CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215887Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	215887
PDUFA Goal Date	April 25, 2023
OSE RCM #	2022-2526
Reviewer Name(s)	Sarah K. Holman, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 24, 2023
Subject	Evaluation of Need for a REMS
Established Name	Tofersen
Trade Name	Qalsody
Name of Applicant	Biogen Inc.
Therapeutic Class	Antisense oligonucleotide
Formulation(s)	100 mg/ 15 ml injection for intrathecal use
Dosing Regimen	100 mg/15 ml injection administered intrathecally for three doses administered at 14-day intervals followed by 100 mg/15 ml injection administered intrathecally every 28 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Qalsody (tofersen) is necessary to ensure the benefits outweigh its risks. Biogen Inc. submitted a New Drug Application (NDA) 215887 for tofersen through the Accelerated Approval pathway with the proposed indication for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene (SOD1-ALS). During the course of the review, the Agency revised the indication to the following: for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene. The risks associated with tofersen include myelitis, radiculitis, aseptic meningitis, papilledema, and elevated intracranial pressure. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of tofersen outweigh its risks. ALS is a fatal, incurable, progressive neuromuscular disease with high unmet medical need, despite three FDA-approved therapies available for treatment. There are no FDA-approved gene-targeted therapies for treatment of SOD1-ALS. The healthcare providers who are likely to prescribe tofersen are specialized clinicians that should be able to manage the risks associated with tofersen. The risks of myelitis, radiculitis, aseptic meningitis, papilledema, and elevated intracranial pressure will be communicated through Section 5: Warnings and Precautions of the labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Qalsody (tofersen) is necessary to ensure the benefits outweigh its risks. Biogen Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 215887 for tofersen through the Accelerated Approval pathway with the proposed indication for treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene.[1] This application is under review in the Division of Neurology 1. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Qalsody (tofersen), a new molecular entity[a], is an antisense oligonucleotide proposed for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene (SOD1-ALS).[2] In SOD1-ALS patients, mutations in the *SOD1* gene lead to

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

accumulation of a toxic form of SOD1 protein causing neurodegeneration. Tofersen binds to the *SOD1* mRNA resulting in degradation of the mRNA and reduction in SOD1 protein synthesis.[3]

Tofersen is proposed for chronic use[b] and will be supplied as 100 mg/15 mL solution in a single-dose vial for intrathecal injection. The recommended dosage is 100 mg administered as an intrathecal bolus injection over 1 to 3 minutes. Prior to administration, 10 mL of cerebrospinal fluid is removed using a lumbar puncture needle. Initial treatment with tofersen will consist of three loading doses administered every 14 days followed by a maintenance dose administered once every 28 days thereafter.[2] Given the intrathecal administration, tofersen is likely to be administered in a healthcare setting. Tofersen was granted orphan drug designation in September 2015 and fast track designation in December 2015. Tofersen is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215887 relevant to this review:

- **09/19/2015**: Orphan drug designation granted for the treatment of amyotrophic lateral sclerosis
- **12/23/2015**: Fast track designation granted for IND 124264 for the treatment of amyotrophic lateral sclerosis
- **05/25/2022**: NDA 215887 submitted through the Accelerated Approval pathway for the treatment of adults with amyotrophic lateral sclerosis associated with a mutation in the superoxide dismutase 1 gene.[1]
- **09/15/2022**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tofersen.[4]
- **10/05/2022**: The Applicant submitted an amendment regarding the plasma neurofilament light chain (NfL) and cerebrospinal fluid (CSF) SOD-1 method validation and analysis for studies 233AS101 part C and 233AS102.[5]
- **10/07/2022**: The Applicant submitted an amendment summarizing subject survival in studies 233AS101 and 233AS102 for patients with the A5V variant.[6]
- **10/12/2022**: Major amendment acknowledgment letter sent to the Applicant based on the amendments submitted on October 5, 2022 and October 7, 2022; PDUFA goal date extended by 3 months.[7]
- **03/22/2023:** Peripheral and Central Nervous System (PCNS) Advisory Committee (AC) Meeting was convened to discuss whether the observed reduction of NfL is reasonably likely to predict clinical benefit and support accelerated approval of tofersen for the treatment of patients with

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

SOD1-ALS. The AC voted 9 in favor of and 0 against regarding whether the available evidence is sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS. The AC voted 3 in favor of, 5 against, and 1 abstained regarding whether clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects of relevant biomarkers, provided convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS. A REMS proposal was not discussed.[8]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

ALS is a fatal[c], incurable, progressive neuromuscular disease that is characterized by progressive degeneration of motor neurons in the brain and spinal cord.[9] The motor degeneration causes muscle atrophy and weakness that leads to muscle stiffness, twitches, and spasms in the early stages of the disease. As the disease progresses, patients experience muscle paralysis, shortness of breath, loss of speech and the ability to eat. Patients with ALS will typically die from respiratory failure.[10] The average life expectancy after diagnosis is two to five years, though some patients may live up to ten years or longer.[11] The most common age of onset of ALS is between 60 and 75 years, although the disease can occur at a younger age.[10,12,13] The specific cause of ALS is unknown, though in approximately 5-10% of cases, family history of ALS is present, known as Familial ALS, often associated with a genetic mutation.[14,15] In the United States, approximately 15,000 to 30,000 people have ALS, with 7000 new cases diagnosed each year.[10,12,13,d] The *SOD1* gene mutation accounts for approximately 15-30% of familial ALS cases and approximately 2% of ALS cases overall, equating to approximately 300-600 people living with SOD1-ALS in the United States.[15]

3.2. Description of Current Treatment Options

There are three pharmacological therapies FDA- approved to treat ALS: Rilutek (riluzole)[16], Radicava (edaravone)[17], and Relyvrio (sodium phenylbutyrate and taurursodiol)[18]. Riluzole, approved in 1995, is thought to reduce glutamate-induced excitotoxicity and consequent neuronal cell death, though the exact mechanism of action is unknown. Hepatic injury, neutropenia and interstitial lung disease are all associated with riluzole therapy.[16] Edaravone, approved in 2017, is a free-radical scavenger that is thought to reduce oxidative stress, which has been implicated in the pathogenesis of ALS. Serious side

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

effects include hypersensitivity reactions and sulfite allergic reactions. Labeling for edaravone includes a Medication Guide for patients.[17] Sodium phenylbutyrate and taurursodiol, approved in 2022, is an endoplasmic reticulum and mitochondrial stress inhibitor. Serious side effects include worsening diarrhea in patients with bile acid circulation disorders, and fluid retention or hypertension in patients sensitive to salt intake given the high sodium content.[18] Though there are three FDA- approved therapies for ALS, there remains a high unmet medical need for new treatments as patients still face rapid morbidity and fatality. There are currently no gene-targeted therapies for the treatment of Familial ALS.

In addition to the FDA-approved drug therapies, non-drug treatments such as physical, occupational, nutritional, and speech therapies can help maintain patients' quality of life, mobility, and ability to communicate with others for as long as possible.[10] Patients often require symptomatic management of ALS symptoms including dysarthria, dyspnea, muscle spasms, sialorrhea, pain, and sleep disturbance. As the patient's clinical course worsens, measures such as ventilatory support and gastrostomy tube placement may be necessary.[19]

4. Benefit Assessment

The efficacy of tofersen in SOD1-ALS was evaluated in one pivotal phase 3 trial, Study 233AS101 Part C (hereafter referred to as Study 101C, National Clinical Trial [NCT] NCT02623699).[20] Study 101C was a multicenter, randomized, double-blind, placebo-controlled study which evaluated 108 subjects (tofersen group=72, placebo group=36) with weakness attributable to ALS and a confirmed *SOD1* mutation. Subjects were randomized 2:1 to receive tofersen 100 mg or placebo over a 24-week treatment period. Subjects received 3 loading doses intrathecally every 14 days followed by maintenance dosing once every 28 days thereafter. Concomitant use of standard of care treatments (i.e. riluzole and/or edaravone) was permitted, with 61-62% using riluzole and 8.3% using edaravone.[20]

The primary endpoint was change from baseline to Week 28 in ALS Functional Rating Scale-Revised (ALSFRS-R)[e] total score.[20] Clinical function was evaluated through the following secondary endpoints: change from baseline to Week 28 in slow vital capacity, handheld dynamometry megascore, time to death or permanent ventilation, and time to death. The primary efficacy analyses were conducted in the modified intention to treat (mITT) population which consisted of a prespecified "fast progressor" population[f] (tofersen group=39, placebo group=21). There was no statistically significant difference demonstrated between tofersen and placebo for the primary endpoint or the secondary endpoints SVC or HHD megascore. Time to death or permanent ventilation and time to death were not assessed due to lack of events.

[e] The ALS Functional Rating Scale-Revised is a 12-item scale that assesses function in four domains: bulbar, fine motor, gross motor, and respiratory. Each item is rated on a scale of 0 to 4, generating a total score of 0 to 48 with higher scores indicating better function.

[f] The prespecified "fast progressor" population was defined based on pre-randomization ALSFRS-R slope decline ≥ 0.2 points/month, SVC ≥ 65%, and mutation type.

Biomarkers were evaluated as key secondary endpoints including change from baseline in total SOD1 cerebrospinal fluid (CSF) protein concentration and change from baseline in plasma neurofilament light chain concentration. SOD1 protein is the target of tofersen and reductions in SOD1 protein in the CSF suggest target engagement.[8] Neurofilament light chain (NfL) is a neuronal protein released as a consequence of neuroaxonal damage, is significantly elevated in ALS, and correlates with ALS disease progression and survival.[8] The tofersen treatment group had a statistically significant reduction in SOD1 protein in the CSF and plasma NfL at Week 28 compared with placebo as outlined in Tables 1 and 2 below.[21]

Table 1. CSF SOD1 Protein Concentration Change from Baseline to Week 28 in mITT Population[21]

	Placebo (N=21)	Tofersen (N=39)
Adjusted Geometric Mean Ratio	1.16	0.71
Geometric Mean Ratio Difference (95% CI)	0.62 (0.49, 0.78)	
Nominal p-value	<0.0001	

Table 2. Plasma NfL Concentration Change from Baseline to Week 28 in mITT Population[21]

	Placebo (N=21)	Tofersen (N=39)
Adjusted Geometric Mean Ratio	1.2	0.4
Geometric Mean Ratio Difference (95% CI)	0.33 (0.25, 0.45)	
Nominal p-value	<0.0001	

An ongoing open-label extension study, Study 233AS102 (hereafter referred to as Study 102, NCT 03070119) provided supportive evidence of efficacy. Correlation and causal inference analyses of Study 101C and Study 102 suggest that reductions in plasma NfL concentrations in tofersen-treated subjects are correlated with less worsening of ALSFRS-R scores.[22] While the Statistical Reviewer noted that there are statistical uncertainties in these analysis, the review team concluded the data may support the predictive value of plasma NfL.[22]

A Peripheral and Central Nervous System (PCNS) Advisory Committee (AC) meeting was held on March 22, 2023, to discuss whether the observed reduction of NfL is reasonably likely to predict clinical benefit and support accelerated approval of tofersen for the treatment of patients with SOD1-ALS. Nine committee members voted “Yes”, and zero members voted “No” regarding whether the available evidence is sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS. Three committee members voted “Yes,” five voted “No,” and one abstained for the question of whether clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects of relevant biomarkers, provided convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS.

The review team concluded that while the efficacy data from Study 101C and Study 102 do not establish the effectiveness of tofersen for treatment of adults with SOD1-ALS, reduction in plasma NfL is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit and support accelerated approval.[g,22] During the course of the review, the Agency revised the indication to the following: for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene.[2]

5. Risk Assessment & Safe-Use Conditions

The primary safety population consists of all subjects in the randomized population who received tofersen in the pivotal phase 3 trial, Study 101C. Data from the open-label extension trial, Study 102 (ongoing) provides additional supportive safety data.[23]

The primary safety population includes 72 subjects randomized to tofersen 100 mg vs 36 subjects randomized to placebo. The mean duration of drug exposure was 28.1 weeks for both the tofersen and placebo-treated groups. Four participants receiving tofersen discontinued the placebo-controlled study early due to congestive heart failure, aseptic meningitis, myelitis, and pulmonary embolism. The most common adverse events (≥10% of tofersen group and occurred at >5% higher frequency than placebo) were pain, myalgia, arthralgia, fatigue, and cerebrospinal fluid (CSF) white blood cells increased.[2,23]

5.1. Serious Adverse Events

5.1.1. Deaths

There was one death that occurred during the pivotal trial, Study 101C, in a participant treated with tofersen. The death occurred in a 63-year-old male with a past medical history of coronary artery disease including prior myocardial infarctions and coronary artery bypass grafting.[23] The participant's cause of death was congestive heart failure which was determined to be unrelated to study treatment. Including the long-term extension study, Study 102, there were 19 deaths reported in participants treated with tofersen at any dose.[23] Most deaths were respiratory in nature, consistent with the cause of death commonly seen in ALS. None of the deaths in the tofersen clinical development program were considered by the clinical reviewer to be treatment-related.[22]

5.1.2. Serious Adverse Events

During the tofersen clinical trials, serious adverse events[h] (SAEs) were reported in 59 subjects (40.1%) which included respiratory disorders, aspiration pneumonia, dysphagia, pneumonia,

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[h] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a

increased intracranial pressure, fall, COVID-19, myelitis, septic shock, back pain, ALS, nephrolithiasis, and fecaloma.[i,23] Eleven subjects reported a total of 16 SAEs that were likely related to the treatment with tofersen including myelitis, aseptic meningitis, papilledema, gastritis, pancreatitis, and back pain. The clinical reviewer concluded that most SAEs observed were events consistent with the subjects' underlying ALS disease.[22] See Sections 5.1.3, 5.1.4, and 5.1.5 for additional discussion of myelitis/radiculitis, aseptic meningitis, and papilledema/elevated intracranial pressure, respectively. The clinical reviewer concluded that these risks do not preclude approval of tofersen and the risk can be mitigated through a description in Section 5: Warnings and Precautions.[22]

5.1.3. Myelitis and Radiculitis

In the combined studies 101C and 102, the SAE of myelitis occurred in four subjects (2.7%) and radiculitis occurred in 2 subjects (1.4%) in subjects who received tofersen compared with no subjects (0%) who received placebo.[23] Myelitis led to discontinuation of tofersen in two subjects. One subject was diagnosed with neurosarcoid transverse myelitis on study day 95 and was treated with methylprednisolone and prednisone. The myelitis resolved on day 198 and the patient subsequently discontinued tofersen. The other subject was diagnosed with inflammatory myelopathy on study day 98 resulting in paraplegia and T10 sensory loss. The subject was treated with methylprednisolone and plasma exchange and the myelopathy resolved in approximately 2 months after tofersen discontinuation. Both subjects with reported SAEs of radiculopathy continued tofersen treatment and symptoms resolved.

The clinical reviewer concluded that the myelitis and radiculitis appear to be associated with the intrathecal route of administration of tofersen and recommended the risk and any necessary management of myelitis and radiculitis be communicated in labeling, Section 5 – Warnings and Precautions.[8,22]

5.1.4. Aseptic Meningitis

In the combined studies 101C and 102, the SAE of aseptic meningitis (also known as chemical meningitis) occurred in two subjects (1%) who received tofersen compared with no subjects (0%) who received placebo.[23] In one subject, aseptic meningitis led to treatment discontinuation with symptom resolution 10 days after discontinuation. In the other subject, the meningitis

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persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[i] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

resolved with treatment after less than 4 weeks and did not lead to permanent discontinuation of tofersen.[23] Non-serious adverse drug reactions of increased CSF white blood cells and increased CSF protein also occurred more frequently with tofersen treatment compared with placebo. In Study 101C, increased CSF white blood cell count occurred in 14% of subjects treated with tofersen compared with 0% treated with placebo; increased CSF protein occurred in 8% of subjects treated with tofersen compared with 3% treated with placebo.

The clinical reviewer concluded that aseptic meningitis appears to be associated with the intrathecal route of administration of tofersen and recommends the risk and any necessary management be communicated in labeling, Section 5 – Warnings and Precautions.[8,22]

5.1.5. Papilledema and Elevated Intracranial Pressure

In the pooled studies 101 (Parts A, B, and C) and Study 102 there were 4 (2.9%) subjects with an SAE of papilledema or elevated intracranial pressure compared to no subjects in the placebo group of Study 101C. The subjects received treatment with standard of care therapies (e.g., acetazolamide) with resolution of symptoms. None of these SAEs led to permanent discontinuation of tofersen.[23]

The clinical reviewer concluded that papilledema and elevated intracranial pressure appear to be associated with the intrathecal route of administration of tofersen and recommends the risk and any necessary management by communicated in labeling, Section 5 – Warnings and Precautions.[8,22]

6. Expected Postmarket Use

Tofersen is likely to be prescribed by specialists, such as neurologists. As the route of administration is intrathecally via lumbar puncture, it should be administered in a healthcare setting by a healthcare professional who has experience in administering intrathecal injections. Given the rapid progression and seriousness of the disease, patients are likely to be closely monitored by experienced clinicians who can manage potential adverse effects of tofersen. As tofersen is a gene-targeted therapy for treatment of ALS, it is unlikely to be used for treatment of other indications.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tofersen beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends accelerated approval of tofersen for treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene based on evidence that reduction in plasma NfL is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit and available safety information.[22]

ALS is a fatal, incurable neuromuscular disease that is characterized by progressive degeneration of motor neurons in the brain and spinal cord leading to muscle weakness, disability, and eventually death. The *SOD1* gene mutation accounts for approximately 2% of ALS cases in the United States. Though there are three FDA-approved therapies for ALS, there remains a high unmet medical need for new treatments as patients face rapid morbidity and fatality. There are currently no gene-targeted therapies for the treatment of SOD1-ALS.

The pivotal, phase 3 clinical trial evaluating the efficacy of tofersen did not demonstrate statistical significance in its primary endpoint and, therefore, did not provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS. However, the review team concluded that reduction in plasma NfL is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit and support accelerated approval. During the course of the review, the Agency revised the indication to the following: for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene.

Serious neurologic adverse events associated with the use of tofersen include myelitis, radiculitis, aseptic meningitis, papilledema, and elevated intracranial pressure. However, these adverse events appear to be related to the intrathecal route of administration of tofersen. Aseptic meningitis has been reported with other therapies administered intrathecally and may be caused by hypersensitivity reactions or meningeal irritation. For example, Spinraza (nusinersen), approved in December 2016, is an antisense oligonucleotide administered intrathecally indicated for treatment of spinal muscular atrophy in pediatric and adult patients.[24] In the postmarket setting, serious infections associated with lumbar puncture, aseptic meningitis, and changes in cerebrospinal fluid volume including hydrocephalus have been reported with use of nusinersen.[24] The proposed label for tofersen includes a Warning and Precaution for myelitis/radiculitis, aseptic meningitis, and papilledema/elevated intracranial pressure.

Given the route of administration, tofersen is expected to be administered by healthcare professionals with experience in administering intrathecal injections. Given the rapid progression and seriousness of the disease, patients are likely to be closely monitored by experienced clinicians who can manage potential adverse effects of tofersen. Therefore, based on the data currently available, this reviewer is not recommending a REMS for the management of the risks of tofersen therapy.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. Healthcare providers who treat ALS are likely to be specialists familiar with management of neurologic adverse events including meningitis, myelitis, radiculitis, and papilledema. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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