS) in adults with a confirmed mutation of the superoxide dismutase 1 (SOD1) gene. The product is provided as liquid for intrathecal injection. The proposed therapeutic dosing regimen is three loading doses of 100 mg administered at 14-day intervals followed by maintenance doses of 100 mg once every 28 days thereafter.

The sponsor requested for TQT waiver based on the absence of cardiovascular safety signal in the nonclinical and clinical studies with BIIB067, as well as the inability for an ASO of a similar chemical class to BIIB067 to have an impact on QTc prolongation at systemic doses 2-times the BIIB067 dose. We recommended integrated nonclinical and clinical approach in our previous review (5/24/2019). The sponsor conducted in vitro hERG assay and monkey toxicology study, which we found reasonable to support the waiver in the previous review (12/23/2020).

The sponsor's QT risk assessment was based on Study 233AS101 Part C. Study 233AS101 included three parts. Part A was a SAD study evaluating a single dose of 10, 20, 40, and 60 mg of tofersen or placebo in 20 patients with ALS. Part B was a MAD study evaluating 20, 40, 60, and 100 mg of tofersen or placebo in 50 patients, administered as 3 loading doses once every 2 weeks and 2 maintenance doses once every 4 weeks by intrathecal injection; intensive PK/ECG were collected at pre-dose and 1, 2, 4, 6 h post-dose on day 1 and day 85 (last maintenance dose). For both Part A and B, a safety review took place prior to dosing of the next higher dose cohort. Part C was the pivotal and QT evaluation study. It was a randomized, double-blind, placebo-controlled study during which 108 patients were randomized to receive tofersen 100 mg or placebo in a 2:1 ratio. The study enrolled patients considered more likely to experience faster disease progression during the study period ("enriched" subgroup) as well as patients considered more likely to experience slower progression ("other" subgroup). 72 subjects (39 in the enriched and 33 in the other subgroup) received at least one dose of 100 mg tofersen and 36 subjects (21 in the enriched and 15 in the other subgroup) received at least one dose of placebo. Study medication was administered via intrathecal bolus injection over 1 to 3 minutes. Three loading doses were administered once every 2 weeks (Days 1, 15, 29), followed by 5 maintenance doses

administered once every 28 days. PK/ECG were collected at pre-dose and 1, 2, 4, 6 h post-dose on day 1 and day 85 in addition to pre-dose only on day 57, 113, 141, 169.

The geometric mean of maximum concentration at steady state following proposed dosing regimen of 100 mg tofersen was 1182 ng/mL (Tmax ~ 4 h) as evaluated on day 85 in Part B (n = 10) and was 602.8 ng/mL (Tmax ~ 4 h) as evaluated on day 85 in Part C (n = 19). The exposure discrepancy in Part B and Part C might be caused by a combination of small number of subjects and large exposure variance due to intrathecal administration. Since Part C was conducted in a larger targeted patient population, the mean Cmax in Part C was considered sufficient to characterize therapeutic exposure.

Due to the class of molecule (antisense oligonucleotide) and route of administration (intrathecal), exposure is not predicted to be affected meaningfully by intrinsic factors (e.g., age, sex, renal/hepatic impairment) or extrinsic factors (e.g., drug interactions or food effects). Therefore, the high clinical exposure would be similar to the therapeutic exposure.

The primary analysis is concentration-QT modeling. There were major deviations in analysis plan. The original analysis plan defined paired concentration and QT records as QT measures collected within 30 minutes. (b) (4) (the CRO) decided to expand the paired time window to be 1 h to reduce the exclusion of data from ~25% to 10% prior to the initiation of analysis. We performed primary analysis considering 30 minutes window and sensitivity analysis considering 1 hour window. There was no significant difference between the primary analysis and the sensitivity analysis.

3.1.2 Nonclinical Safety Pharmacology Assessments

The sponsor assessed the effects of tofersen (BIIB067) on hERG current (study report P067-19-04, link). Original electrophysiology records for ion channel studies were provided by the sponsor. We reanalyzed these records of hERG assay to assess data quality and verify study report conclusions (see Appendix).

The GLP in vivo study (666853-AS1) assessed pharmacological effects of BIIB067 on the cardiovascular system including ECG changes (see Appendix).

Reviewer's comment: *The hERG results showed that BIIB067 has a large hERG safety margin (>16576x), suggesting BIIB067 has a low risk for QT prolongation by directly inhibiting the hERG current at clinical exposure. The hERG assay met most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The large safety margin precluded the need for reference drugs and concentration verification.*

ECGs in the TK study are not informative because concentration at 0 and 24 hours on day 84 are subtherapeutic. ECGs were not collected at Tmax. At exposure ratio of 48x with 35mg dose, tofersen was well tolerated and no adverse events were noted.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for tofersen was based on exposure-response analysis, please see section 3.2.3 for additional details.

Sponsor presented some descriptive statistics for QTc and HR.

Reviewer's comment: *FDA reviewer provided descriptive statistics for all intervals. Descriptive statistics of QTc and HR are not directly comparable with the sponsor's results. Sponsor presented one hour window data, ΔΔQTc not grouped by days and the difference between HR from its baseline. We presented placebo-corrected change from baseline for each interval (QTc, HR, PR and QRS) of thirty minutes window data grouped by days. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

Sponsor presented categorical analysis for QTcF and ΔQTcF. None of the subjects experienced QTcF >500 msec and ΔQTcF >60 msec. FDA reviewer could not locate categorical analysis for other intervals (HR, PR and QRS).

Reviewer's comment: *FDA reviewer's analyses showed similar results for QTcF and ΔQTcF. It also showed that 10 subjects experienced HR >100 beats/min. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. However, in addition to treatment and tofersen concentration the sponsor also included day of sampling (categorized as less than day 85, less than day 141, and less than day 169) and clock-time of sampling (time of the day) as predictors of ΔQTcF (See page 49 of 187 of the sponsor's Concentration-QTc Analysis report). The results of the sponsor's analysis show an absence of significant QTc prolongation.

In the final analysis, the mean ΔΔQTcF increased with increasing tofersen concentration with a slope of approximately zero. Therefore, the mean and upper limit of the confidence region were below a ΔΔQTcF of 10 ms for the 5th to 95th percentiles of the observed tofersen concentration range.

Reviewer's comment: *In contrast to the sponsor's analysis, the reviewer analyzed data from day 1 and day 85. In addition, the reviewer included time after dose instead of clock-time as predictor of* ΔQTcF. *Despite the differences, the results from the reviewer's analysis indicate absence of significant QTc prolongation and are therefore consistent to those reported by the sponsor (See Section 4.5).*

3.2.4 Safety Analysis

In Study 233AS101 Part C, adverse events (AEs) were balanced between the tofersen group (69/72 [95.8%]) and the placebo group (34/36 [94.4%]) in the safety population.

One subject (b) (6) who received tofersen died during the study. This subject was in the "enriched" subgroup, in which subjects were considered more likely to experience faster

disease progression during the study period. The subject experienced a Grade 5 SAE of congestive cardiac failure that was not considered treatment related by the investigator:

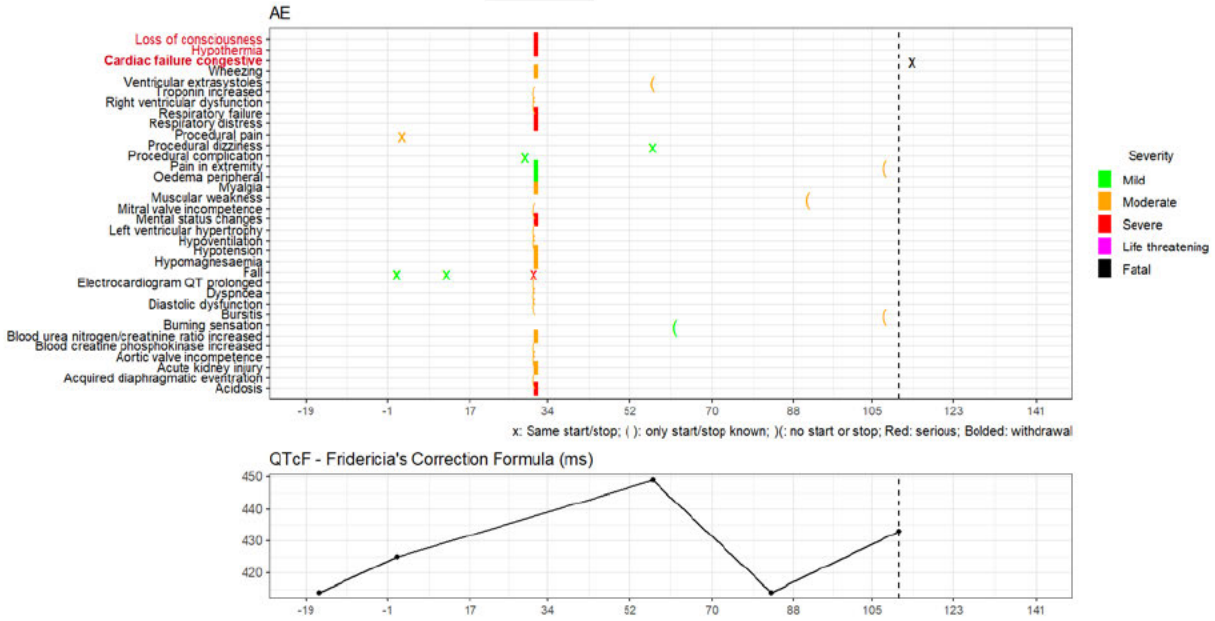
<u>Cardiac failure congestive:</u> Subject (b) (6), a 63-year-old male, was enrolled into Study 233AS101 Part C and began a treatment regimen of tofersen 100 mg from (b) (6) to (b) (6). The subject received study treatment for 111 days. The subject's medical history included: type II diabetes mellitus, hypercholesterolemia, hypertension, hypertriglyceridemia, incomplete right bundle branch block ECG finding, inferior infarct ECG finding, mild cardiomegaly, coronary artery disease (myocardial infarction (b) (6) and (b) (6)), coronary artery bypass grafting surgery, left main coronary artery stenosis, percutaneous coronary intervention, and subtotal occlusion of the right coronary artery. On (b) (6) (Day 31), AEs of hypothermia and loss of consciousness were reported, which were classified as SAEs by the Investigator. The most recent dose was given on (b) (6) (Day 29). The event was resolved on (b) (6) (Day 32). The Investigator assessed the events as severe and considered to be unrelated to study treatment. No action was taken with study treatment. On (b) (6) (Day 114), an AE of cardiac failure congestive was reported, which was classified as an SAE by the Investigator. The most recent dose given on (b) (6) (Day 111). On (b) (6), the subject was found deceased by their aide. It appeared that the subject had fallen and impacted his head as blood was seen on the floor. Death certification indicated congestive heart failure as the immediate cause of death. As the subject was not admitted to hospital and had passed away when they were found, no diagnostic test was done. The medical examiner completed the death certificate, indicating death of natural causes secondary to congestive heart failure. No autopsy was performed, and the subject was found unresponsive so there was no way to be certain as to the etiology of the fall. There was no change in treatment prior to the event of congestive heart failure. There was no treatment for the event given its nature.

Figure 1 showed the narrative plot for this subject. He had a TEAE of moderate electrocardiogram QT prolonged starting on Day 31. His baseline (Day 1) QTcF was 425 msec and on Day 57 QTcF was 449 msec pre-dose. The event was considered not resolved and unrelated to treatment. He also experienced a moderate ventricular extrasystoles on Day 57 that was considered not resolved and unrelated to treatment.

The incidence of SAEs was higher in the tofersen group (18.1%) compared with the placebo group (5.6%). More subjects in the "enriched" subgroup experienced SAEs compared with the "other" subgroup. Within the "enriched" subgroup, the incidence of SAEs was higher in the tofersen group (28.2%) compared with the placebo group (19.0%). The most frequently reported SAEs overall (≥ 2%) were dyspnea, pulmonary embolism, aspiration pneumonia, dehydration, and atelectasis.

AEs that led to discontinuation of study treatment were only reported in the tofersen group (4/72 subjects [5.6%]) and included the following PTs: congestive cardiac failure [SAE], myelitis, chemical meningitis, and pulmonary embolism (1/72 subjects [1.4%] each).

Figure 1. Narrative Plot for Subject (b) (6).



Two subjects (2.8%) in the tofersen group had cardiac disorder AEs (Table 2). One subject (b) (6) had a mild tachycardia that was considered not resolved and unrelated to treatment. The other subject (b) (6) had all the other cardiac disorder AEs in Table 2 except for the tachycardia (see the narrative above and Figure 1). Both subjects were in the enriched group and no subjects had cardiac events in the placebo group.

Table 2. AE of Cardiac Disorders (SOC).

	placebo (N=36) n (%)	tofersen 100 mg (N=72) n (%)
Aortic valve incompetence	0	1 (1.4)
Cardiac failure congestive	0	1 (1.4)
Diastolic dysfunction	0	1 (1.4)
Left ventricular hypertrophy	0	1 (1.4)
Mitral valve incompetence	0	1 (1.4)
Right ventricular dysfunction	0	1 (1.4)
Tachycardia	0	1 (1.4)
Ventricular extrasystoles	0	1 (1.4)

The incidence of abnormalities in ECG measurements was slightly higher in the tofersen group compared to the placebo group, with 8 subjects (11.3%) displaying a maximum increase from baseline in QTcF > 30 to 60 msec in the tofersen group compared to 2 subjects (5.6%) in the placebo group. No subjects in the tofersen or placebo group displayed an increase from baseline in QTcF > 60 msec, and no subjects displayed maximum postbaseline QTcF > 480 msec.

Reviewer's comment: *One subject receiving tofersen had a fatal cardiac failure congestive AE. There were no seizure or significant ventricular arrhythmias in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall Quality

719 digital ECGs and 197 paper ECGs were submitted. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. In the protocol, the sponsor proposed to collect paired concentration and QT data within 30 minutes window. FDA statistical reviewer used data from 30 minutes window for the primary analysis and presented in the report. FDA statistical reviewer also performed sensitivity analysis using one hour window data. Data analysis results are similar for 30 minutes window data and one hour window data. The statistical reviewer evaluated the ΔQTcF effect using descriptive (parametric) statistics.

4.3.1 QTc

Figure 2 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment and treatment days are shown in Table 3.

Figure 2: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

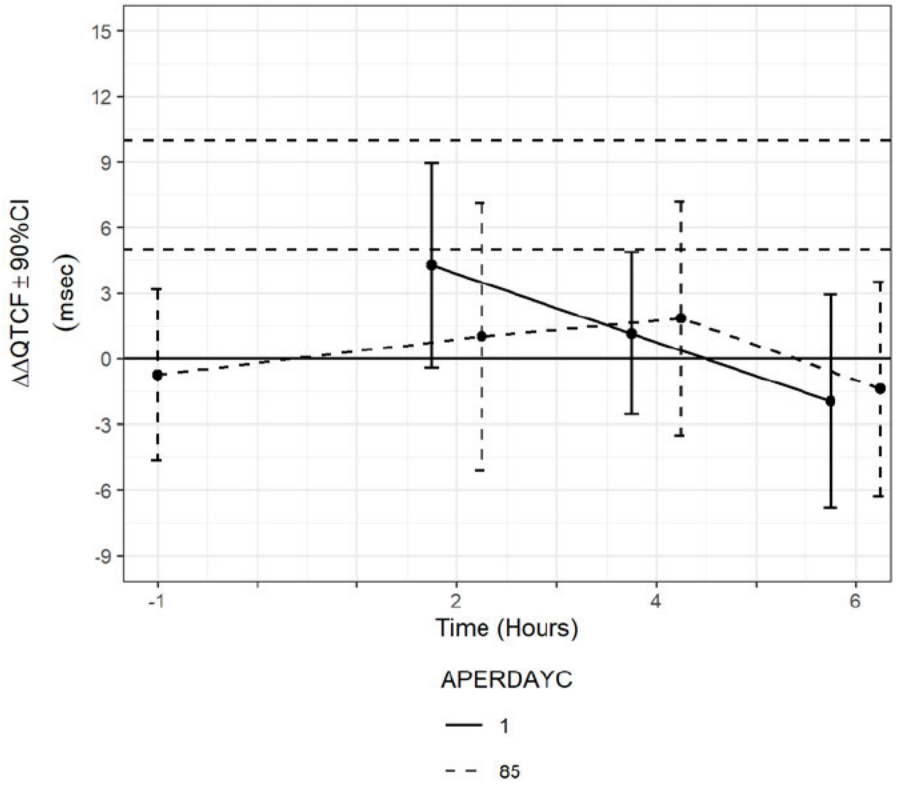


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Tofersen 100 mg	1	19 / 15	2.0	4.3	(-0.4 to 8.9)
Tofersen 100 mg	85	18 / 15	4.0	1.8	(-3.5 to 7.2)

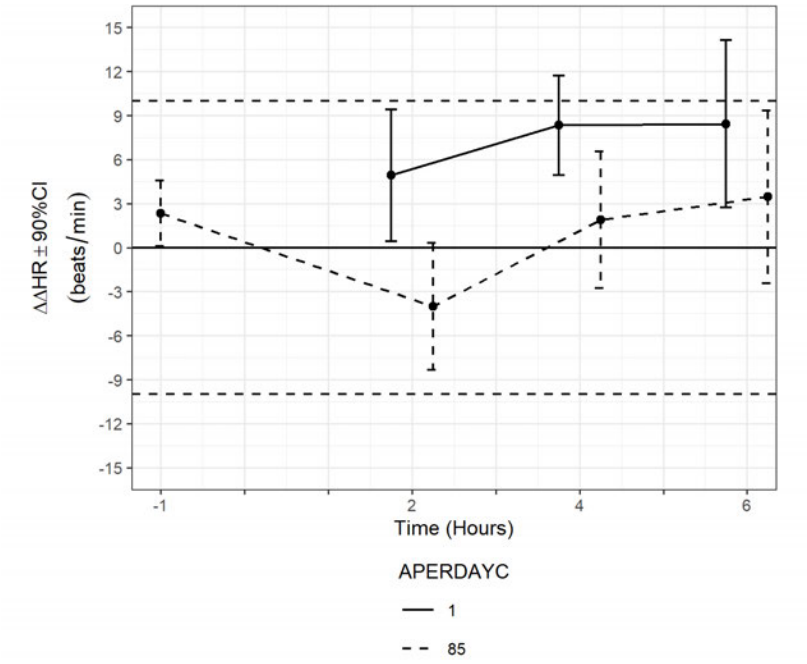
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 3 displays the time profile of ΔΔHR for different treatment groups.

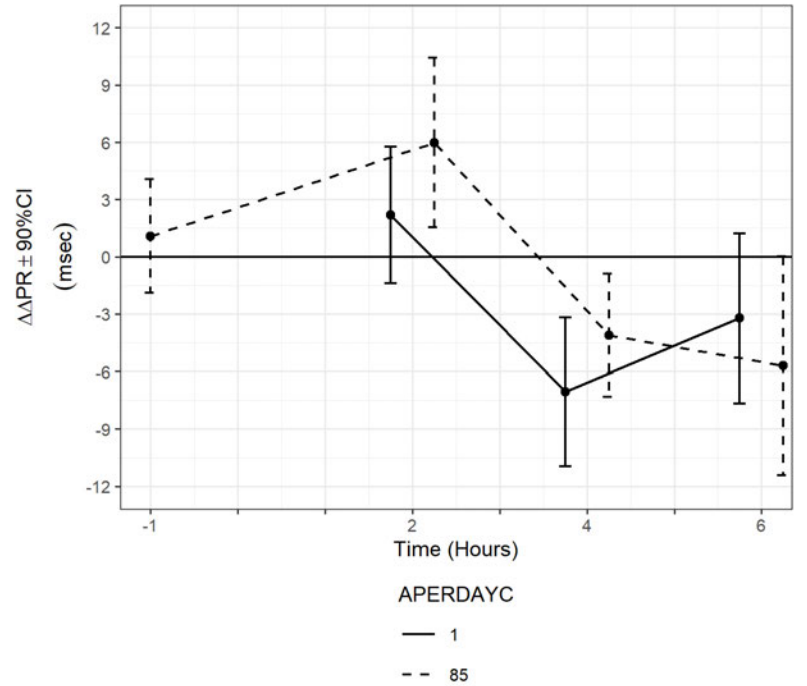
Figure 3: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 4 displays the time profile of ΔΔPR for different treatment groups.

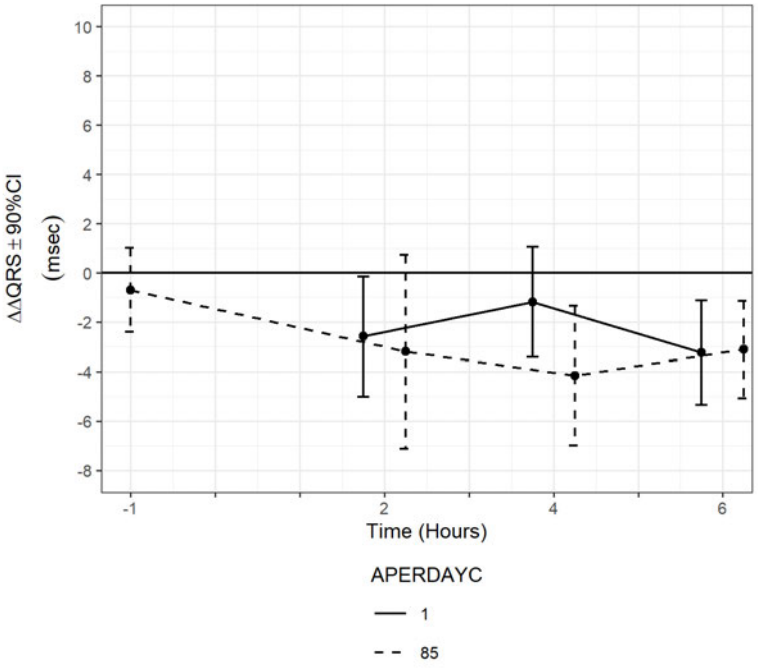
Figure 4: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 5 displays the time profile of ΔΔQRS for different treatment groups.

Figure 5: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF values > 500 msec and/or ΔQTcF > 60 msec in the treatment arm of tofersen 100 mg.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). Ten subjects in tofersen 100 mg group experienced HR >100 beats/min. Percentage of subjects with HR > 100 beats/min is balanced between placebo and tofersen.

Table 4: Categorical Analysis for HR (maximum)

Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tofersen 100 mg	72	518	62 (86.1%)	493 (95.2%)	10 (13.9%)	25 (4.8%)
Placebo	36	289	31 (86.1%)	278 (96.2%)	5 (13.9%)	11 (3.8%)

4.4.3 PR

None of the subjects experienced PR >220 msec; with 25% increase over baseline in tofersen 100 mg group.

4.4.4 QRS

None of the subjects experienced QRS >120 msec; with 25% increase over baseline.

4.5 Exposure-Response Analysis

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. On days 1 and 85, data were available from 22 and 21 subjects respectively in the tofersen arm, while from the placebo arm, data were available from 15 subjects. As stated in section 4.3, time matched PK/ECG data from within a 30-minute observation window was used for the C-QTc analysis.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 3 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 6 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 7 shows the relationship between drug concentration and ΔQTcF, and supports the use of a linear model.

Figure 6: Time-course of Drug Concentration (top) and QTcF (bottom)[1]

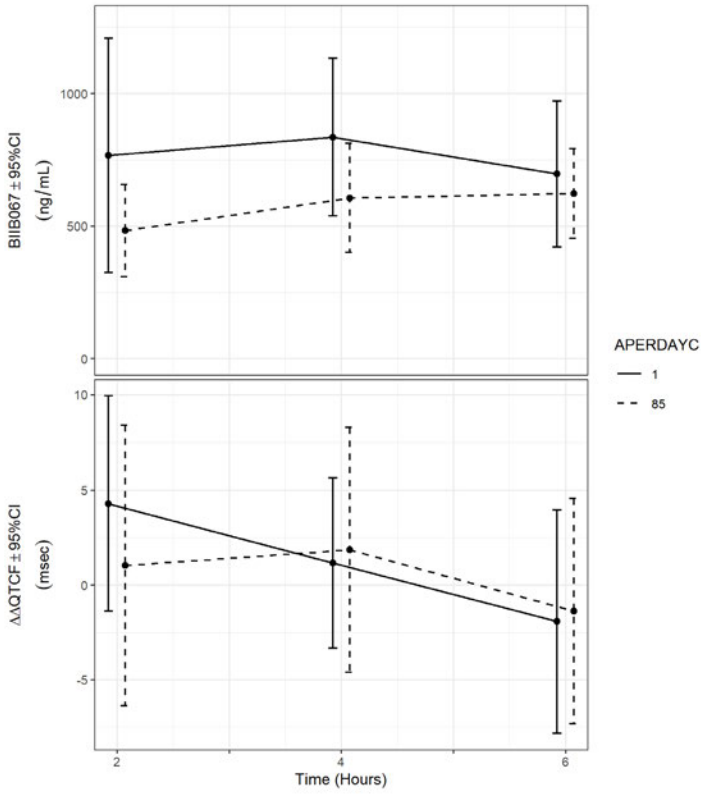
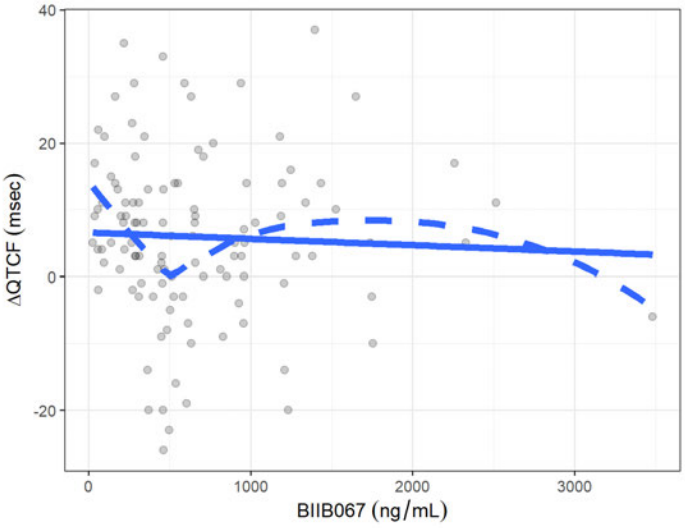


Figure 7: Assessment of Linearity of the Concentration-QTcF Relationship



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 2

Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 8. Predictions from the concentration-QTcF model are provided in Table 5.

Figure 8: Goodness-of-fit Plot for QTcF

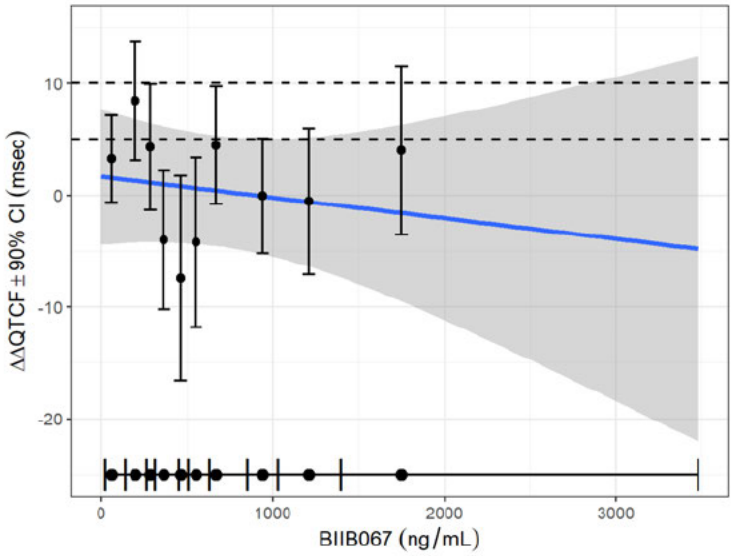


Table 5: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	BIIB067 (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Tofersen 100 mg	Day 1, Part C (N=72)	731	0.3	(-4.7 to 5.2)
BIIB067 concentration shown as geometric mean Cmax from all PK time points				

4.5.1.1 Assay Sensitivity

Not applicable. The clinical study did not include a positive control and QT effects were evaluated at the anticipated therapeutic exposures.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX: REVIEW OF SUPPORTING NONCLINICAL DATA

The sponsor is developing tofersen (BIIB067), an antisense oligonucleotide, for the treatment of amyotrophic lateral sclerosis (ALS) in adults with a confirmed mutation of the superoxide dismutase 1 (SOD1) gene. Previously the IRT recommend an integrated nonclinical and clinical approach to support a TQT study waiver for this oligonucleotide. The sponsor now submitted the hERG raw data for review.

5.1 IN VITRO HERG ASSAY

5.1.1 Sponsor's submission

The GLP hERG study report P067-19-04 (link) describes the potential effects of BIIB067 on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (33-35ºC), using the hERG current protocol recommended by the FDA (link). The positive control article terfenadine inhibited hERG potassium current by (Mean ± SD; n = 2) 76.1 ± 5.2% at 60 nM. Solution samples were collected from the outflow of the perfusion apparatus for drug concentration verification. The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

BIIB067 inhibited hERG current by (Mean ± SEM; n = 4) 9.3 ± 1.3% at 1 µM, 14.0 ± 2.8% at 3 µM, 6.1 ± 1.8% at 10 µM and 9.1 ± 4.0% at 34 µM versus 15.8 ± 1.7% (n = 4) in control. the IC50 for the inhibitory effect of BIIB067 on hERG potassium current could not be calculated but was estimated to be greater than 34 µM.

Reference drug verapamil inhibited hERG potassium current by (Mean ± SEM; n = 4) 10.5 ± 1.5% at 0.03 µM, 25.5 ± 0.9% at 0.1 µM, 40.8 ± 1.8% at 0.3 µM and 79.1 ± 1.3% at 1 µM. The IC50 for the inhibitory effect of verapamil on hERG potassium current was 0.3 µM (Hill coefficient = 1.0).

5.1.2 Reviewer's assessment and data reanalysis

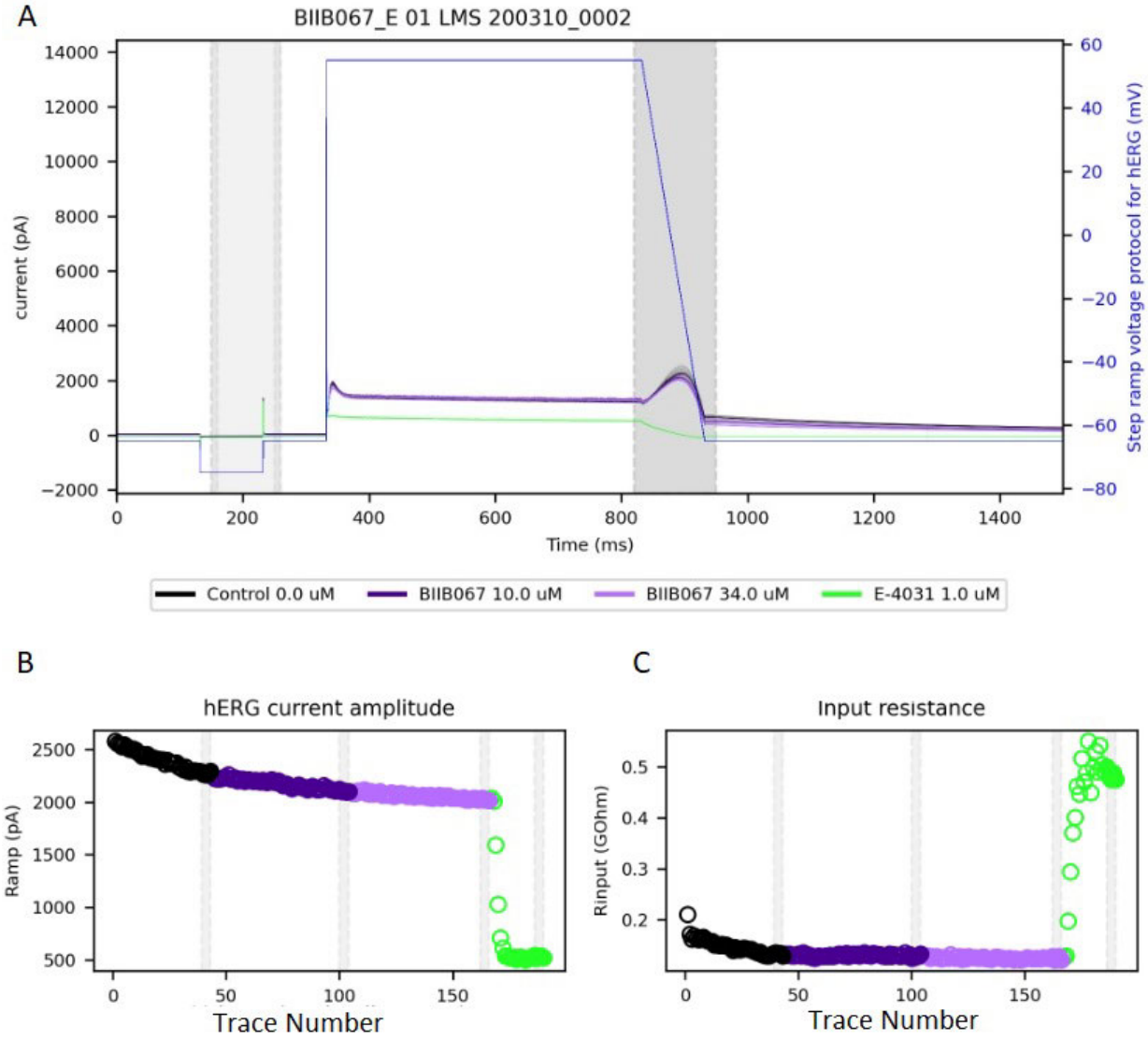
Original electrophysiology records for the hERG assay provided by the sponsor. An IRT reviewer reanalyzed these records to assess data quality and verify study report conclusions. For data quality assessment, current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The hERG current was assessed at near-physiological temperature (33-35ºC), at the stimulating frequency of 0.2 Hz (every 5 seconds), using the recommended hERG voltage protocol that is available at IRT's website (link). The positive control verapamil was evaluated at four concentrations (0.03, 0.1, 0.3 and 1 µM) to allow for the estimation of the IC50 against hERG channel. A full hERG blocker (1 µM E-4031) was added at the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. Solution samples were collected from outflow of perfusion apparatus for drug concentration verification. The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

Representative analysis from one cell of hERG study (Cell ID: BIIB067_E 01 LMS 200310_0002) is shown in Figure 9. The panel A shows recorded traces of each treatment group from this cell.

The voltage waveform used to evoke hERG current is shown in blue. The small hyperpolarizing voltage pulse from -80 to -90 mV is designed to calculate input resistance according to Ohm's law. Two shaded gray areas on the left show measurement cursors used to calculate baseline currents at -80 mV and at -90 mV, respectively. The gray shade on the right highlights the region where peak hERG tail current was measured. Traces recorded in control solution are shown in black, following 10 µM BIIB067 application in dark purple; 34 µM BIIB067 in light purple; and 1 µM E-4031in green at the end of the experiment. Time course plots for peak ramp current and input resistance are shown on panels B and C, respectively.

Figure 9: Representative analysis (Cell ID: BIIB067 E 01 LMS 200310 0002)



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solutions (dark purple and light purple solid circles represent drug concentration at 10 and 34 µM, respectively) were then averaged to calculate % inhibition by that concentration.

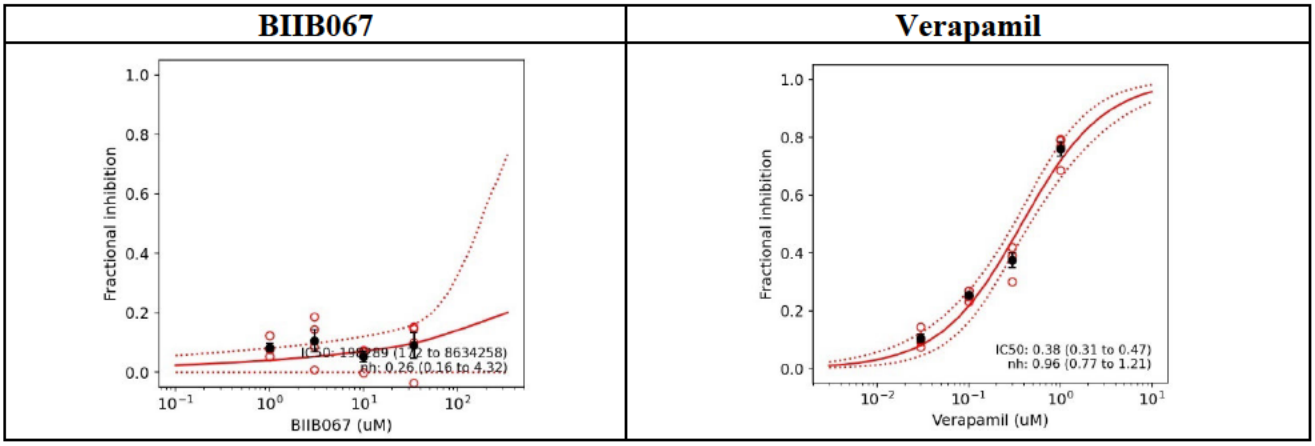
Results (with E-4031 subtraction) of BIIB067 and verapamil on hERG current are summarized in Table 6.

Table 6. Effects of BIIB067 and verapamil on hERG current

Test article	N	Inhibition (fraction)	SEM	IC50 (μM)
BIIB067 0 μM	4	0.14	0.02	>34
BIIB067 1μM	4	0.08	0.01	
BIIB067 3 μM	4	0.11	0.04	
BIIB067 10 μM	4	0.05	0.02	
BIIB067 34 μM	4	0.09	0.04	
Verapamil 0.03 μM	4	0.10	0.01	0.38 μM
Verapamil 0.1 μM	4	0.25	0.01	
Verapamil 0.3 μM	4	0.37	0.03	
Verapamil 1 μM	4	0.76	0.03	

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that BIIB067 inhibited the hERG current by 5% and 9% at 10 and 34 μM, respectively. The IC50 of BIIB067 on hERG current is expected to be larger than 34 μM. The positive control verapamil inhibited the hERG current with an IC50 of 0.38 μM, which is similar to the mean IC50 value (0.33 μM) of verapamil on hERG current from FDA (DARS lab) in the HESI-BAA project. The concentration-response curves of BIIB067 and positive control verapamil on hERG currents are summarized in Figure 10.

Figure 10. Effects of BIIB067 and verapamil on hERG current



5.1.3 In vitro Summary

The comparisons of sponsor's hERG assay and the best practice recommendations by the new draft ICH S7B Q&A 2.1 are summarized in Table 7.

Table 7. Comparison of sponsor's hERG assays with the new draft ICH S7B Q&As best practice recommendations

Best Practice Elements	Deviations/limitations	Impact from Deviations
Temperature (35-37°C)	None	
Voltage protocol	None	
Recording quality	None	
IC50 Calculation	None	
Concentration verification	Unknown whether samples were collected from satellite or real experiment	Drug loss won't impact interpretation of large safety margin
Positive Control	Verapamil may not be an adequate reference compound because due to its multi-ion current inhibition. Its low TdP risk is confounded by its additional effects in the calcium current.	TdP risk of BIIB067 could be underestimated
Negative Control (vehicle)	None	
Good Laboratory Practice	None	

Table 8. Safety Margins of BIIB067 on hERG Current

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (μM)	Mol Weight (g/mol)	Safety Margin (Ratio)
BIIB067	731	98%	14.62	>34 (9% inhibition)	7127.86	>16576x
Verapamil	400	90%	40	0.38	454.6	4.3x

largest geometric mean Cmax: 731 ng/mL. High clinical exposure has not been evaluated. Verapamil: Cmax 125~400 ng/mL at 120 mg q6h (label).

5.2 IN VIVO STUDY

5.2.1 Sponsor's submission

The GLP in vivo study (666853-AS1) assessed the systemic toxicity and pharmacokinetics of BIIB067 following repeat-dose intrathecal (IT) lumbar bolus injection for 13 weeks in the cynomolgus monkeys. BIIB067 formulations were administered intrathecally by lumbar bolus injection at level L3-L4 after anesthesia at a dose volume of 1.00 mL, followed by a 0.25 mL cerebrospinal fluid (CSF) flush, bi-weekly for the first month (Days 1, 14, and 28), then monthly thereafter (Days 56 and 84) at doses of 0, 4, 12 and 35 mg/dose (Groups 1 through 4). Group 5 received BIIB067 at a dose level of 12 mg/dose on Days 1. Blood, CSF and tissues were collected from all animals for toxicokinetic evaluation. ECG were performed on all animals (non-anesthetized temporarily restrained animals) once during the predose phase (during the morning hours), on Day 84 (5th dose) of the dosing phase (0 and 24 hours ± 30 minutes post-dose) and for all surviving animals at the end of the recovery phase (during the morning hours). No drug related

QTc prolongations were observed at all tested doses. The PK data showed the exposures (Cmax) were 35100 ng/mL and 26400 ng/mL on Day 1 and Day 84 at 35 mg/kg, respectively. The Tmax were ~2h at doses of 12 and 35 mg. No positive drugs were used in the study.

Reviewer's comment: ECGs are not informative because concentration at 0 and 24 hours on day 84 are subtherapeutic. ECGs were not collected at Tmax.

5.3 NON-CLINICAL SUMMARY

In summary, the hERG assay meet most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG results showed that BIIB067 has a large hERG safety margin (>16576x), suggesting BIIB067 has a low risk for QT prolongation by directly inhibiting the hERG current at clinical exposure**.** The large safety margin precluded the need for reference drugs and concentration verification.

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CHRISTINE E GARNETT
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 13, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 215887
Product Name and Strength:	Qalsody (tofersen) injection, 100 mg/15 mL (6.7 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biogen Inc.
FDA Received Date:	May 25, 2022; July 29, 2022
OSE RCM #:	2022-1035
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Qalsody (tofersen) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Qalsody prescribing information (PI), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, carton labeling, and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Biogen Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Administration site, technique, and procedure can be improved for clarity.	The current administration site, technique, and procedure language includes “intrathecal bolus injection over 1-3 minutes” in the HPI and “lumbar	To reduce the risk for administration site, technique, and procedure medication errors, we recommend specifying which intrathecal regions (lumbar only vs cervical

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		puncture" in Section 2; however, it is unclear if the lumbar region is the only acceptable site. We note the cervical space and use of Ommaya ports occur in practice for other intrathecally administered medications such as Spinraza.	and lumbar, or other) and types of access (direct injection via lumbar puncture needle, use of ports, or other if applicable) are acceptable for administration of the proposed product. We defer to the Division make the clinical determination based on standards of care and clinical trial experience.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The recommended dosage statement (b) (4)	The recommended dosage is fixed (100 mg or 15 mL); (b) (4)	We recommend revising the recommended dosage statement from (b) (4) to read "100 mg (15 mL)."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statements in Section 16.2 do not appear to be complete and may contain errors.	Improper storage may increase the risk for degraded product medication errors.	We recommend clarifying whether the statement "removed from the original carton" should read "removed from refrigeration". We also recommend clarifying the max temperature excursion allowed for product removed and returned to the fridge. Once finalized, we recommend the final room temperature storage language be added to the carton labeling.

5 RECOMMENDATIONS FOR BIOGEN INC.

Table 3. Identified Issues and Recommendations for Biogen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The displayed formats of the expiration date placeholder do not align. The format on the carton read “000000”, while the container reads “MM/YYYY”.	We are unable to assess the expiration date from a medication error perspective.	Identify the expiration date format you intend to use, and specify whether the month will be represented with numerical or alphabetical characters. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The usual dosage statements do not align	Can be improved for consistency.	We recommend revising the following statements:

Table 3. Identified Issues and Recommendations for Biogen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	with language used in the PI.		(b) (4) [redacted] to read: "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	We note the product is to remain in the original carton for storage; however, not all storage condition statements are presented on the carton labeling.	Improper storage may increase the risk for degraded product medication errors.	We recommend adding alternate storage conditions statements to the side panel of the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Qalsody that Biogen Inc. submitted on May 25, 2022.

Table 4. Relevant Product Information for Qalsody	
Initial Approval Date	n/a
Active Ingredient	tofersen
Indication	treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene
Route of Administration	Intrathecal bolus
Dosage Form	injection
Strength	100 mg/15 mL (6.7 mg/mL)
Dose and Frequency	100 mg • Loading dose: every 14 days for 3 doses • Maintenance dose: every 28 days
How Supplied	Carton containing one single dose vial
Storage	• Store refrigerated between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. • Do not freeze. • If no refrigeration is available, QALSODY may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days. • Prior to administration, unopened vials of QALSODY can be removed from and returned to the refrigerator, if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 36 hours at a temperature that does not exceed 30°C (86°F).
Container Closure[a]	(b) (4) Type I clear glass vials. Each vial is closed with a (b) (4) rubber stopper. The stoppered vial is sealed with an aluminum closure with a flip-off plastic button.

[a] Container closure specifications available at: \\CDSESUB1\evsprod\nda215887\0001\m3\32-body-data\32p-drug-prod\tofersen-solution-for-injection\32p7-cont-closure-sys\container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 3, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Qalsody, tofersen, IND 124264, and NDA 215887. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Qalsody labels and labeling submitted by Biogen Inc. on May 25, 2022.

- Container label
- Carton labeling
- Prescribing Information (Image not shown), available from \\CDSESUB1\evsprod\nda215887\0001\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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