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APPLICATION NUMBER:

215887Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	215887
Priority or standard	PRIORITY
Submit date(s)	5/25/2022
Received date(s)	5/25/2022
PDUFA goal date	4/25/2023
Division/office	Division of Neurology I (DNI)
Review completion date	4/24/2023
Established/proper name	BIIB067 / Tofersen
(Proposed) proprietary name	Qalsody
Pharmacologic class	Antisense oligonucleotide
Other product name(s)	Qalsody (tofersen)
Applicant	BIOGEN IDEC INC
Dosage form(s)/formulation(s)	INJECTION, SOLUTION
Dosing regimen	100 milligrams (15 mL) intrathecally per administration Initiate QALSODY treatment with 3 loading doses administered at 14-day intervals. A maintenance dose should be administered once every 28 days thereafter.
Applicant-proposed indication(s)/ population(s)	Treatment of amyotrophic lateral sclerosis (ALS) in adults with a confirmed mutation of the superoxide dismutase 1 (SOD1) gene.
SNOMED CT code for proposed indication disease term(s)1	86044005 | Amyotrophic lateral sclerosis (disorder)
Regulatory action	Accelerated approval
Approved dosage (if applicable)	100 mg intrathecally every 14 days × 3 doses and then every 28 days
Approved indication(s)/ population(s) (if applicable)	For the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene
SNOMED CT code for approved indication disease term(s)[1]	86044005

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AC	advisory committee
ADA	antidrug antibodies
ADL	Associate Director for Labeling
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSAQ-5	Amyotrophic Lateral Sclerosis Assessment Questionnaire 5-item
ALSFRS-R	ALS Functional Rating Scale-Revised
ANCOVA	analysis of covariance
ASO	antisense oligonucleotide
AUC	area under the concentration-time curve
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
COA	clinical outcome assessment
COU	context of use
DILI	drug-induced liver injury
DMC	data monitoring committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EQ-5D	European Quality of Life Five Dimension Questionnaire
EQ-5D-5L	European Quality of Life Five Dimension Five Level Questionnaire
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FSS	Fatigue Severity Scale
GMR	geometric mean ratio
HHD	handheld dynamometry
HR	hazard ratio
ICH	International Council for Harmonisation
ICV	intracerebroventricular
IND	investigational new drug
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOOCV	leave-one-out-cross-validation
MAD	multiple-ascending-dose
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures

NDA	new drug application
NfL	neurofilament light chain
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamic
PI	Prescribing Information
PBPK	physiologically based pharmacokinetic
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TQT	thorough QT
VAS	visual analog scale
WBC	white blood cell

I. Executive Summary

1. Summary of Regulatory Action

The Applicant (Biogen, Inc.) submitted a New Drug Application (NDA) 215887 for tofersen. Tofersen is an antisense oligonucleotide (ASO) designed to bind and degrade superoxide dismutase (SOD1) mRNA to reduce synthesis of the SOD1 protein. It is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS) who have a mutation in the *SOD1* gene (SOD1-ALS). The Applicant is seeking accelerated approval based on reduction in plasma neurofilament light chain (NfL) concentrations as a surrogate endpoint reasonably likely to predict clinical benefit in patients with SOD1-ALS.

NDA 215887 was reviewed by a multidisciplinary review team, which did not identify any issues that preclude accelerated approval. Despite some statistical limitations to the analyses described in this review, each discipline is supportive of accelerated approval. I, the signatory authority for this application, concur with those recommendations and agree that the benefit-risk assessment supports accelerated approval.

The submission contains efficacy, safety, and biomarker results from a single adequate and well-controlled study (Study 233AS101 Part C, noted as Study 101C in this review) with support from an open-label extension study (Study 233AS102, noted as Study 102). Study 101C was a 28-week randomized, double-blind, placebo-controlled study in 108 adult patients with SOD1-ALS. The primary clinical endpoint was the change from baseline at Week 28 in the ALS Functional Rating Scale-Revised (ALSFRS-R). The change from baseline at Week 28 in plasma NfL concentration was a secondary endpoint that serves as the endpoint to support accelerated approval.

The single pivotal study failed to demonstrate a statistically significant treatment difference on the prespecified primary clinical endpoint. However, a reduction in plasma NfL, a marker of neuronal degeneration, was observed at Week 28 in the tofersen group compared to the placebo group (67% difference in geometric mean ratios for tofersen to placebo, nominal $p<0.0001$). Total CSF SOD1, an indirect measure of target engagement, was also evaluated and noted to have a reduction at Week 28 in the tofersen group compared to the placebo group (34% difference in geometric mean rations for tofersen to placebo, nominal $p<0.0001$). In the ongoing open-label extension study, there were consistent favorable trends for tofersen on clinical endpoints, although the results were not nominally statistically significant. In additional post hoc, exploratory analyses, nominally significant improvements with separation over time were noted in both the ALSFRS-R and survival, as well as additional secondary clinical endpoints, for patients originally randomized to tofersen compared to patients originally randomized to placebo. Despite the notable limitations of a failed study and the exploratory nature of many post hoc analyses that were conducted after the conclusion of the study, the data suggest a treatment effect of tofersen in patients with SOD1-ALS. This is a very rare and devasting disease and there would be substantial challenges to conducting a second study in the same population; therefore, it is of utmost importance that full consideration is given to all of the available data.

During the review, the review team identified several factors that may have reduced the ability to detect a drug effect of tofersen in Study 101C, including that the study was greatly underpowered, and the heterogeneity of the disease progression rate was not well-controlled in the mITT population, despite intention to do so with an enriched, fast-progressor population. Additionally, a 28-week treatment duration may not have been sufficient to observe a treatment benefit.

The review team has evaluated plasma NfL as a reasonably likely surrogate endpoint for SOD1-ALS. The following factors were considered in the evaluation: the mechanistic evidence that tofersen reduces SOD1 protein, the intended target of the drug and a known contributor to the pathophysiology of SOD1-ALS; the scientific evidence demonstrating the prognostic value of plasma NfL in predicting disease progression and survival in ALS; and the observed correlation between reduction in NfL and a reduction of decline of clinical outcomes such as the ALSFRS-R. The Division has determined that the observed reduction in plasma NfL concentration is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit in adult patients with SOD1-ALS.

A meeting of the Peripheral and Central Nervous System Advisory Committee was held on March 22, 2023. At that meeting, the committee voted unanimously, 9 to 0, that the available evidence supports that a reduction in NfL concentration observed in tofersen-treated patients with SOD1-ALS is reasonably likely to predict clinical benefit for these patients.

Accelerated approval is intended for serious conditions where the drug provides a meaningful advantage over available therapies, and is based on an outcome that is reasonably likely to predict clinical benefit, rather than on clinical benefit itself. These outcomes predictive of benefit are generally surrogate markers of disease of some sort, but may also be an intermediate clinical endpoint that can be measured earlier than the outcome of ultimate clinical importance. Substantial evidence of effectiveness is required on such an endpoint to support accelerated approval, just as it is required for an endpoint supporting standard approval.

With regard to the evidence of effectiveness to support accelerated approval on the basis of a reduction in plasma NfL concentration, the requirement is met. Study 101C was adequate and well-controlled. Although the reduction in plasma NfL is nominally statistically significant, the change in NfL observed in a single study, Study 101C, is large, robust, consistent, and convincing. Additionally, reductions in SOD1 protein support the mechanism of action of tofersen and provide confirmatory evidence. Therefore, these data are able to provide substantial evidence of effectiveness of a treatment effect of tofersen on NfL in patients with SOD1-ALS to support accelerated approval. This determination takes into account the severity, rarity and prevalence of SOD1-ALS, and the significant unmet clinical need.

Based on the data submitted, tofersen has an acceptable safety profile and intrathecal tofersen was generally well tolerated. The most commonly observed adverse events (AEs) (≥10% of tofersen treated patients and occurred at >5% higher frequency than placebo) associated with the use of tofersen in the 28-week placebo-controlled study were pain, myalgia, arthralgia, fatigue, and CSF white blood cell increased. The proportion of subjects experiencing serious adverse events (SAEs) was 18% in the tofersen group and 14% in the placebo group. Although a majority of SAEs were related to underlying disease progression, there were serious neurologic events that occurred only in patients receiving tofersen, and not in patients receiving placebo. Myelitis occurred in five subjects (2.7%) in Studies 101C and 102 who received tofersen, and

radiculitis occurred in two subjects (1.4%). Two subjects who received tofersen had serious adverse events (SAEs) of aseptic meningitis or chemical meningitis (one subject [1.4%] in Study 101C and one subject [0.7%) in Study 102). In the pooled Studies 101 and 102, 4 of 139 (2.9%) subjects had an SAE of papilledema or intracranial pressure increased, compared to 0% in the placebo group of Study 101C. The risks of myelitis, radiculitis, drug-induced aseptic meningitis, papilledema, and elevated intracranial pressure may be related to the intrathecal route of administration; similar findings have been reported with intrathecal administration of other ASOs. The risks should be described in the Warnings and Precautions section of the prescribing information but these safety signals do not preclude approval, particularly when considering the seriousness of the indication.

1.1. The overall benefit-risk is favorable, as described in the Benefit-Risk Framework. For detailed information on the basis for this approval, please refer to the detailed reviews in this Interdisciplinary Assessment document.

A postmarketing requirement (PMR) will be issued to the Applicant to verify the clinical benefit of tofersen by completing the ongoing Study 233AS303 (ATLAS), a Phase 3 randomized, placebo-controlled study in presymptomatic adults with a confirmed SOD1 mutation, who will be enrolled into a natural history run-in period, followed by a randomized, double-blind, placebo-controlled period. Patients will remain in the double-blind period until they develop clinically manifest ALS. The primary endpoint is the proportion of subjects with emergence of clinically manifested ALS.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Amyotrophic lateral sclerosis (ALS) is a progressive and fatal motor neuron disease. It is characterized by the gradual degeneration and death of the motor neurons responsible for voluntary control of muscles. • Most cases of ALS are sporadic. Five to ten percent of ALS cases are familial and are associated with approximately 30 genes. The superoxide dismutase 1 (SOD1) gene is associated with 20% of familial cases. • The overall incidence of ALS (sporadic and familial) is 2 per 100000 per year with approximately 6000 new cases per year in the United States. The estimated prevalence in the United States is 5 per 100000 population with approximately 16000 cases. The prevalence of SOD1-ALS in the United States is estimated at fewer than 500 cases. • ALS most frequently affects people between 40 and 70 years of age (median age 55). Familial ALS generally has a 10-year earlier onset than sporadic ALS. • ALS patients become progressively weaker, losing the ability to move their bodies. Respiratory muscles are also affected, leading to respiratory failure and the death of most patients within 3 to 5 years from the onset of symptoms. Approximately 10% of ALS patients survive for 10 or more years. Shorter survival is associated with older age at onset, bulbar onset, and faster rate of decline in respiratory function. • The A5V variant SOD1 mutation (also known as p.Ala5Val, ala4val, or A4V), present in approximately 50% of all North American families with identifiable SOD1 variants, is associated with a rapid average disease course of 1 year.	SOD1-ALS is a very rare, serious, and life-threatening disease that causes disability due to weakness and death due to respiratory failure.
Current treatment options	• There is no cure for ALS. Most available treatments are intended to relieve symptoms, such as cramps and spasticity, and improve the quality of life. • There are three FDA-approved treatments for ALS: riluzole which prolongs survival by about 3 months and extends the time before ventilatory support is needed; edaravone, which demonstrated a 33% smaller functional decline compared to placebo after 24 weeks in patients within 2 years of diagnosis and with a forced vital capacity (FVC) of at least 80%; and sodium phenylbutyrate with taurursodiol, which had less worsening in the ALSFRS-R total score from baseline to	There are no available therapies specific to SOD1-ALS. Despite the currently available treatment options, ALS remains a progressive disease that leads to respiratory failure and death. There remains a significant unmet clinical need for effective treatments for SOD1-ALS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Week 24 in Relyvrio-treated patients compared to placebo-treated patients.	
Benefit	• The primary efficacy endpoint for the pivotal Study 101C was the change from baseline to Week 28 (Day 197) in the ALS Functional Rating Scale-Revised (ALSFRS-R) total score. – This study failed to show a statistically significant difference between the tofersen and placebo groups for the primary endpoint. – There was a nominal difference of 1.2 favoring tofersen in ALSFRS-R change from baseline at Week 28 (-7.0-point decline in the tofersen group and -8.1-point decline in the placebo group; joint rank test + multiple imputation p=0.9689), but this difference was not statistically significant. • A key secondary efficacy endpoint for Study 101C was the change from baseline in neurofilament light chain (NfL) concentration in plasma at Week 28. – A reduction in plasma NfL was observed at Week 28 in the tofersen group compared to the placebo group (67% difference in geometric mean ratios for tofersen to placebo, nominal p<0.0001). – Correlation and causal inference analysis suggests that reduction in plasma NfL was associated with reduction in the decline of ALSFRS-R total score at Week 28. • The change from baseline in total SOD1 concentration in CSF at Week 28 was also a key secondary endpoint. – A reduction in total CSF SOD1 protein was observed at Week 28 in the tofersen group compared to the placebo group (38% difference in geometric means ratio for tofersen to placebo, nominal p<0.0001) in the mITT population. • Data from the pivotal (Study 101C) and open-label extension (Study 102) studies were integrated to enable 52 weeks of assessment of early-start (72 participants who initiated tofersen 100 mg in Study 101C and continued to receive tofersen during the open-label study 102) vs. delayed-start (36 participants who received placebo in Study 101C and later initiated tofersen 100 mg in Study 102, ~6 months later) tofersen. – Analysis at Week 52 of ALSFRS-R changes compared to baseline showed nominally less worsening in the early-start tofersen group (-6) compared to the delayed-start group (-9.5).	The efficacy data from the randomized, placebo-controlled Study 101C and its open label extension Study 102 are suggestive of a potential treatment benefit with tofersen that is not statistically persuasive. There is mechanistic evidence that tofersen reduces SOD1 protein, the intended target of the drug and known contributor to the pathophysiology of neuronal degeneration in patients with SOD1-ALS, and reduces NfL, a biomarker of neurodegeneration that is substantially elevated in patients with ALS and is predictive of disease progression. Evidence from the literature demonstrates the prognostic value of plasma NfL for disease progression and survival in ALS. Reductions in NfL plasma levels in tofersen-treated subjects were correlated with less worsening of ALSFRS-R scores in the pivotal Study 101C and the open-label extension Study 102. Reduction in plasma NfL is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit. Although the reduction in NfL plasma levels in tofersen-treated patients was nominally statistically significant, the change is large, robust, and convincing. Reductions in SOD1 protein support the mechanism of tofersen and provide confirmatory evidence. Together, the data provide substantial evidence of effectiveness of a treatment effect of tofersen on NfL for SOD1-ALS that supports accelerated approval, taking into account the severity, rarity, and prevalence

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Analysis at Week 52 of slow vital capacity (SVC) percent predicted changes compared to baseline showed nominally less worsening in the early-start (−9) compared to the delayed-start tofersen group (−19). – Analysis at Week 52 of handheld dynamometry (HHD) megascore changes compared to baseline showed nominally less worsening in the early-start (−0.2) compared to the delayed-start tofersen group (−0.5). – The early-start tofersen group had nominally less worsening of quality of life and fatigue compared to the delayed-start group as measured by change from baseline at Week 52 in the ALSAQ-5 total score (10 early-start, 20 late-start), EQ-5D-5L utility score (−0.1 early-start, -0.3 late-start), EQ-5D-VAS (−7 early-start, −13 late-start), and FSS (1 early-start, 5 late-start). – There were nominally fewer events of death or permanent ventilation in the early-start (17%) compared to the delayed-start tofersen group (22%). – There were nominally fewer events of death in the early-start tofersen group (11%) compared to the delayed-start group (17%). • The A5V variant (also known as p.Ala5Val, ala4val, or A4V) of SOD1 ALS, present in approximately 50% of all North American families with identifiable SOD1 variants, is consistently associated with a rapid average disease course and survival of only 1 year. The longest reported survival after disease onset of a patient with A5V SOD1 ALS is 4 years. – One subject with A5V SOD1-ALS who is receiving tofersen has survived 4.3 years since ALS onset, exceeding the maximum survival duration for A5V SOD1-ALS patients reported in the scientific literature. – A second A5V subject receiving tofersen is nearing the 4-year threshold with a survival time of 3.6 years at the time of the report.	of ALS and the significant unmet clinical need for effective treatments for this life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The safety database for tofersen includes the randomized, placebo-controlled study and the open-label extension study in 147 adult subjects with ALS and SOD1 mutation. • The most commonly observed adverse events (≥10% of tofersen-treated patients and occurred at >5% higher frequency than placebo) associated with the use of tofersen in the 28-week placebo-controlled study were pain, myalgia, arthralgia, fatigue, and CSF white blood cell increased. • Permanent dose discontinuation due to AEs occurred in 6% of the tofersen group and 0% of the placebo group. The adverse events that caused these four subjects to stop taking tofersen in the placebo-controlled study were cardiac failure congestive, myelitis, meningitis chemical, and pulmonary embolism, respectively. The adverse events that caused more than one subject to stop taking tofersen across all clinical studies were respiratory failure (8%), respiratory arrest (1%), and ALS (1%). • One subject in the tofersen group (1/72 participants [1.4%]) died during the placebo-controlled study from congestive heart failure. This subject had a prior history of cardiac disease. There were no deaths in the placebo group. • The proportion of subjects experiencing AEs was 96% in the tofersen group and 94% in the placebo group. • The proportion of subjects experiencing SAEs was 18% in the tofersen group and 14% in the placebo group. • Myelitis occurred in five subjects (2.7%) in Studies 101C and 102 who received tofersen and radiculitis occurred in two subjects (1.4%). No subjects receiving placebo in Study 101C experienced these SAEs. • Two subjects who received tofersen had SAEs of aseptic meningitis (one subject [0.7%] in Study 102) or chemical meningitis (one subject [1.4%] in Study 101C). No subjects receiving placebo in Study 101C experienced these SAEs. • In the pooled Studies 101C and 102, 4 of 139 (2.9%) subjects had an SAE of papilledema or intracranial pressure increased, compared to 0% in the placebo group of Study 101C.	The safety profile of tofersen is acceptable to support an approval. The risks of myelitis, radiculitis, drug-induced aseptic meningitis, papilledema, and elevated intracranial pressure should be described in the Warnings and Precautions section of the Prescribing Information. Enhanced pharmacovigilance will also be requested for cases of myelitis and radiculitis in the postmarket setting.

Abbreviations: AE, adverse event; ALSAQ-5, amyotrophic lateral sclerosis assessment questionnaire 5-item; CSF, cerebrospinal fluid; EQ-5D-5L, European quality of life 5-domain 5-level; EQ-5D-VAS, European quality of life 5-domain visual analog scale; FSS, fatigue severity scale; mITT, modified intent-to-treat; SAE, serious adverse event

2.2. litConclusions Regarding Benefit-Risk

Despite current treatment options, the severe progressive weakness of ALS leads to respiratory failure and the death of most patients. There remains a significant unmet clinical need for effective treatments for ALS that slow progression and improve long-term function and survival. There are no available treatments that target SOD1-ALS.

Tofersen is an intrathecal ASO that targets the SOD1 mRNA to reduce synthesis of SOD1 protein. The mechanism by which mutations in the SOD1 gene cause ALS are not fully understood; however, gain-of-function mutations in SOD1 are thought to cause the formation and accumulation of toxic SOD1 protein aggregates. It is hypothesized that the reduction in SOD1 protein caused by tofersen will also lead to decreased toxic aggregates of SOD1 protein.

The safety profile of tofersen is acceptable to support approval. The risks of myelitis, radiculitis, drug-induced aseptic meningitis, papilledema, and elevated intracranial pressure should be described in the Warnings and Precautions section of the Prescribing Information.

The conclusion of this review is that the efficacy data from the randomized, placebo-controlled Study 101C and its open-label extension Study 102 are suggestive of a potential treatment benefit with tofersen that is not statistically persuasive. The effectiveness of tofersen has not been established for the treatment of adults with SOD1-ALS to support full approval.

However, reductions in NfL plasma levels in tofersen-treated subjects were found to be correlated with less worsening of ALSFRS-R scores in the pivotal Study 101C and the open-label extension Study 102. NfL is a biomarker of neuroaxonal damage that is generally accepted in the scientific literature to be predictive of the rate of ALS progression. Reduction in plasma NfL is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit. Although the reduction in NfL plasma levels in tofersen-treated subjects was nominally statistically significant, the change is large, robust, and convincing. Reductions in SOD1 protein support the mechanism of tofersen and provide confirmatory evidence, and together, the data provide substantial evidence of effectiveness of a treatment effect of tofersen on NfL for SOD1-ALS that supports accelerated approval, taking into account the severity, rarity, and prevalence of ALS and the significant unmet clinical need for effective treatments for this life-threatening disease.

II. Interdisciplinary Assessment

3. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal motor neuron disease. It is characterized by the gradual degeneration and death of the motor neurons responsible for voluntary control of muscles. Five to ten percent of ALS cases are familial and are associated with approximately 30 genes. The superoxide dismutase 1 (SOD1) gene is associated with 20% of familial cases, and up to 2% of cases of sporadic ALS.

The overall incidence of ALS (sporadic and familial) is 2 per 100,000 per year. The incidence of ALS is 2 per 100,000 per year with approximately 6000 new cases per year in the United States. The estimated prevalence in the United States is 5 per 100,000 population with approximately 16,000 cases. The prevalence of SOD1-ALS in the United States is estimated at fewer than 500 cases.

Similar to sporadic ALS, SOD1-ALS patients can present with weakness and muscle atrophy in different areas of the body, with about 75% of patients first experiencing weakness in their limbs, and about 25% presenting with difficulty swallowing and/or speaking (i.e., bulbar-onset ALS). Respiratory muscles are also affected, leading to respiratory failure and death of most patients within 3 to 5 years from the onset of symptoms. Approximately 10% of ALS patients survive for 10 or more years. Shorter survival may be associated with older age at onset, bulbar-onset disease, and faster rate of respiratory dysfunction. In general, SOD-1 ALS has similar clinical characteristics to sporadic ALS, with a combination of upper and lower motor neuron involvement. However, the degree of upper versus lower motor neuron involvement, age of onset, and rate of progression can vary greatly as a function of the SOD1 pathogenic variant. The A5V variant SOD1 mutation (also known as p.ALA5Val, ala4val, or A4V), present in approximately 50% of all North American families with identifiable SOD1 variants, is associated with a rapid average disease course of 1 year.

There is no cure for ALS. Most available treatments are intended to relieve symptoms, such as cramps and spasticity, and improve the quality of life. There are three FDA-approved treatments for ALS: riluzole, which prolongs survival by about 3 months and extends the time before ventilatory support is needed; edaravone, which demonstrated a 33% smaller functional decline compared to placebo after 24 weeks in patients within 2 years of diagnosis and with a forced vital capacity (FVC) of at least 80%; and sodium phenylbutyrate with taurursodiol, which had less worsening in the ALSFRS-R total score from baseline to Week 24 in treated patients compared to placebo-treated patients. Despite these treatment options, most patients with SOD1-ALS continue to progress rapidly, with significant muscle weakness, which ultimately leads to respiratory failure and death. There remains a significant unmet need for effective treatments for patients with ALS. There are no approved therapies targeted to the SOD1 mutation in ALS.

Tofersen is an antisense oligonucleotide designed to bind and degrade SOD1 mRNA to reduce synthesis of SOD1 protein. Clinical studies evaluated subjects with amyotrophic lateral sclerosis (ALS) associated with a mutation in the SOD1 gene. A 28-week randomized, double-blind, placebo-controlled study of tofersen in 108 adult subjects (72 tofersen and 36 placebo) with

SOD1-ALS evaluated clinical function using the ALS Functional Rating Scale-Revised (ALSFRS-R) total score, respiratory function by slow vital capacity (SVC), quantitative strength measurement by handheld dynamometry (HHD), and time to death or permanent ventilation. Other assessments included biomarkers such as blood and CSF concentrations of NfL and misfolded or mutant SOD1 protein. Long-term safety data were gathered for 139 subjects who completed the 28-week pivotal study or Phase 1 studies and continued to receive tofersen in an open-label extension study for a mean of 111 weeks (~2 years) of treatment.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. NfL as a Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit in SOD1-ALS

Determine whether the available evidence supports that a reduction in NfL observed in tofersen-treated patients with ALS secondary to a mutation in SOD1 (SOD1-ALS) is reasonably likely to predict clinical benefit for these patients (see Section 6).

3.1.2. Key Safety Review Issues

The following list of key safety review issues is discussed in Section 7.7.

3.1.2.1. Myelitis and Radiculitis

3.1.2.2. Aseptic Meningitis/Cerebrospinal Fluid Protein and White Blood Cell Levels Increased

3.1.2.3. Papilledema/Elevated Intracranial Pressure

3.1.2.4. Renal and Urinary Disorders

3.1.2.5. Respiratory Failure

3.2. Approach to the Clinical Review

Efficacy and safety were assessed by evaluating the results from the randomized, placebo-controlled Study 233AS101 Part C (referred to as Study 101C in the text) and the open-label extension Study 233AS102 (referred to as Study 102 in the text) in adult subjects with amyotrophic lateral sclerosis with a SOD1 mutation. The effectiveness assessment focused on the clinical interpretability of the study endpoints and the Applicant's reported results for Study 101C. Confirmation of the efficacy analyses was provided by the biometrics reviewer for this

application. Given the negative results of the primary efficacy analyses, the main foci of the review were analyses by the Office of Clinical Pharmacology, which focused on the biomarker data, including CSF levels of SOD1 protein, and plasma neurofilament light chain (NfL) data, in consideration of a possible accelerated approval pathway using NfL as a surrogate endpoint reasonably likely to predict clinical benefit.

The safety assessment was based on the Applicant's reports and data analyst and clinical reviewer analyses of the submitted data. The clinical reviewer acknowledges the data analyses of FDA analyst Elizabeth Booth, Pharm.D.

Table 2. Clinical Studies/Studies Submitted in Support of Efficacy and/or Safety Determinations[1] for Tofersen

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
233AS101 Part C	Adults with ALS and SOD1 mutation	Randomized, double-blind, placebo-controlled	Drug: tofersen Dosage: 100 mg intrathecal Number treated: 108 Duration: 28 weeks	Primary: Change from baseline in ALSFRS-R Secondary: Change from baseline to Week 28 in percent predicted SVC, total CSF SOD1 protein, plasma NfL and HHD megascore	108 participants randomized and all randomized participants dosed	32 study sites in 9 countries
233AS102	Adults with ALS and SOD1 mutation	Open-label extension	Drug: tofersen Dosage: 100 mg intrathecal Number treated: 139 Duration: Up to 360 weeks	Primary: ALSFRS-R Secondary: SVC, HHD, time to death, CSF SOD1, CSF and plasma NfL	139 subjects enrolled, received at least 1 dose of study treatment, and were included in the safety population	37 study sites in 13 countries

Source: Reviewer
[1] Includes all submitted clinical studies, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; CSF, cerebrospinal fluid; HHD, handheld dynamometry; NCT, national clinical study; NfL, neurofilament light chain; SOD1, superoxide dismutase 1; SVC, slow vital capacity

4. Patient Experience Data

Table 3. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	6.2.1.1 and 17.1
☒	Observer-reported outcome	
☒	Clinician-reported outcome	
☒	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	16.2
☐	Observational survey studies	
☒	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

In Vitro

Tofersen (5’-CAGGATACATTTCTACAGCT) is designed to target the 3’-untranslated region (3’UTR) of human SOD1 mRNA. Based on sequence alignment (i.e., BLAST), there is a single mismatch to monkey SOD1 mRNA, and more than five mismatches to mouse and rat SOD1 mRNA. Incubation of tofersen with the human SH-SY5Y and A-431 cell lines indicated IC_{50} values of 1.1 and 0.65µM, respectively, while incubation with monkey hepatocytes indicated an IC_{50} of 1.0µM.

In Vivo

In vivo proof-of-concept studies were conducted in transgenic mice and rats that express a mutant form of human SOD1 in which there is a single amino acid substitution at codon 93 (i.e., G93A). Following intracerebroventricular (ICV) administration of tofersen, human SOD1 mRNA was decreased in spinal cord (lumbar: ED_{50} 64 µg; cervical: ED_{50} 44 µg) and brain cortex (ED_{50} 144 µg) of transgenic $SOD1^{G93A}$ mice, and in spinal cord (lumbar: ED_{50} 48 µg; cervical: ED_{50} 93 µg), and brain caudal cortex (ED_{50} 534 µg) in $SOD1^{G93A}$ transgenic rats. Based on electrophysiology and histopathology evaluations in female $SOD1^{G93A}$ mice, administration of a single ICV dose of 300 µg tofersen resulted in improvements in motor neuron conductivity and muscle activity relative to a control (inactive ASO) group. Additionally, histopathology of the tibialis anterior muscle in female $SOD1^{G93A}$ mice administered ICV injections of 100 µg tofersen on Days 50 and 94 indicated a reduction in fiber-type switching from fast to slow myosin. Single ICV doses of 10, 30, and 100 µg tofersen in $SOD1^{G93A}$ mice resulted in a dose-dependent slowing of serum phosphorylated-neurofilament heavy chain (pNfH) loss. ICV injection of 100 or 300 µg tofersen in female $SOD1^{G93A}$ mice on Days 50 and 94 increased mean survival and rotarod performance relative to a control (i.e., inactive ASO) group.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 4. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Mechanism of action	Tofersen is an antisense oligonucleotide that causes degradation of human SOD1 mRNA by binding to the human SOD1 mRNA which results in reduction of SOD1 protein synthesis.
Active moieties	Tofersen
QT prolongation	At the recommended dosing regimen, tofersen does not prolong the QTc interval to any clinically relevant extent (refer to the IRT Review in DARRTS dated 9/22/22).
General Information	
Bioanalysis	Validated assays using hybridization ELISA were used to support the bioanalysis of tofersen in CSF and plasma. A suitable assay utilizing an automated, two-site sandwich, chemiluminometric immunoassay with the [redacted] (b) (4) platform was used for bioanalysis of NfL in human plasma. A suitable assay with the human Cu/Zn SOD (SOD1) Platinum ELISA Kit was used to quantitate total SOD1 in human CSF. Refer to Section 14.3 for more details.
Healthy subjects versus patients	Not available due to limited PK data in healthy subjects to allow reliable comparison with PK in patients
Drug exposure at steady state following the therapeutic dosing regimen	**Parameter** / **Mean±SD** CSF C_{trough} 24±24 ng/mL Plasma AUC_{0-24} 13566±8082 h·ng/mL Plasma AUC_{ss} 26060±11457 h·ng/mL Plasma C_{max} 704±406 ng/mL
Range of effective dose(s) or exposure	100 mg (tested in Study 233AS101 Part C)
Maximally tolerated dose or exposure	Not available. 100 mg is the highest tested dose.

Characteristic	Drug Information
Dose proportionality	Tofersen exposure in CSF increased with dose in a less-than-dose-proportional manner, with steady-state CSF concentrations of the 100 mg dose being approximately 2- to 3-fold higher than those observed for the 20 mg dose. Dose proportionality cannot be reliably evaluated in plasma; however, there were roughly dose-proportional increases in C_{max} and AUC values over the evaluated dose range from 20 mg to 100 mg.
Accumulation	No accumulation in CSF or plasma exposure with monthly dosing
Time to achieve steady-state	At the end of loading dose period (3 doses administered every 2 weeks)
Bridge between to-be-marketed and clinical study/study formulations	Not applicable (NA). The to-be-marketed formulation was used in the clinical studies.
Absorption	
Bioavailability	Tofersen is administered intrathecally
T_{max}	2 to 6 h in plasma
Food effect (fed/fasted) Geometric least square mean and 90% CI	NA
Distribution	
Volume of distribution	58.2 L (central volume of distribution)
Plasma protein binding	98%
Drug as substrate of transporters	Not a substrate of BCRP, MDR1, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters
Elimination	
Mass balance results	Human mass balance study was not conducted
Clearance	9 L/h in plasma
Half-life	Approximate 1 month in CSF and unknown in blood
Metabolic pathway(s)	Expected pathway is nuclease-mediated hydrolysis based on experiences with similar classes of ASOs and animal studies
Primary excretion pathways (% dose)	Unknown
Intrinsic Factors and Specific Populations	
Body weight	Bodyweight does not affect the PK of tofersen based on results from population PK analysis
Age	Age does not affect the PK of tofersen based on results from population PK analysis
Renal impairment	Not evaluated
Hepatic impairment	Not evaluated but the risk of increase in exposure in patients with hepatic impairment is considered low because tofersen does not undergo hepatic metabolism
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Not an inducer or inhibitor of CYP450 in vitro
Inhibition/induction of transporter systems	Not an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC, BCRP, BSEP, and MDR1 transporters in vitro

Characteristic	Drug Information
Immunogenicity (If Applicable)	
Bioanalysis	A multitiered ADA assay based on ELISA was used to detect ADA against tofersen in ALS patients
Incidence	58.4% of patients developed treatment-emergent ADAs
Clinical impact	The presence of ADA appears to decrease plasma clearance by 32%. Effect of ADA on tofersen concentration in CSF is unknown. No discernible effect of ADA status on total SOD1 protein reduction or plasma NfL reduction was observed. Effect of ADA on efficacy is unknown. No discernible effect of ADA on safety was found.

Source: Reviewer's analysis and compiled data from 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods and 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: ADA, antidrug antibodies; ALS, amyotrophic lateral sclerosis; ASO, antisense oligonucleotide; AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to time 24; AUC_{ss}, area under the concentration-time curve steady-state; CI, confidence interval; C_{max}, maximum concentration; CSF, cerebrospinal fluid; Ctrough, trough concentration; CYP450, cytochrome P450; DARRTS, Document Archiving, Reporting and Regulatory Tracking System; ELISA, enzyme-linked immunosorbent assay; IRT, Interdisciplinary Review Team; NfL, neurofilament light chain; PK, pharmacokinetic; SD, standard deviation; SOD1, superoxide dismutase 1; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The proposed dosing regimen for tofersen consists of three loading doses of tofersen 100 mg once every 2 weeks, followed by 100 mg maintenance doses once every 4 weeks administered via intrathecal (IT) bolus injection. The selected dose (i.e., 100 mg) was the highest dose evaluated in clinical Study 233AS101 Part B and showed a higher reduction in CSF total SOD1 protein and plasma NfL compared to other evaluated doses (i.e., 20, 40, 60 mg monthly dosing, refer to Section 14.1 for a detailed discussion).

The efficacy of the proposed dose was evaluated and supported by the findings from clinical studies 101C and 102, using NfL reduction as a reasonably likely surrogate to predict slowing of clinical function decline (refer to Section 6.3 for a detailed discussion). Other results from PK-SOD1/NfL modeling and PBPK modeling were also submitted by the Applicant to support the dose selection. There are some uncertainties for these modeling and simulations that limit their interpretability (refer to Section 14.9 for a detailed discussion). However, the selected dosing regimen of 100 mg tofersen, administered via IT injection, is considered appropriate and is supported by the predicted clinical benefit using reduction in NfL as a surrogate endpoint via the accelerated approval pathway.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Study 233AS101 (Part C)

6.2.1.1. Design, Study 233AS101 (Part C)

Overview and Objective

Study 101C was a Phase 3, multinational, randomized, double-blind, placebo-controlled, study of tofersen in adult subjects with ALS and a confirmed pathogenic or likely pathogenic SOD1 mutation (SOD1-ALS).

The primary objective was to evaluate the efficacy of tofersen in adult subjects with SOD1-ALS.

The secondary objective was to evaluate the safety, tolerability, pharmacodynamics (PD), and biomarker effects of tofersen in adult subjects with SOD1-ALS.

Study Design

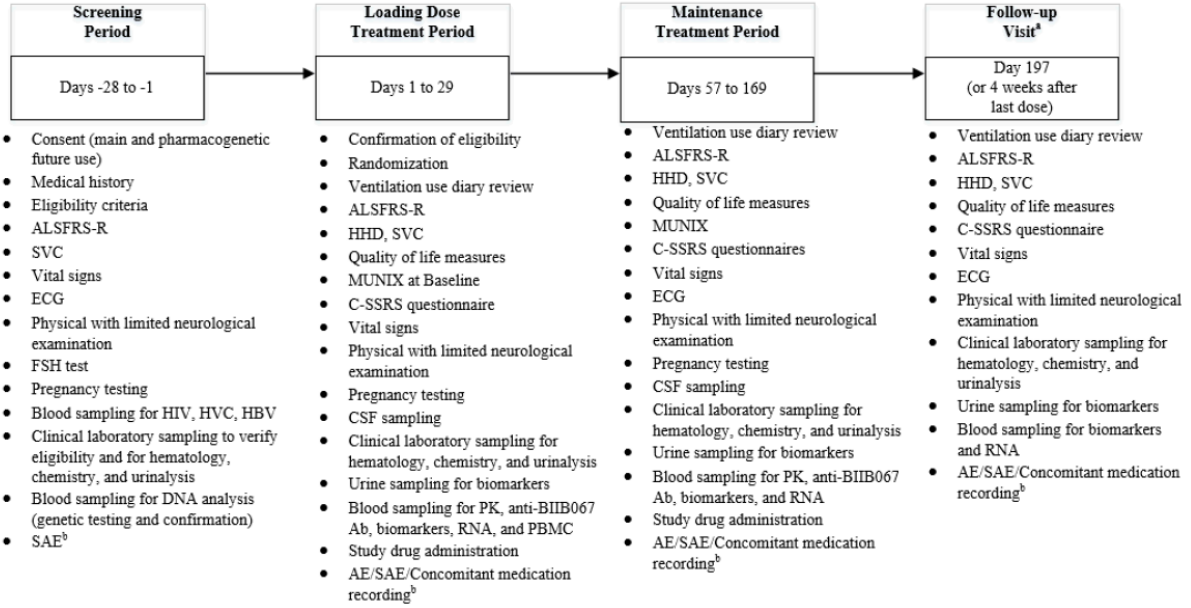
Study 101C was a multicenter (32 study sites), multinational (nine countries), randomized, double-blind, placebo-controlled, Phase 3 study of tofersen in adult subjects with SOD1-ALS. The planned study size was N=60 for patients defined as “fast progressors”; the actual number randomized was N=108 (72 to tofersen and 36 to placebo). “Fast progressors” were defined as patients with mutations known to be associated with fast disease progression and with a prerandomization decline in ALSFRS-R score of ≥0.2/month OR with other SOD1 mutations and a prerandomization decline in ALSFRS-R score of ≥0.9/month. Patients were randomized 2:1 (active: placebo) and stratified according to three factors: whether the subject was a potential fast progressor based on the mutation and ALSFRS-R slope criteria; edaravone use at baseline (with or without riluzole), and riluzole use at baseline.

The total study duration was up to approximately 32 weeks: comprising an up to 4-week screening period, 24-week treatment period (consisting of three loading doses of BIIB067 administered approximately once every 2 weeks, followed by five maintenance doses of BIIB067, administered approximately once every 4 weeks), and a follow-up visit 4 weeks after the last dose.

The mean (SD) duration in the study (period from the first dose until end of study) was 190 (29) days in the tofersen group and 195 (16) days in the placebo group.

The study design is shown in Figure 1.

Figure 1. Study Design: 233AS101 Part C



Source: Study 101C Protocol
[a] Participants who do not roll over into the LTE study (233AS102) will have an additional safety FU visit at Week 32 to collect AEs, SAEs, and concomitant medications or procedures. Participants with delays between their Week 28 Visit and enrolment into the LTE study will have a Safety FU (Alternative EOS) Visit to collect AEs, SAEs, and concomitant medications or procedures.
[b] SAE monitoring will be ongoing starting at the Screening Visit; AE and concomitant medication monitoring will be ongoing starting on Day 1
Abbreviations: Ab, antibody; AE, adverse event; ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CSF, cerebrospinal fluid; C-SSRS, Columbia suicide severity rating scale; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; FU, follow-up; HBV, hepatitis B virus; HVC, hepatitis C virus; HHD, handheld dynamometry; LTE, long-term extension; MUNIX, motor unit number index; PBMC, peripheral blood mononuclear cells; PK, pharmacokinetic; SAE, serious adverse event; SVC, slow vital capacity

Study 101C Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for Study 101C was the change from baseline to Week 28 (Day 197) in the ALS Functional Rating Scale-Revised (ALSFRS-R) total score. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS. Each item is scored from 0 to 4, with higher scores representing greater functional abilities. The ALSFRS-R total score ranges from 0 (maximum disability) to 48 (no disability). The ALSFRS-R is an acceptable primary endpoint that is considered clinically meaningful to patients, as discussed in the Guidance for Industry, Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment.

Key Secondary Efficacy Endpoints for Study 101C

Below are the four key secondary efficacy endpoints for Study 101C.

1. Change from baseline to Week 28 (Day 197) in slow vital capacity (SVC): The SVC measures the volume of air expired from the lungs in an unforced manner and is an acceptable endpoint measuring respiratory function in ALS. Although forced vital capacity (FVC) is the most commonly used method for respiratory assessment, the patient must expel air quickly and forcefully, which may cause fatigue, bronchospasm,

and underestimation of actual lung capacity. SVC, which involves exhalation of air in a slow, gentle manner after maximal inspiration, is easier for a patient with ALS to perform even in the presence of loss of facial strength, difficulty coordinating respiratory movements, and muscle weakness. A decline in respiratory function is a direct result of the pathophysiology of ALS. The demonstration of a treatment benefit on respiratory endpoints such as SVC may provide evidence of effectiveness.

2. Change from baseline to Week 28 (Day 197) in handheld dynamometry (HHD) megascore to assess muscle strength, as measured by the HHD device: HHD is a quantitative measure of strength and is an acceptable endpoint in ALS. Because loss of strength is a hallmark of disease progression in ALS, a valid measurement of muscle strength may be an appropriate endpoint for treatments intended to increase or preserve muscle strength.

3. Time to death or permanent ventilation (≥22 h of mechanical ventilation [invasive or noninvasive] per day for ≥21 consecutive days): This endpoint is acceptable. As described in the ALS Guidance for Industry, the independent assessment of survival should be combined with an evaluation of the need for full-time (or nearly full-time) respiratory support because such support can affect survival time.

4. Time to death: This endpoint is acceptable. As described in the ALS Guidance for Industry, an effect on mortality is important to the consideration of the overall safety and effectiveness profiles. If patient function is intended to be assessed by the primary outcome (e.g., ALSFRS-R), mortality should be integrated into the primary outcome by an analysis method that combines survival and function into a single overall measure, such as the joint rank test. The independent assessment of a drug effect on survival should be a secondary endpoint.

Tertiary/Exploratory Objective for Study 101C

The tertiary/exploratory objective is to evaluate the PK of tofersen and other potential biomarkers in adult subjects with SOD1-ALS.

- Pharmacokinetic endpoints:
  - Plasma concentrations of tofersen
  - CSF concentrations of tofersen
- Additional biomarkers:
  - Blood and CSF concentrations of NFL
  - Urinary p75ECD
  - Misfolded or mutant SOD1

6.2.1.2. Eligibility Criteria, Study 233AS101 (Part C)

The criteria listed below from the submitted protocol appear adequate to enroll patients with SOD1-ALS representative of the U.S. population.

Key Inclusion Criteria

To participate in this study, candidates were required to meet the following eligibility criteria at Screening:

- Age ≥18 years at the time of informed consent.
- Weakness attributable to ALS and confirmed SOD1 mutation at the Screening visit. Additionally:
  - Fast progressor criteria:
    - a. One of the following SOD1 mutations and a prerandomization ALSFRS-R decline slope ≥0.2 per month (calculated as [48-baseline score]/time since symptom onset): p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly

    or

    - b. SOD1 mutation other than those listed in item 'a.' with prerandomization ALSFRS-R decline slope ≥0.9 per month (calculated as [48-baseline score]/time since symptom onset)
  - Non-fast progressor criterion: SOD1 mutation other than those listed in item 'a.' (no ALSFRS-R decline slope requirement).
- For fast progressors, SVC ≥65% of predicted value as adjusted for sex, age, and height (from the sitting position). For non-fast progressors, SVC ≥50% of predicted value as adjusted for sex, age, and height (from the sitting position).
- If taking riluzole, subject must be on a stable dose for ≥30 days prior to Day 1 and expected to remain at that dose until the final study visit.
- If taking edaravone, subject must have initiated edaravone ≥60 days (two treatment cycles) prior to Day 1 and expected to remain at that dose until the final study visit, unless the Investigator determines that edaravone should be discontinued for medical reasons, in which case it may not be restarted during the study. Edaravone may not be administered on dosing days of this study.

Key Exclusion Criteria

Subjects meeting any of the following criteria were ineligible for the study:

- Treatment with another investigational drug (including investigational drugs for ALS through compassionate-use programs), biological agent, or device within 1 month or five half-lives of study agent, whichever is longer. Specifically, no prior treatment with small interfering RNA, stem cell therapy, or gene therapy was allowed.
- Female subjects who are pregnant or currently breastfeeding.

6.2.1.3. Statistical Analysis Plan, Study 233AS101 (Part C)

The primary efficacy population (mITT) was used for all analyses of efficacy data. In addition, descriptive statistics and/or analyses were performed on the non mITT population as specified.

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 28 in the ALSFRS-R total score, which will be analyzed using the joint rank test methodology to account for mortality for the primary inference. When implementing the joint rank test methodology, multiple imputation (MI) will be used to handle withdrawals. The estimates will be obtained from an analysis of covariance (ANCOVA) for change from baseline in ALSFRS-R at Week 28 with missing data imputed using multiple imputation. The corresponding nominal p-value from the ANCOVA will be presented as sensitivity analysis.

Secondary Efficacy Endpoints

- The primary analysis for percent predicted SVC was the joint rank method using joint rank +MI for the mITT population.
- The muscle strength as measured by HHD was summarized by individual muscles and megascore. The normalization of individual muscles was performed separately for the mITT and non-mITT populations using the relevant baseline mean and standard deviation for the population. The change from baseline in HHD megascore was analyzed using the ANCOVA based on MI imputed datasets for the mITT population. The primary inference was based on the treatment comparison at Day 197.
- Time to death or permanent ventilation was defined as the time to the earliest occurrence of one of the following events:
  - Death.
  - Permanent ventilation (≥22 h of mechanical ventilation [invasive or noninvasive] per day for ≥21 consecutive days).
- Time to death or permanent ventilation was determined in a blinded fashion by a central, independent Endpoint Adjudication Committee.
- The overall survival was analyzed as a time to event endpoint, i.e., time to death. Kaplan-Meier estimates of the cumulative probability of death over time were calculated for the mITT population. Treatment comparison for survival time will be based on a stratified log-rank test. Stratification factors were riluzole or edaravone use. Kaplan-Meier plots will be presented. The median survival time, percentiles (5th, 10th, 25th, 75th) and associated 95% confidence limits, and proportion of subjects who met an event by Day 197 were estimated using the Kaplan-Meier. A Cox proportional hazards model was used to obtain the hazard ratio and 95% confidence intervals. The Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRSR total score, and riluzole or edaravone use.

Reviewer's Comment: Blood and CSF concentrations of NFL and CSF SOD1 protein levels were originally tertiary/exploratory endpoints in the study protocol and were later elevated in importance to key secondary endpoints for post hoc analysis (see below).

6.2.1.4. Results of Analyses, Study 233AS101 (Part C)

Demographics of the pivotal placebo-controlled Study 101C are described in Table 5, Table 6, and Table 7, based on the submitted data. Study 101C enrolled 108 subjects. Forty-six (43%)

were female. This proportion of females is consistent with the epidemiology of ALS, which is slightly more common in men than women. At screening, age and race were adequately balanced between the placebo and tofersen groups. Overall, there appears to be an acceptable balance of demographic characteristics between the control and treatment groups that adequately represents the demographics of the intended patient population.

Table 5. Baseline Demographic and Clinical Characteristics, Safety Population, Study 233AS101 Part C

Characteristic	Tofersen 100 mg N=72	Placebo N=36
Sex, n (%)		
Female	29 (40.3)	17 (47.2)
Male	43 (59.7)	19 (52.8)
Age, years		
Mean (SD)	48.1 (12.6)	51.2 (11.6)
Median (min, max)	47.5 (23, 78)	51.5 (28, 73)
Age group, years, n (%)		
18 to <35	10 (13.9)	2 (5.6)
35 to <50	32 (44.4)	15 (41.7)
50 to <65	21 (29.2)	14 (38.9)
≥65	9 (12.5)	5 (13.9)
Age group ≥75, years, n (%)		
≥75	1 (1.4)	0
Race, n (%)		
Asian	5 (6.9)	4 (11.1)
Black or African American	1 (1.4)	0
Not reported	21 (29.2)	7 (19.4)
Other	1 (1.4)	0
White	44 (61.1)	25 (69.4)
Ethnicity, n (%)		
Hispanic or Latino	4 (5.6)	1 (2.8)
Not Hispanic or Latino	47 (65.3)	28 (77.8)
Not reported	21 (29.2)	7 (19.4)
Country of participation, n (%)		
Belgium	3 (4.2)	4 (11.1)
Canada	10 (13.9)	8 (22.2)
Germany	5 (6.9)	0
Denmark	1 (1.4)	0
France	3 (4.2)	2 (5.6)
Great Britain	4 (5.6)	1 (2.8)
Italy	5 (6.9)	0
Japan	3 (4.2)	4 (11.1)
United States	38 (52.8)	17 (47.2)

Source: adsl.xpt; software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Table 6. Patient Screening and Enrollment, Study 233AS101 Part C

Disposition	Study 233AS101 Part C
Patients screened	162
Screening failures	54
Patients enrolled[1]	108
Patients randomized	108

Source: ds.xpt and Clinical Study Report; Software: R
[1] This study enrolled participants aged ≥18 years with a weakness attributable to ALS and a confirmed SOD1 mutation.
Abbreviations: ALS, amyotrophic lateral sclerosis; SOD1, superoxide dismutase 1

Table 7. Patient Disposition, Study 233AS101 Part C

Disposition Outcome	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Patients randomized	72	36	NA
ITT population	72	36	NA
mITT population	39	21	NA
Per-protocol population	34	20	NA
Safety population	72	36	NA
Discontinued study	8 (11.1)	3 (8.3)	2.8 (-8.8, 14.4)
Adverse event	2 (2.8)	0	2.8 (-1.0, 6.6)
Death	1 (1.4)	0	1.4 (-1.3, 4.1)
Progressive disease	3 (4.2)	2 (5.6)	-1.4 (-10.2, 7.4)
Withdrawal by subject	2 (2.8)	1 (2.8)	0 (-6.6, 6.6)
Discontinued study drug	9 (12.5)	3 (8.3)	4.2 (-7.7, 16.0)
Adverse event	3 (4.2)	0	4.2 (-0.4, 8.8)
Death	1 (1.4)	0	1.4 (-1.3, 4.1)
Other	1 (1.4)	0	1.4 (-1.3, 4.1)
Progressive disease	3 (4.2)	2 (5.6)	-1.4 (-10.2, 7.4)
Withdrawal by subject	1 (1.4)	1 (2.8)	-1.4 (-7.4, 4.6)

Source: ds.xpt and adsl.xpt; software: R
Duration is approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; n, number of patients in specified population or group; N, number of patients in treatment arm; NA, not applicable

Efficacy Results – Primary Endpoint

The primary efficacy endpoint for Study 101C was the change from baseline to Week 28 (Day 197) in the ALSFRS-R total score. This study failed to show a statistically significant difference between the tofersen and placebo groups for the primary endpoint, as shown in Table 8. There was a numerical difference of 1.2 favoring tofersen in ALSFRS-R change from baseline at Week 28 (−7.0-point decline in the tofersen group and −8.1-point decline in the placebo group; joint rank test plus multiple imputation p=0.9689), but this difference was not statistically significant.

Table 8. Primary Endpoint Analysis in Faster- and Slower-Progressing Disease Subgroups Defined Using Protocol-Defined Criteria, Median Baseline Plasma NfL and Run-In Slope

		Placebo n = 36	Tofersen n = 72
Change from baseline to Week 28 on ALSFRS-R total score			
Faster-progressing subgroups	**mITT**		
	N	21	39
	Adjusted mean	-8.14	-6.98
	Tof - plac: Adj. mean difference (95% CI)		1.2 (-3.2, 5.5)
	p-value (Joint-rank + MI)		0.9689
	Nominal p-value (ANCOVA + MI)		0.5998
Slower-progressing subgroups	**Non-mITT**		
	N	15	33
	Adjusted mean	-2.73	-1.33
	Tof - plac: Adj. mean difference (95% CI)		1.4 (-1.1, 3.9)
	Nominal p-value (ANCOVA + MI)		0.2726

Source: Study 233AS101 (Part C) Clinical Study Report, p. 92
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; ANCOVA, analysis of covariance; CI, confidence interval; MI, multiple imputation; mITT, modified intent-to-treat; NfL, neurofilament light chain; plac, placebo; Tof, tofersen

Efficacy Results – Secondary and Other Relevant Endpoints

Key secondary endpoints were analyzed and tested based on a sequential testing procedure in the rank order as presented below for the mITT population.

Change (i.e., ratio) from baseline in total SOD1 concentration in CSF: A reduction in total CSF SOD1 protein was observed at Week 28 in the tofersen group compared to the placebo group (38% difference in geometric mean ratios for tofersen to placebo, nominal p<0.0001 [ANCOVA + MI] in the mITT population, and 26% difference in geometric mean ratios for tofersen to placebo, nominal p=0.0007 [ANCOVA + MI] in the non-mITT population).

Change (i.e., ratio) from baseline in NfL concentration in plasma: A reduction in plasma NfL was observed at Week 28 in the tofersen group compared to the placebo group (67% difference in geometric mean ratios for tofersen to placebo, nominal p<0.0001 [ANCOVA + MI] in the mITT population and 48%, nominal p<0.0001 [ANCOVA + MI] in the non-mITT population).

Reviewer Comment: Note that blood and CSF concentrations of NFL were originally tertiary/exploratory endpoints in the study protocol and were later elevated in importance for the post hoc analysis. The biomarker results are more fully analyzed in Section 6.3.2.1.

Change from baseline to Day 197 in SVC: Change from baseline to Week 28 in percent predicted SVC showed nominally less decline in the tofersen group (adjusted mean -14.3) compared to the placebo group (adjusted mean -22.2) that was not statistically significant (7.9% predicted treatment difference, nominal p=0.3233 [joint rank test + MI] in the mITT population.

Change from baseline to Day 197 in HHD megascore: Change from baseline to Week 28 in HHD megascore did not show any statistically significant difference in muscle strength in the

tofersen group (adjusted mean -0.34) compared to the placebo group (adjusted mean -0.37; 0.02-point treatment difference, nominal p=0.8390 [ANCOVA + MI] in the mITT population).

Time to death or permanent ventilation: The median time to death or permanent ventilation could not be estimated due to the small number of events observed.

Time to death: The proportion of participants who died at 28 weeks and median survival time from the Kaplan-Meier analysis could not be estimated as there was only one death.

6.2.2. Study 233AS102

6.2.2.1. Overview and Design, Study 233AS102

Overview and Objective

Study 102 is an ongoing open-label extension study to assess the long-term safety, tolerability, pharmacokinetics, and effect on disease progression of tofersen administered to previously treated adults with amyotrophic lateral sclerosis caused by superoxide dismutase 1 mutation.

Primary Objective and Endpoint

The primary objective of the study is to evaluate the long-term safety and tolerability of tofersen in subjects with SOD1-ALS. The associated primary endpoint is the incidence of AEs and SAEs.

Secondary Objectives and Endpoints

The secondary objectives are to evaluate the PK, PD, biomarker effects, and efficacy of tofersen administered to subjects with SOD1-ALS.

The endpoints include the following:

- PK endpoints: Plasma and CSF levels of tofersen
- PD endpoint: Change from baseline in total SOD1 protein in CSF
- Biomarker endpoint: Change from baseline in NfL concentration in plasma

Efficacy endpoints:

Changes over time in the following:

- Total ALSFRS-R score
- SVC
- HHD Megascore and individual muscle strength
- Time to death or permanent ventilation (≥22 h of mechanical ventilation [invasive or noninvasive] per day for ≥21 consecutive days)
- Time to death

Study Design

Study 102 is an ongoing, open-label, multicenter, long-term extension study to assess the long-term effects of 100 mg tofersen in subjects who previously completed Study 101. Subjects from Parts A and B of Study 101 underwent a washout period of at least 16 weeks between the last dose in Study 101 and their first dose in Study 102. As subsequent dose levels were approved by the Safety Surveillance Team for Study 101, subjects in Study 102 increased their dose level to the highest dose approved in Study 101. In parallel with initiation of Study 101 Part C, Study 102 was amended to accept subjects who completed Part C of Study 101. These participants did not have a washout period prior to dosing in Study 102. Instead, to maintain the blind of Study 101, a blinded loading dose period was incorporated in Study 102, followed by open-label treatment with tofersen. To protect the integrity of data collected in Study 102, the individual subject blind for Study 101 was maintained through completion of Study 102. Furthermore, a firewalled team without access to individual subject data is overseeing the conduct of Study 102.

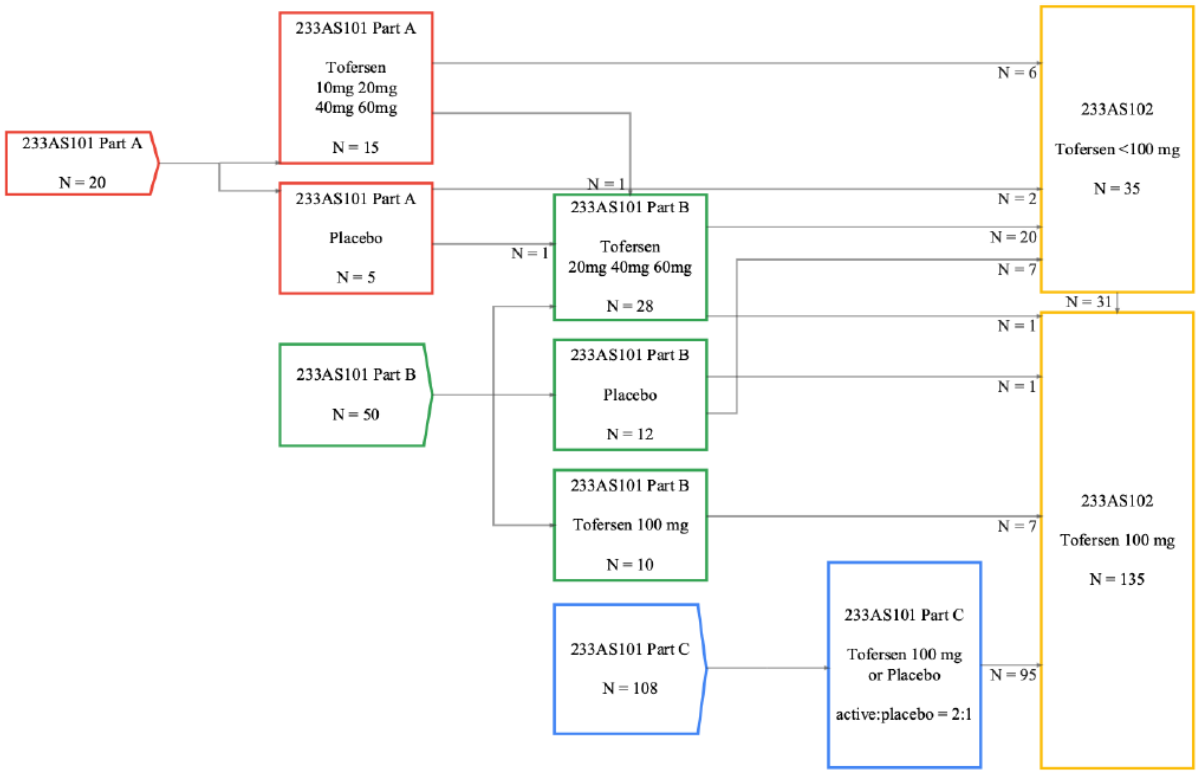
Subjects who have completed Study101C had a blinded Loading-Dose Period, during which subjects who received tofersen in Study 233AS101 received two doses of tofersen, on Days 1 and 29, and placebo on Day 15, and subjects who received placebo in Study 233AS101 received three doses of tofersen, on Days 1, 15, and 29.

For all participants, the Loading-Dose Period was followed by an unblinded maintenance dose period, during which subjects received up to 90 doses of tofersen, approximately every 4 weeks.

Two interim analyses for Study 102 are described in this application:

1. Data from a data cutoff of July 16, 2021, which coincided with completion of Study 101C, at which time all subjects enrolled in Study 101C had the opportunity for at least 6 months of follow-up.
2. Data from a data cutoff of January 16, 2022, at which time all subjects enrolled in Study 101C had the opportunity for at least 12 months of follow-up.

Figure 2. Data Flow for Subjects in 233AS101 and 233AS102 Studies



Source: Integrated Summary of Efficacy Statistical Analysis Plan v. 2, p. 10
Counts are summarized using the data cut-off on July 16 2021.

Study 102 Endpoints

See Study 101C endpoints.

6.2.2.2. Eligibility Criteria, Study 233AS102

To enroll in Study 102, patients must have a diagnosis of SOD1-ALS and must have completed the End of Study Visit for Part A, B, or C of Study 233AS101 (i.e., were not withdrawn). If taking riluzole, subjects must have been receiving a stable dose for ≥30 days prior to Day 1. If taking edaravone, subjects must have initiated edaravone ≥60 days (two treatment cycles) prior to Day 1. Edaravone was not administered on dosing days during this study.

6.2.2.3. Statistical Analysis Plan, Study 233AS102

Prespecified Statistical Methods

The final version of the statistical analysis plan (SAP) prior to database lock for Study 101C (which occurred on August 16, 2021) was SAP V2, which was finalized on August 14, 2021. This section describes the analysis methods prespecified in SAP V2 for select endpoints.

The primary analysis of change from baseline in ALSFRS-R at Week 28 was based on an ANCOVA of joint ranked scores[1] in the mITT population, adjusting for baseline ALSFRS-R, edaravone or riluzole use, and time since symptom onset. Multiple imputation (MI) was used for missing data in survivors. The analysis of the secondary endpoint, percent predicted SVC at Week 28, was based on an ANCOVA of joint ranked scores in the mITT population, adjusting for baseline percent predicted SVC, baseline ALSFRS-R, edaravone or riluzole use, and time since symptom onset, with MI for missing data. The analysis of the secondary endpoints, time to death or permanent ventilation and time to death, were based on a log-rank test stratified by riluzole or edaravone use, and a Cox proportional hazards model adjusting for time since symptom onset, baseline ALSFRS-R, and edaravone or riluzole use was used to estimate hazard ratios and confidence intervals (CIs).

The mITT population was to be used for all analyses of primary and secondary endpoints. The SAP stated that descriptive analyses may be conducted for the non-mITT and ITT populations but that there would be no formal hypothesis testing.

A sequential testing strategy was used to control the Type I error probability across the multiple endpoints, with testing of secondary endpoints in the following order (if the primary analysis was statistically significant): change from baseline (i.e., ratio) to Week 28 (Day 197) in total CSF SOD1 protein; change from baseline (i.e., ratio) to Week 28 (Day 197) in NfL in plasma; change from baseline to Week 28 (Day 197) in SVC; change from baseline to Week 28 (Day 197) in HHD megascore to assess muscle strength, as measured by the HHD device; time to death or permanent ventilation, defined as the time to the earliest occurrence of death or permanent ventilation (≥22 h of mechanical ventilation [invasive or noninvasive] per day for ≥21 consecutive days); and time to death.

The Study 102 SAP V2 (this was the final version of the open-label extension (OLE) SAP prior to any unblinding; finalized on August 12, 2021) and the integrated summary of efficacy SAP V2 (this was the final version of the integrated summary of efficacy SAP prior to any unblinding; finalized on August 14, 2021) also specified endpoints, objectives, and analyses for Study 102 (the OLE), and for combined data from Study 101C and Study 102. The primary objective of Study 102 was to evaluate long-term safety and tolerability of tofersen, with adverse events and serious adverse events specified as primary endpoints. Secondary endpoints included PK endpoints, biomarker and PD endpoints, and efficacy endpoints. Efficacy endpoints included changes over time in ALSFRS-R, SVC, and HHD, time to death or permanent ventilation, and time to death. For ALSFRS-R, descriptive statistics were to be calculated at different time points, along with an ANCOVA, with MI for missing data. For time to death or permanent ventilation and time to death, Kaplan-Meier estimates were to be calculated, along with a Cox proportional hazards model. The prespecified adjustment covariates for the ANCOVA and Cox models were the same as in the double-blind phase. Given the design and objectives of Study 102 and that

[1] The joint rank methodology (Berry 2013) allows for a statistical test of the treatment effect on the endpoint while accounting for truncation of data due to deaths. In this analysis, a subject's joint rank score is calculated by comparing each subject to every other subject in the study, resulting in a score of +1 if the outcome was better than the subject being compared, -1 if worse, and 0 if the same. The subject's score is then be calculated by summing their comparison to all the other subjects in the study.

efficacy analyses of the OLE data were not part of the planned multiple testing strategy for Study 101C, these efficacy analyses are exploratory in nature.

Additional Applicant Analyses

The Applicant has also conducted a variety of additional analyses of data from the double-blind phase and the OLE phase based on statistical methods that were determined after access to unblinded data. The Applicant finalized an additional SAP (V3) on February 2, 2022. This was after the endpoints of time to death, time to death or permanent ventilation, and ALSFRS-R change through Week 40 in the combined Study 101 Part C and OLE dataset had already been unblinded, analyzed, and presented in the November 2021 Type C meeting briefing package.

These additional analyses carried out by the Applicant included changes to prespecified analysis methods such as a focus on the ITT rather than the mITT population, replacing time since symptom onset with baseline NfL as an adjustment covariate (or use of less than versus greater than or equal to the median baseline NfL as a stratification factor for log-rank tests), and changes to the MI model (adding NfL as a covariate). Baseline NfL was not included as an adjustment covariate or stratification factor in the primary and secondary endpoint analyses in either SAP V2 or the earlier V1 (dated 2 months after the study started).

6.2.2.4. Results of Analyses, Study 233AS102

Study 102 Disposition

Participant disposition in the OLE period (Study 102) for Study 101C participants is shown in Table 9. For the ITT population, 88 to 89% of the placebo and tofersen groups participated in Study 102. For the mITT population, 19/21 [90%] placebo and 33/39 [85%] tofersen subjects participated in Study 102.

Table 9. Participant Disposition of Integrated Analysis of Studies 101 Part C and 102

	ISE based on Jul 2021 data cut		ISE based on Jan 2022 data cut	
Participants	Early-start Tofersen 100 mg (n = 72)	Placebo/delayed-start Tofersen 100 mg (n = 36)	Early-start Tofersen 100 mg (n = 72)	Placebo/delayed-start Tofersen 100 mg (n = 36)
Dosed in Study 101 Part C n (%)	72 (100)	36 (100)	72 (100)	36 (100)
Dosed in Study 102 n (%)	63 (88)	32 (89)	63 (88)	32 (89)
Completed Study 101 Part C but not enrolled in Study 102 n (%)	1 (1)	1 (3)	1 (1)	1 (3)
Ongoing in Study 102 n (%)	54 (75)	22 (61)	49 (68)	18 (50)
Died while on trial n (%)	7 (10)	4 (11)	8 (11)	6 (17)
Withdrew from trial n (%) - AE - Consent withdrawn - Death - Disease progression	17 (24) 2 (3) 3 (4) 7 (10) 5 (7)	13 (36) 0 3 (8) 4 (11) 6 (17)	22 (31) 2 (3) 4 (6) 8 (11) 8 (11)	17 (47) 0 4 (11) 6 (17) 7 (19)
Post-withdrawal vital status not collected[a]	N/A	N/A	5 (7)	3 (8)
Total deaths including post-withdrawal death[a]	N/A	N/A	12 (17)	11 (31)

[a] Post-withdrawal vital status was collected retrospectively for participants who withdrew from Study 101 Part C or Study 102 or who completed Study 101 Part C and did not enroll in Study 102.

Source: Applicant's Summary of Clinical Efficacy, p. 74.
Abbreviations: AE, adverse event; ISE, integrated summary of efficacy; N/A, not applicable

Efficacy Results – Primary Endpoint

As noted in the statistical methods section, efficacy analyses in Study 102 were exploratory in nature, and analyses were planned at multiple time points during the OLE. This section focuses on results of the prespecified analyses of ALSFRS-R, percent predicted SVC, and NfL through Week 52, as well as analyses of time to death or permanent ventilation and time to death through the interim data cutoff in January 2022.

At Week 52 of the OLE, results for ALSFRS-R were similar to those observed at Week 28 of the double-blind period, with roughly similar estimates and lack of statistical evidence of differences between arms. In the mITT population, the estimated mean difference was 2.5 (95% CI: -3.2, 8.3), p=0.39 based on the planned ANCOVA+MI approach. In the ITT population, the estimated difference was 2.7 (95% CI: -0.9, 6.2), p=0.14. The ANCOVA analysis of joint rank scores was not prespecified for the OLE but it yielded similar results, with a difference of 1.1 (95: CI: -8.7, 10.8), p=0.83 in the mITT population, and 4.2 (95% CI: -7.4, 15.8), p=0.48 in the ITT population. Only 28/36 (78%) placebo/delayed-start tofersen and 57/72 (79%) early tofersen subjects had nonmissing ALSFRS-R scores at Week 52 in the ITT population for the final January 2022 data cut-off (note that 1 [2.8%] placebo and 4 [5.6%] tofersen subjects had died by Week 52).

Table 10. Mean Change in ALSFRS-R at Week 52 From Study 101 Part C Baseline Through Studies 101 Part C and 102 Based on Prespecified Analysis Methods

Population	Summary Measure	Placebo N=21 mITT N=15 Non-mITT	Tofersen N=39 mITT N=33 Non-mITT	Week 52 Mean Difference (95% CI) ANCOVA+MI
mITT	Baseline mean	35.4	36.0	2.5 (-3.2, 8.3)
	Week 52 LS mean change	-12.3	-9.7	Joint rank p=0.83
				ANCOVA+MI p=0.39
Non-mITT	Baseline mean	39.9	38.1	2.6 (-0.7, 6.0)
	Week 52 LS mean change	-3.9	-1.2	Joint rank p=0.90
				ANCOVA+MI p=0.12
ITT	Baseline mean	37.3	36.9	2.7 (-0.9, 6.2)
	Week 52 LS mean change	-9.3	-6.6	Joint rank p=0.48
				ANCOVA+MI p=0.14

Source: Statistical Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; LS, least squares; MI, multiple imputation; mITT, modified intent-to-treat

There were slightly more favorable results for the first key secondary endpoint, percent predicted SVC during the OLE than the double-blind period, although differences were not nominally statistically significant. In the mITT population, the estimated mean difference was 8.7 (95% CI: -5.7, 23.2), p=0.23 based on the planned ANCOVA+MI approach. In the ITT population, the estimated difference was 7.5 (95% CI: -0.7, 15.7), p=0.07. The ANCOVA analysis of joint rank scores for SVC and survival was not prespecified for the OLE but it yielded similar results, with a difference of 3.9 (95% CI: -6.1, 14.0), p=0.44 in the mITT population, and 8.9 (95% CI: -3.6, 21.5), p=0.16 in the ITT population.

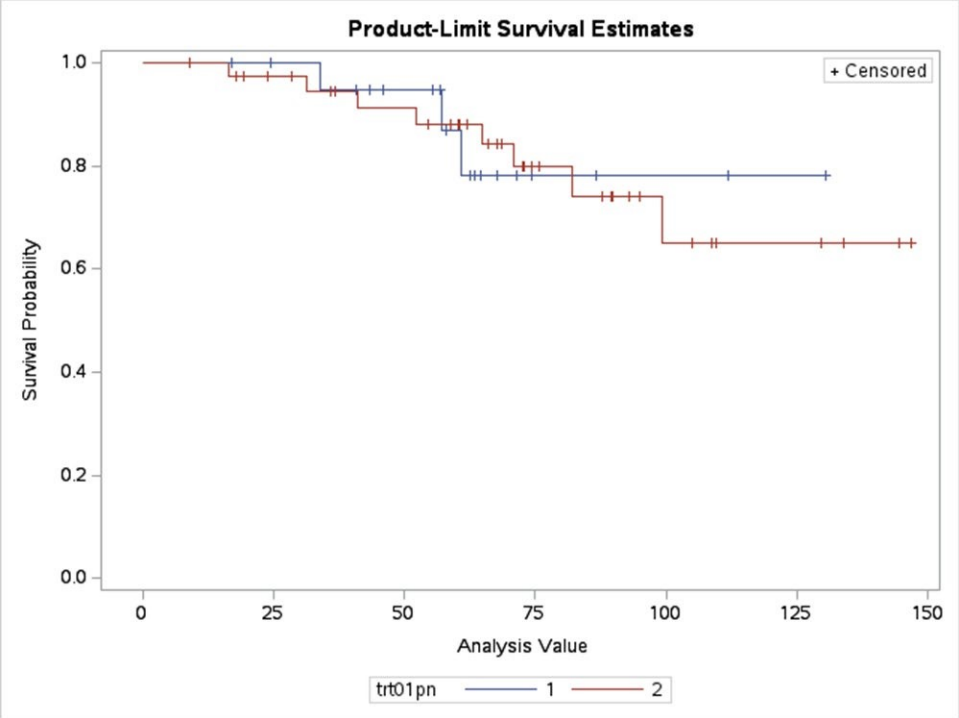
Results for the secondary endpoints of CSF total SOD1 and NfLs with tofersen demonstrated subjects in the tofersen group maintaining their lowered levels, and subjects in the placebo/delayed-start tofersen group showing reduced levels. Results are discussed in more detail in Section 6.3.2.2.

For time to death or permanent ventilation and time to death through all follow-up (up to 150 weeks), trends went in different directions in the mITT and ITT populations. Uncertainty around estimates was large due to the small numbers of events, and differences between arms were not nominally statistically significant. In the mITT population, 12 of 39 (30.8%) subjects on tofersen and 5 of 21 (23.8%) subjects on placebo/delayed-start tofersen died or went on permanent ventilation, for an estimated hazard ratio (HR) of 1.69 (95% CI: 0.53, 5.40), p=0.38. For time to death alone, 8 of 39 (20.5%) subjects on tofersen and 3 of 21 (14.3%) subjects on placebo/delayed-start tofersen died, for an estimated HR of 1.67 (95% CI: 0.39, 7.10), p=0.49. These numerical trends favored placebo over tofersen in the mITT population. In the ITT population, 12 of 72 (16.7%) subjects on tofersen and 8 of 36 (22.2%) subjects on placebo/delayed-start tofersen died or went on permanent ventilation, for an estimated HR of 0.70 (95% CI: 0.28, 1.75), p=0.45. For time to death alone, there were 8 of 72 (11.1%) events on tofersen as compared to 6 of 36 (16.7%) on placebo/delayed-start tofersen, for a HR of 0.64 (95% CI: 0.22, 1.88), p=0.41. Kaplan-Meier plots of the probability of survival over time in the mITT and ITT populations are shown in Figure 3 and Figure 4.

It is difficult to adjust for the multiplicity of survival analyses that have been conducted, as multiple time-to-event endpoints have been analyzed by the Applicant at several calendar times, in both the mITT and ITT populations, and with and without post-withdrawal vital status follow-

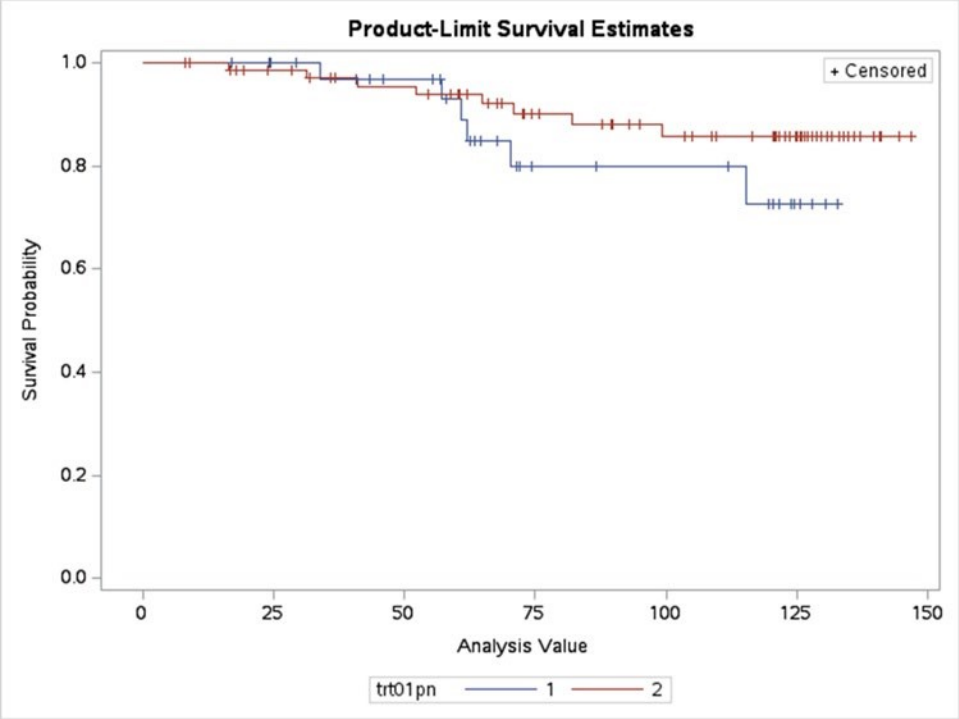
up. The potential for data-driven choices of analyses to emphasize findings can introduce bias and create challenges in interpreting results. Also note that follow-up is not complete in the analyses using post-withdrawal vital status follow-up. In particular, five (7%) of tofersen and three (8%) of tofersen placebo/delayed-start tofersen subjects did not have post-withdrawal vital status collected. There was additional missing data for permanent ventilation in the time to death and permanent ventilation analyses, given that events after withdrawal or for nonsubjects in Study 102 could have been missed. With the low number of events, this incomplete follow-up could be impactful.

Figure 3. Kaplan-Meier Curves for Time to Death in the mITT Population (Adjudicated Events)



Source: Statistical Reviewer's analysis
Note: trt01pn 1, Placebo/delayed-start tofersen; 2, early-start tofersen; analysis value is the time of the event in weeks
Abbreviation: mITT, modified intent-to-treat

Figure 4. Kaplan-Meier Curves for Time to Death in the ITT Population (Adjudicated Events)



Source: Statistical Reviewer's analysis
Note: trt01pn 1, placebo/delayed-start tofersen; 2, early-start tofersen
Abbreviations: ITT, intent-to-treat

Additional Analyses of Study 101C and the OLE (Study 102) by the Applicant

As noted above in the statistical methods section, the Applicant has conducted a variety of additional analyses based on statistical methods determined after access to unblinded data. These additional analyses carried out by the Applicant included changes to prespecified analysis methods such as a focus on the ITT rather than the mITT population, replacing time since symptom onset with baseline NfL as an adjustment covariate, and changes to the MI model (adding NfL as a covariate).

Results for the primary endpoint in Study 101C, change from baseline in ALSFRS-R at Week 28, using these post hoc analysis methods were more favorable for tofersen than the prespecified primary analysis but still did not reach nominal statistical significance, with an estimated mean difference of 2.1 (95% CI: -0.33, 4.54), p=0.09.

Results for ALSFRS-R, percent predicted SVC, and HHD megascore at Week 52 of the OLE are shown in Table 11, Table 12, and Table 13, respectively. Results for survival endpoints through the OLE are shown in Table 14. These analyses show trends in favor of tofersen and some of these analyses achieve nominal statistical significance. However, these analyses are likely biased due to imputation of missing data after death with a numerically higher proportion of deaths by the timepoint for the analysis in the drug group (four (5.6%) tofersen-treated subjects and one (2.8%) placebo subject died by Week 52). This practice of imputing missing data caused by

death has long been recognized[2] as not meaningful or appropriate. In addition, the results are very challenging to interpret, as post hoc, potentially data-driven modeling choices can induce substantial bias toward greater effect sizes than the truth. Of particular note is that prespecification of covariates is critical for the validity of models with covariate adjustment. The FDA draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (2021) states that "Sponsors should prospectively specify the covariates and the mathematical form of the covariate adjusted estimator in the statistical analysis plan before any unblinding of comparative data. FDA will generally give more weight in review to the prespecified primary analysis than to post hoc analyses using different models or covariates."

The Applicant has provided some reasonable scientific justifications for the modeling choices, for example, providing data to support that NfL is prognostic of functional decline and that the prespecified mITT primary analysis population defined by genetic mutation and prerandomization ALSFRS-R slope may have missed some fast progressors (Section 6.3.2.3.1.) However, adjustment for prognostic covariates is not necessary for valid inference on treatment effects—the prespecified analyses of this study were statistically valid and should be weighted heavily. Furthermore, there are always a variety of alternative modeling choices that can be justified scientifically after viewing the data from a study, and it is clear that at least part of the reason why these analyses are being explored is data driven, i.e., due to the lack of evidence in the prespecified analyses of the double-blind and OLE periods.

Table 11. Change in ALSFRS-R From Study 101 Part C Baseline in Studies 101 Part C and 102 (ITT Population) Based on Applicant Analysis Methods Determined after Data Unblinding

		ISE Based on Jul 2021 Data cut*	ISE Based on Jan 2022 Data cut**
	Endpoint	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 40**	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 52**
ITT	**Adjusted for baseline plasma NfL**		
	N: Tof; Placebo	72; 36	72; 36
	Adjusted means: Tof; Placebo	-5.8; -8.5	-6.0, -9.5
	Tofersen-placebo: adjusted mean difference (95% CI)	2.6 (-0.4, 5.7)	3.5 (0.4, 6.7)
	p-value (ANCOVA+MI)	N/A	0.0272

Source: Summary of Clinical Efficacy, Table 19, p. 76
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; ANCOVA, analysis of covariance; ISE, integrated summary of efficacy; ITT, intent-to-treat; MI, multiple imputation; N/A, not applicable; NfL, neurofilament light chain; Tof, tofersen

[2] National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The Prevention and Treatment of Missing Data in Clinical . Washington (DC): National Academies Press (US); 2010. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209904/ doi: 10.17226/12955

Table 12. Change in SVC From Study 101 Part C Baseline in Studies 101 Part C and 102 (ITT Population) Based on Applicant Analysis Methods Determined after Data Unblinding

		ISE Based on Jul 2021 Data cut*	ISE Based on Jan 2022 Data cut**
	Endpoint	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 40**	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 52**
ITT	**Adjusted for baseline plasma NfL** N: Tof; Placebo Adjusted means: Tof; Placebo Tofersen-placebo: adjusted mean difference (95% CI) p-value (ANCOVA+MI)	 72; 36 -8.6, -20.8 12.2 (4.3, 20.1) N/A	 72; 36 -9.4; -18.6 9.2 (1.7, 16.6) 0.0159

Source: Summary of Clinical Efficacy, Table 20, p. 76
Abbreviations: ANCOVA, analysis of covariance; ISE, integrated summary of efficacy; ITT, intent-to-treat; MI, multiple imputation; N/A, not applicable; NfL, neurofilament light chain; SVC, slow vital capacity; Tof, tofersen

Table 13. Change in HHD Megascore From Study 101 Part C Baseline in Studies 101 Part C and 102 (ITT Population) Based on Applicant Analysis Methods Determined After Data Unblinding

		ISE Based on Jul 2021 Data cut*	ISE Based on Jan 2022 Data cut**
	Endpoint	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 40**	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 52**
ITT	**Adjusted for baseline plasma NfL** N: Tof; Placebo Adjusted means: Tof; Placebo Tofersen-placebo: adjusted mean difference (95% CI) p-value (ANCOVA+MI)	 72; 36 -0.21; -0.51 0.30 (0.09, 0.51) N/A	 72; 36 -0.17; -0.45 0.28 (0.047, 0.517) 0.0186

Source: Summary of Clinical Efficacy, Table 21, p. 76
Abbreviations: ANCOVA, analysis of covariance; HHD, handheld dynamometry; ISE, integrated summary of efficacy; ITT, intent-to-treat; MI, multiple imputation; N/A, not applicable; NfL, neurofilament light chain; Tof, tofersen

Table 14. Time-to-Event Analyses in Studies 101 Part C and 102 (ITT Population) Based on Applicant Analysis Methods Determined After Data Unblinding

	ISE Based on Jan 2022 Data cut	
Endpoint	**Early-start tofersen 100 mg (n=72)**	**Placebo/delayed-start tofersen 100 mg (n=36)**
Time to death or permanent ventilation		
Number of events/Total number subjects (%)	12/72 (16.7%)	8/36 (22.2%)
Hazard ratio (95% CI)*		0.36 (0.137, 0.941)
Cox regression p-value*		0.0373
Log-rank test p-value**		0.0687
Time to death		
Number of events/Total number subjects (%)	8/72 (11.1%)	6/36 (16.7%)
Hazard ratio (95% CI)*		0.27 (0.084, 0.890)
Cox regression p-value*		0.0313
Log-rank test p-value**		0.0879

	ISE Based on Jan 2022 Data cut	
Endpoint	**Early-start tofersen 100 mg (n=72)**	**Placebo/delayed-start tofersen 100 mg (n=36)**
Time to death with additional post-withdrawal vital status data****		
Number of events/Total number subjects (%)	12/72 (16.7%)	11/36 (30.6%)
Hazard ratio (95% CI)*		0.24 (0.096, 0.602)
Cox regression p-value*		0.0023
Log-rank test p-value**		0.0096
Time to death, permanent ventilation, or withdrawal due to disease progression		
Number of events/Total number subjects (%)	18/72 (25.0%)	13/36 (36.1%)
Hazard ratio (95% CI)*		0.38 (0.180, 0.821)
Cox regression p-value*		0.0135
Log-rank test p-value**		0.0217

Note: Analysis for Studies 101 Part C & 102 is based on January 2022 data cut and was prespecified. All p-values are nominal.
Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Participants who do not meet the endpoint definition are censored at the participant's last known alive date. Similarly, time to death, permanent ventilation or withdrawal due to disease progression is defined from first dose to first of these events. Only events that were adjudicated by the Endpoint Adjudication Committee are included for these analyses. Withdrawal due to disease progression is based on the investigator assessment reported on the end of study CRF.
*Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
**Based on a log rank test stratified by median baseline plasma NfL.
Note: Median time was not estimable.
****Analysis incorporates vital status data obtained after discontinuation from Studies 101 Part C or 102 for participants who discontinued for reasons other than death.
Source: Summary of Clinical Efficacy, Table 22, p. 89
Abbreviations: CRF, case report form; ISE, integrated summary of efficacy; ITT, intent-to-treat; NfL, neurofilament light chain

Statistical Comments on the Results of Study 101C and Study 102 Open-Label Extension

This section focuses on statistical issues with the primary and secondary clinical endpoint results of Study 101C and its OLE (Study 102).

The primary analysis of Study 101C did not provide evidence of a treatment effect for tofersen. There was also no evidence of an effect on ALSFRS-R at Week 28 in the (exploratory) ITT population, nor was there evidence of effects on the secondary endpoints of percent SVC or HHD megascore based on the prespecified analyses of the 28-week double-blind period (in either the mITT or ITT population). Results for ALSFRS-R, SVC, and HHD megascore, as well as results for time to death and time to death or permanent ventilation, were also explored in the OLE. Based on the prespecified analyses, while there were some trends toward benefit, results did not achieve nominal statistical significance. This includes analyses in the (exploratory) ITT population. In addition, it is challenging to interpret the OLE results given the exploratory nature of this phase of the study and the lack of evidence in the primary analysis of the double-blind phase.

The Applicant has emphasized additional analyses that provide more favorable results for tofersen. However, these analyses were based on methods that deviated from those prespecified and were determined after data unblinding. For example, the ALSFRS-R analysis included a shift from the mITT to ITT population, a change in covariates (replacing time since symptom onset with baseline NfL), and changes to the MI approach (adding baseline NfL). The Applicant provides some scientific justification for the modeling changes, and some of these post hoc results seem promising. However, due to the lack of evidence observed in the prespecified analyses of both the double-blind and OLE periods, and the potential data-driven nature of these additional analyses, the results are very challenging to interpret.

We also note additional issues with design considerations for Study 101C and Study 102 (refer to issues with sample size planning and issues with method of imputation of missing data in Section 15.1). One reason the study failed may have been that decline in both the placebo and treatment groups was much less than expected. The sample size justification was based on an assumed mean slope of decline of -3.83 per month for the placebo participants (i.e., 24.7-point decline over 28 weeks) and -0.74 per month for the tofersen 100 mg participants (approximately a 4.8-point decline over 28 weeks), with a pooled SD of 3.166. The actual observed decline over 28 weeks was approximately an 8.1 decline in the placebo arm and a 7-point decline in the tofersen arm, a mean difference of about 1 point instead of the 20-point difference that was assumed. The survival rate in both arms combined was 59/60 (one death in the tofersen arm). Assuming these observed rates of decline and a common survival rate of 59/60 and leaving the other assumptions unchanged, a future study would need 12,000 participants to achieve 80% power to detect a mean difference of 1.1-point decline in ALSFRS-R, noting the uncertainty about the effect of a 1.1-point change. Thus, either tofersen has a very small effect or the study is severely underpowered; both are possible.

6.3. Key Efficacy Review Issues

6.3.1. NfL as a Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit in SOD1-ALS as a Reasonably Likely Surrogate Endpoint

Issue

Whether the available evidence supports that a reduction in NfL in tofersen-treated patients with SOD1-ALS is reasonably likely to predict clinical benefit for these patients.

6.3.1.1. Background of the Issue

Tofersen is an antisense oligonucleotide (ASO) designed to bind and degrade SOD1 mRNA to reduce synthesis of SOD1 protein. A toxic form of SOD1 protein is implicated in the pathophysiology of SOD1-ALS. Tofersen targets the 3'-UTR of the mRNA for human SOD1 to suppress SOD1 protein synthesis and accumulation.

A single 28-week, randomized, double-blind, placebo-controlled pivotal study (Study 101C) was conducted in 108 adult patients with SOD1-ALS. Patients were randomized 2:1 to tofersen or placebo. Randomization was stratified by fast progressor and non-fast progressor. Fast progressors were defined by genetic mutation and prerandomization slope on the ALSFRS-R, and fast progressors comprised the primary analysis population (mITT population); see Section 6.2.1.1.

This study did not show a statistically significant difference between the tofersen and placebo groups for the primary or secondary endpoints in the prespecified primary analysis in the fast progressor population (Section 6.2.1.4).

Additional assessments in the study included biomarkers such as total SOD1 protein in cerebrospinal fluid (CSF) and NfL in plasma. NfL is a reported marker of neuroaxonal damage. Most recently, scientific literature has established NfL as a biomarker that is significantly elevated in patients with ALS, even more so than in many other neurodegenerative diseases, and NfL levels have been shown to be prognostic for disease progression in ALS.[3,4]

In the prespecified mITT population, a reduction in total CSF SOD 1 protein was observed at Week 28 in the tofersen group compared to the placebo group (38% difference in geometric mean ratio for tofersen to placebo, nominal $p<0.0001$; Section 6.3.2.1). In the mITT population, a 55% reduction in plasma NfL was observed at Week 28 in the tofersen group compared to a

[3] Gille B, De Schaepdryver M, Goossens J, et al. Serum neurofilament light chain levels as a marker of upper motor neuron degeneration in patients with amyotrophic lateral sclerosis. Neuropathol Appl Neurobiol. 2019;45(3):291-304. doi:10.1111/nan.12511

[4] Brodovitch A, Boucraut J, Delmont E, et al. Combination of serum and CSF neurofilament-light and neuroinflammatory biomarkers to evaluate ALS. Sci Rep. 2021;11(1):703. Published 2021 Jan 12. doi:10.1038/s41598-020-80370-6

mean 12% increase in NfL in the placebo group (67% difference in geometric mean ratio for tofersen to placebo, nominal p<0.0001; Section 6.3.2.1).

Following completion of the placebo-controlled study, all participants had the opportunity to enroll in an OLE study (Study 102), where they received open-label tofersen treatment but remained blinded to the treatment received in the double-blind study. The primary objective of the extension study was to evaluate safety and tolerability, but it also provided additional biomarker and clinical endpoint data through Week 52 (Section 6.2.2.1). After switching to tofersen in the OLE, patients previously receiving placebo experienced a similar reduction in NfL (44% from baseline of Study 102) after 24 weeks of treatment in the open-label period, followed by an apparent reduction in decline in ALSFRS-R total score at Week 52. Analyses based on the prespecified methods of ALSFRS-R and other secondary clinical endpoints in the OLE showed favorable trends for tofersen, although the results were not nominally statistically significant, and some results were inconsistent (e.g., the numerical trend for time to death favored tofersen over placebo in the ITT population but not in the mITT population). The Applicant also carried out additional post hoc, exploratory analyses of treatment benefit in the OLE, and nominally significant improvements were noted in both the ALSFRS-R and survival for patients originally randomized to tofersen compared to patients originally randomized to placebo. Based on the ALSFRS-R total score, the early-start tofersen group showed a numerically lesser decline in the ALSFRS-R total score than the delayed-start group, which was consistent from Week 28 to Week 52. The consistent separation on ALSFRS-R between the two groups from Week 8 further supports the potential treatment effect of tofersen. However, these exploratory OLE analyses have limitations (e.g., post hoc choice of covariate and time points, multiplicity issues) that hamper interpretation of the results (Section 6.2.2.4).

Although Study 101C is a negative clinical study that did not show a statistically significant treatment effect in the prespecified primary analysis population, the study, as designed, was markedly underpowered and thus limited in its ability to detect a treatment difference if there was a drug effect. There are available data from that study that indicate target engagement of the therapy and a reduction in a biomarker that has been shown to be correlated with disease progression and prognosis in patients with ALS. There are also post hoc exploratory analyses from the OLE study that may be suggestive of a clinical benefit with a longer duration of treatment.

The literature on NfL in ALS has evolved since the design and initiation of the pivotal study for tofersen, including a more recent emphasis on the role of NfL in ALS disease progression. To be considered for accelerated approval, a drug must demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; studies to demonstrate such an effect must be adequate and well controlled. In that vein, reduction in NfL by tofersen is proposed as a biomarker endpoint that is reasonably likely to predict clinical benefit in SOD1-ALS to support the accelerated approval of tofersen.

6.3.1.2. Background of NfL

NfL is a neurofilament protein highly expressed in myelinated axons. Elevated levels of NfL in the CSF and blood are found in a variety of neurological disorders including ALS,[5] and are a consequence of axonal damage.[6,7,8] Neurofilament levels in the plasma and CSF, including neurofilament heavy chain (pNF-H) and NfL are significantly elevated in patients with ALS compared to other neurodegenerative diseases.[8,9,10,11] For SOD1-mutation carriers of ALS patients, elevated serum NfL levels have been observed as early as 1 year before symptom onset.[12]

Several independent studies have recently reported that NfL levels are correlated with disease severity, disease progression rate, and survival in patients with ALS.,[13,14] A meta-analysis of published literature findings on NfL in ALS demonstrated a correlation between the rate of disease progression and plasma NfL level (Section 14.5.1). Additionally, higher levels of neurofilament were associated with a higher risk of unfavorable clinical outcomes, including death, tracheostomy, and/or permanent ventilation. NfL was reported to have a stronger association than other candidate biomarkers with ALS progression rate and survival.[15] These findings offer support for the utility of NfL as a prognostic biomarker for ALS disease progression and survival.[15] Also, a reduction of neurofilament levels has been reported for products approved for the treatment of other neurological diseases, including multiple sclerosis,

[5] Verber NS, Shepheard SR, Sassani M, et al. Biomarkers in Motor Neuron Disease: A State of the Art Review. Front Neurol. 2019;10:291. Published 2019 Apr 3. doi:10.3389/fneur.2019.00291

[6] Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90(8):870-881. doi:10.1136/jnnp-2018-320106

[7] Yuan A, Nixon RA. Neurofilament Proteins as Biomarkers to Monitor Neurological Diseases and the Efficacy of Therapies. Front Neurosci. 2021;15:689938. Published 2021 Sep 27. doi:10.3389/fnins.2021.689938

[8] Olsson B, Portelius E, Cullen NC, et al. Association of Cerebrospinal Fluid Neurofilament Light Protein Levels With Cognition in Patients With Dementia, Motor Neuron Disease, and Movement Disorders. JAMA Neurol. 2019;76(3):318-325. doi:10.1001/jamaneurol.2018.3746

[9] Gaiottino J, Norgren N, Dobson R, et al. Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. PLoS One. 2013;8(9):e75091. Published 2013 Sep 20. doi:10.1371/journal.pone.0075091

[10] Behzadi A, Pujol-Calderón F, Tjust AE, et al. Neurofilaments can differentiate ALS subgroups and ALS from common diagnostic mimics. Sci Rep. 2021;11(1):22128. Published 2021 Nov 11. doi:10.1038/s41598-021-01499-6

[11] Heckler I, Venkataraman I. Phosphorylated neurofilament heavy chain: a potential diagnostic biomarker in amyotrophic lateral sclerosis. J Neurophysiol. 2022;127(3):737-745. doi:10.1152/jn.00398.2021

[12] Benatar M, Wuu J, Andersen PM, Lombardi V, Malaspina A. Neurofilament light: A candidate biomarker of presymptomatic amyotrophic lateral sclerosis and phenoconversion. Ann Neurol. 2018;84(1):130-139. doi:10.1002/ana.25276

[13] Lu, Ching-Hua et al. “Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis.” Neurology vol. 84,22 (2015): 2247-57. doi:10.1212/WNL.0000000000001642

[14] Dreger M, Steinbach R, Otto M, Turner MR, Grosskreutz J. Cerebrospinal fluid biomarkers of disease activity and progression in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2022;93(4):422-435. doi:10.1136/jnnp-2021-327503

spinal muscular atrophy, and hereditary transthyretin-mediated amyloidosis,[16,17,18] which provides additional context regarding the use of NfL as a pharmacodynamic biomarker that may correlate with clinical benefit.

6.3.2. Assessment

6.3.2.1. Overview of Biomarker Results

NfL in Plasma

Change in NfL (i.e., ratio to baseline) at Week 28 in the mITT population was the second endpoint listed among the secondary objectives after the primary and four key secondary endpoints included in the multiple testing hierarchy of Study 101C. Plasma NfL was sampled before dosing at each visit in which treatment was administered (Days 1, 15, 29, and every 4 weeks thereafter) and at the final visit (4 weeks after the last dose).

The plasma NfL assay used to support clinical Study 101C was validated for one specific context of use (COU): to quantify the plasma NfL concentrations for the purpose of assessing the changes in NfL concentration after exposure to tofersen in treated subjects as well as the differences in the change of NfL concentration over time between treated and untreated subjects. The method validation demonstrated acceptable assay performance characteristics, including the precision, selectivity, specificity, parallelism, stability, and accuracy (relative to the nominal concentration assigned by the Applicant). Therefore, the assay is suitable for the described COU to support clinical Study 101C. However, the reported NfL concentrations are considered nominal values which are specific to (1) the NfL calibration material (including the concentration assignment) and (2) the NfL assay method implemented in the bioanalytical program. Therefore, the NfL concentrations derived by this assay/study cannot serve as reference values for any study enrollment or patient stratification (a new COU different from that for which the assay was validated). Scientific verifications to confirm that the nominal concentration values remain comparable will be necessary if there are any changes to the calibration material or NfL assay method. Refer to Section 14.3.1 for detailed discussion on the plasma NfL assay.

The Applicant's prespecified secondary analysis of NfL in the mITT population yielded an estimated geometric mean ratio of 0.33 (95% CI: 0.25, 0.45; nominal p<0.0001). The supportive results from the non-mITT population were an estimated geometric mean ratio of 0.52 (95% CI: 0.43, 0.63; nominal p<0.0001) (Table 15).

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[15] Thompson AG, Gray E, Verber N, et al. Multicentre appraisal of amyotrophic lateral sclerosis biofluid biomarkers shows primacy of blood neurofilament light chain. Brain Commun. 2022;4(1):fcac029. Published 2022 Feb 9. doi:10.1093/braincomms/fcac029

[16] Darras BT, Crawford TO, Finkel RS, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol. 2019;6(5):932-944. Published 2019 Apr 17. doi:10.1002/acn3.779

[17] Sormani MP, Haering DA, Kropshofer H, et al. Blood neurofilament light as a potential endpoint in Phase 2 studies in MS. Ann Clin Transl Neurol. 2019;6(6):1081-1089. Published 2019 May 28. doi:10.1002/acn3.795

[18] Ticau S, Sridharan GV, Tsour S, et al. Neurofilament Light Chain as a Biomarker of Hereditary Transthyretin-Mediated Amyloidosis. Neurology. 2021;96(3):e412-e422. doi:10.1212/WNL.0000000000011090

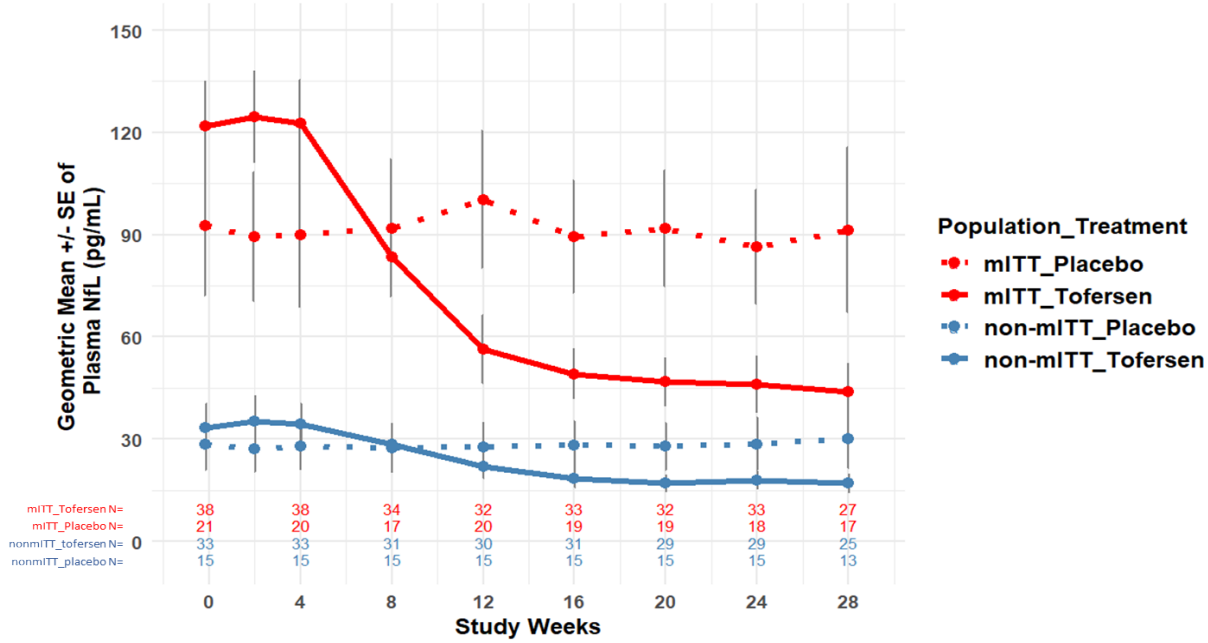
Because the assessment of NfL as a surrogate endpoint will include data from all patients, NfL reduction was also quantified for the ITT population. In the ITT population, plasma NfL was reduced by 55% (geometric mean ratio to baseline) in the tofersen-treated subjects, compared to a 12% increase in placebo-treated subjects at Week 28 (difference [ratio] in geometric mean ratios for tofersen to placebo 0.4; post hoc nominal p<0.0001) (Table 15). The NfL reduction driven by tofersen plateaued at Week 16 and was sustained at the end of treatment at Week 28 (Figure 5). Given the lack of evidence of statistical significance of the primary analysis of this study and the prespecified hierarchical testing plan, the effect of tofersen on NfL is considered nominally statistically significant. However, the NfL reduction was consistently observed for all subgroups based on sex, disease duration since symptom onset, site of onset (i.e., limb versus bulbar), and riluzole/edaravone use. In Study 101C, similar reductions in NfL were also observed in the CSF following tofersen treatment (difference in geometric mean ratios for tofersen to placebo of 69%; nominal p<0.0001, ITT population).

Table 15. Study 101 Part C: Summary of Adjusted Geometric Mean Ratio to Baseline in Plasma NfL at Week 28

Population	Parameter	Placebo	Tofersen
ITT	N	36	72
	Adjusted GMR to baseline	1.12	0.45
	Tof:plac difference in GMR (95% CI)		0.40 (0.33, 0.49)
	Nominal p-value (ANCOVA+MI)		<0.0001
mITT	N	21	39
	Adjusted GMR to baseline	1.20	0.40
	Tof:plac difference in GMR (95% CI)		0.33 (0.25, 0.45)
	Nominal p-value (ANCOVA+MI)		<0.0001
Non-mITT	N	15	33
	Adjusted GMR to baseline	0.95	0.50
	Tof:plac difference in GMR (95% CI)		0.52 (0.43, 0.63)
	Nominal p-value (ANCOVA+MI)		<0.0001

Source: CSR Study 101 Part C, Table 2
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the nonmissing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 4.9 pg/mL) in calculations.
NOTE 3: MI was used for missing data. Model included treatment, use of riluzole or edaravone, relevant baseline score and postbaseline values (natural log transformed data). Separate models for mITT and non-mITT were used and combined for ITT analyses.
NOTE 4: Adjusted geometric mean ratios to baseline, treatment differences in adjusted geometric mean ratios to baseline and corresponding 95% CIs and nominal p-values were obtained from the ANCOVA model for change from baseline including treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, relevant baseline score, and use of riluzole or edaravone. The analysis was based on natural log transformed data.
Abbreviations: ANCOVA, analysis of covariance; GMR, geometric mean ratio; ITT, intent-to-treat; MI, multiple imputation; mITT, modified intent-to-treat; NfL, neurofilament light chain; plac, placebo; Tof, tofersen

Figure 5. Plasma NfL (pg/mL) Geometric Mean Values ±SE by Visit (Observed Data) in Study 101C

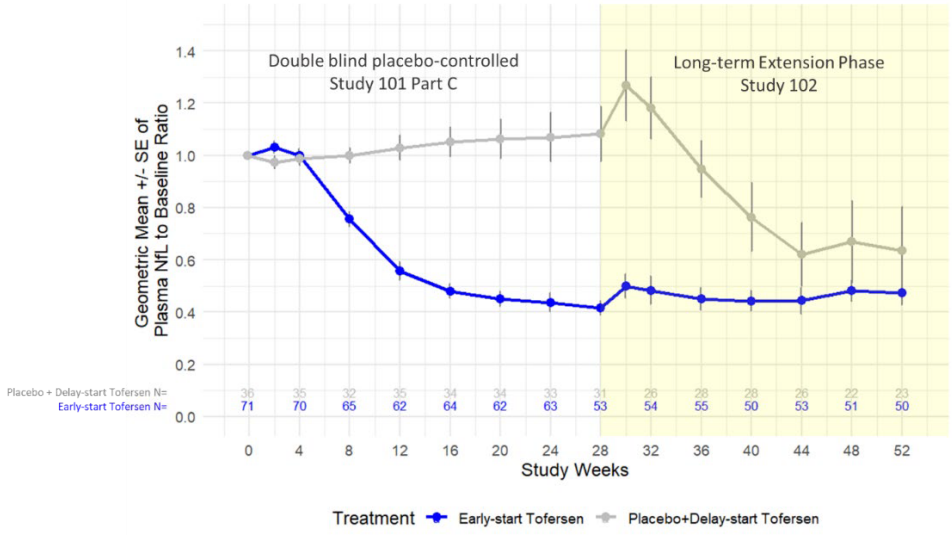


Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: mITT, modified intent-to-treat; NfL, neurofilament light chain

It is also of interest that notable differences were observed in baseline plasma NfL levels between the treatment arms in the mITT population. The geometric mean baseline plasma NfL level in subjects receiving placebo (93 pg/mL, SD of 94 pg/mL) was lower compared to geometric mean of baseline plasma NfL level in those receiving tofersen (122 pg/mL, SD of 83 pg/mL) in the mITT population (Section 6.3.2.3.1 for a detailed discussion of the role of baseline NfL in explaining the heterogeneity and imbalances in disease progression).

In the ITT population of Study 102, subjects who had received tofersen in Study 101C (early-start tofersen group) maintained the previously lowered plasma NfL levels following the 24 weeks of continued tofersen treatment (Figure 6). In subjects in the delayed-start tofersen group (received placebo in Study 101C), 24 weeks of treatment with open-label tofersen reduced plasma NfL levels by 44% (GMR to baseline of Study 102) in the ITT population.

Figure 6. Plasma NfL Baseline to Ratio Geometric Mean Values ±SE by Visit (Observed Data) From Study 101 Part C and Study 102

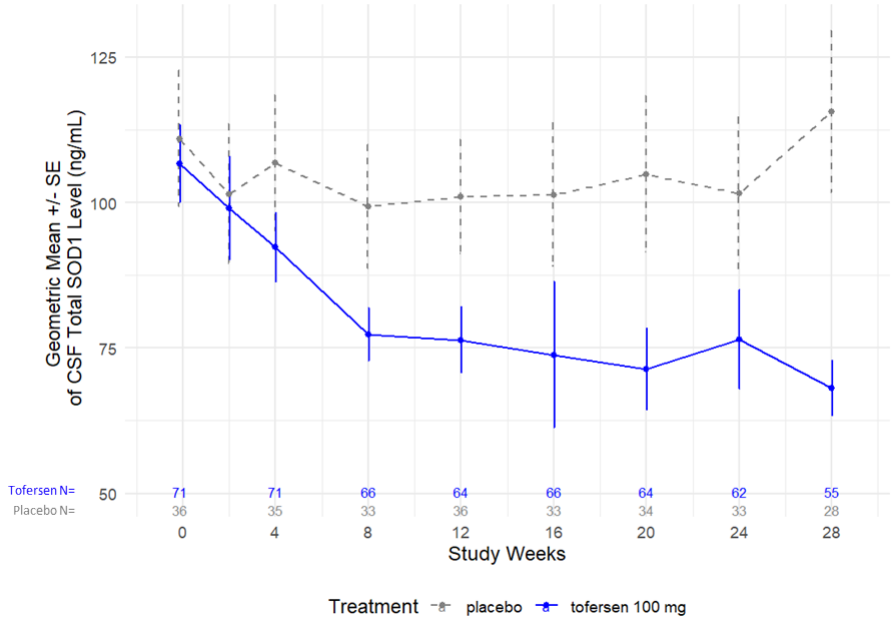


Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: NfL, neurofilament light chain

Total SOD1 in CSF

In Study 101C, another secondary PD endpoint was the change from baseline at Week 28 in total SOD1 concentration in CSF for the mITT population. In Study 101C, CSF was sampled before dosing at each visit in which treatment was administered (Days 1, 15, 29, and every 4 weeks thereafter) and at the final visit (4 weeks after the last dose). A reduction in total CSF SOD1 protein was observed at Week 28 in the tofersen group compared to the placebo group (38% difference in geometric means ratio for tofersen to placebo, nominal $p<0.0001$) in the mITT population. At Week 28 in the intent-to-treat (ITT) population, reductions in total CSF SOD1 protein of approximately 35% (geometric mean ratio [GMR] to baseline) in the tofersen group and a decrease of approximately 2% in the placebo group were observed (difference in GMRs for tofersen to placebo: approximately 34%; nominal $p<0.0001$, Figure 7).

Figure 7. Total CSF SOD1 Protein Level (Geometric Mean ±SE) by Visit (Observed Data) From Study 101 Part C, ITT Population



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: CSF, cerebrospinal fluid; ITT, intent-to-treat; SOD1, superoxide dismutase 1

Other biomarkers, including deamidated SOD1 peptide in CSF, NfL in CSF, phosphorylated neurofilament heavy chain (pNfH) in CSF and plasma, were also evaluated in Study 101C as exploratory biomarkers. Refer to Section 14.7 for detailed discussion.

6.3.2.2. Assessment of Plasma NfL as a Surrogate Endpoint Reasonably Likely to Support Accelerated Approval

Plasma NfL was evaluated as a reasonably likely surrogate endpoint to support accelerated approval for tofersen in the treatment of SOD1-ALS, based on the following approach:

- Mechanistic evidence that plasma NfL is a biomarker reasonably likely to predict clinical function based on the pathophysiology of SOD1-ALS and the pharmacology of tofersen.
- Evidence from the literature and tofersen clinical program to demonstrate the prognostic value of plasma NfL in predicting disease progression and survival in ALS.
- Evidence from the tofersen clinical program to demonstrate the relationship between tofersen-driven NfL reduction and changes in clinical decline using longitudinal changes in NfL and ALSFRS-R total score, correlation analysis, and causal inference analysis.

Sections 6.3.2.2.1 to 6.3.2.2.3 describe various aspects of the Clinical Pharmacology team's assessment of plasma NfL as a surrogate endpoint. Section 6.3.2.3 summarizes comments on this topic, including perspectives from the Clinical Pharmacology review team and the Statistical Review team.

6.3.2.2.1. Mechanistic Support Based on Understanding of the Disease Pathophysiology and the MOA of Tofersen

Current understanding of the pathophysiology of SOD1-ALS and the pharmacology of tofersen provides mechanistic support that plasma NfL is a biomarker reasonably likely to predict clinical benefit

In SOD1-ALS, the pathologic mutation in the SOD1 gene is closely linked to the development and clinical progression of the disease. Mutations in the SOD1 gene may cause toxic accumulation of mutated or misfolded SOD1 protein.[19,20,21] Although the underlying mechanism is not fully understood, the level of misfolded SOD1 is correlated with the vulnerability of neurons in the spinal cord.[1919] The release of NfL into CSF and blood is a consequence of axonal injury and the level of NfL may reflect the degree of axonal damage.[6,7] The degeneration and loss of motor neurons, hallmarks of ALS, lead to a decline in clinical function that is typically assessed by ALSFRS-R.

Tofersen is an ASO targeting the mRNA for human SOD1. If tofersen does reduce neuronal injury by lowering SOD1, a reduction in NfL would be the expected outcome. Based on the pathophysiology of SOD1-ALS, this reduction in NfL could slow clinical functional decline.

6.3.2.2.2. Reported Prognostic Value of Plasma NfL Levels in ALS

The prognostic value of plasma NfL in ALS was evaluated using data from the literature and ALS clinical studies.

Evidence From the Literature

The Clinical Pharmacology review team conducted a meta-analysis on the prognostic value of NfL in patients with ALS to quantify the relationship between both (A) plasma NfL and disease progression slope for ALSFRS-R total score; and (B) plasma NfL and unfavorable clinical outcomes (death, tracheostomy, and/or permanent assisted ventilation). Figure 8 shows the correlation between NfL and the disease progression slope from all published

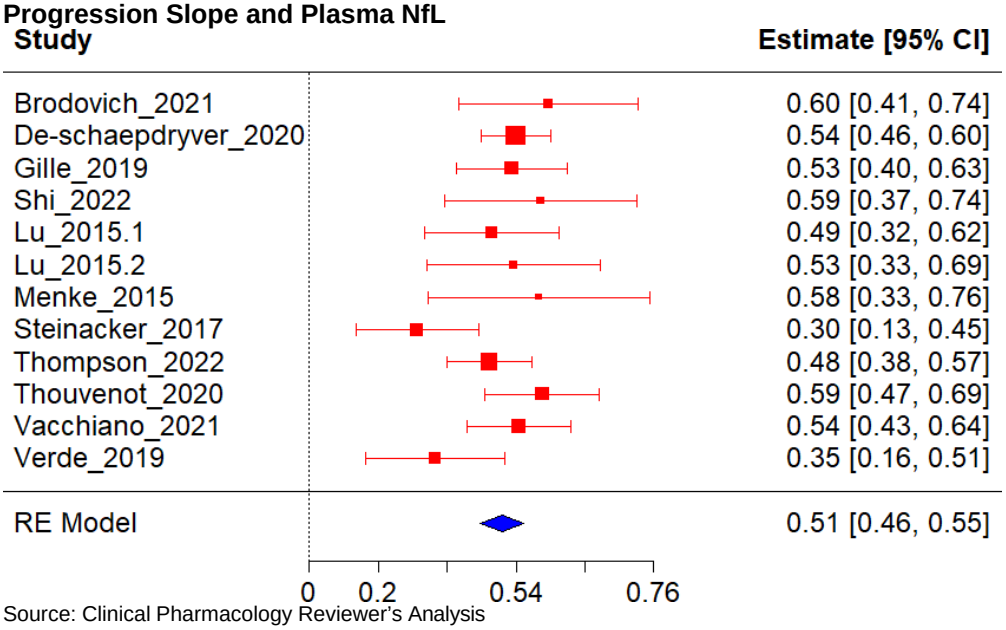
[19] Genc B, Gozutok O, Kocak N, Ozdinler PH. The Timing and Extent of Motor Neuron Vulnerability in ALS Correlates with Accumulation of Misfolded SOD1 Protein in the Cortex and in the Spinal Cord. Cells. 2020;9(2):502. Published 2020 Feb 22. doi:10.3390/cells9020502

[20] Brotherton TE, Li Y, Cooper D, et al. Localization of a toxic form of superoxide dismutase 1 protein to pathologically affected tissues in familial ALS. Proc Natl Acad Sci U S A. 2012;109(14):5505-5510. doi:10.1073/pnas.1115009109

[21] Trist BG, Genoud S, Roudeau S, et al. Altered SOD1 maturation and post-translational modification in amyotrophic lateral sclerosis spinal cord. Brain. 2022;145(9):3108-3130. doi:10.1093/brain/awac165

studies.[3,4,13,15,,22,23,24,25,26,27,28] The overall correlation coefficient between disease progression (slope of ALSFRS-R total score) and plasma NfL in a meta-analysis was 0.51 (95% CI: 0.46, 0.55), which suggests that higher blood NfL levels in ALS patients are associated with more rapid disease progression. We note that a large number of these studies were published in the last 3 years, reflecting the increasingly recognized relationship between NfL and the prognosis in patients with ALS.

Figure 8. Forest Plots Showing the Correlation Coefficients for the Relationship Between Disease Progression Slope and Plasma NfL



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: CI, confidence interval; NfL, neurofilament light chain; RE, random effect

The relationship between plasma NfL levels and unfavorable clinical outcomes (death, tracheostomy and/or permanent assisted ventilation) was quantified using multivariate Cox-

[22] De Schaepdryver M, Lunetta C, Tarlarini C, et al. Neurofilament light chain and C reactive protein explored as predictors of survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2020;91(4):436-437. doi:10.1136/jnnp-2019-322309

[23] Shi J, Qin X, Chang X, Wang H, Guo J, Zhang W. Neurofilament markers in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis. J Cell Mol Med. 2022;26(2):583-587. doi:10.1111/jcmm.17100

[24] Menke RA, Gray E, Lu CH, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. Ann Clin Transl Neurol. 2015;2(7):748-755. doi:10.1002/acn3.212

[25] Steinacker P, Huss A, Mayer B, et al. Diagnostic and prognostic significance of neurofilament light chain NF-L, but not progranulin and S100B, in the course of amyotrophic lateral sclerosis: Data from the German MND-net. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(1-2):112-119. doi:10.1080/21678421.2016.1241279

[26] Thouvenot E, Demattei C, Lehmann S, et al. Serum neurofilament light chain at time of diagnosis is an independent prognostic factor of survival in amyotrophic lateral sclerosis. Eur J Neurol. 2020;27(2):251-257. doi:10.1111/ene.14063

[27] Vacchiano V, Mastrangelo A, Zenesini C, et al. Plasma and CSF Neurofilament Light Chain in Amyotrophic Lateral Sclerosis: A Cross-Sectional and Longitudinal Study. Front Aging Neurosci. 2021;13:753242. Published 2021 Oct 22. doi:10.3389/fnagi.2021.753242

[28] Verde F, Steinacker P, Weishaupt JH, et al. Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90(2):157-164. doi:10.1136/jnnp-2018-318704

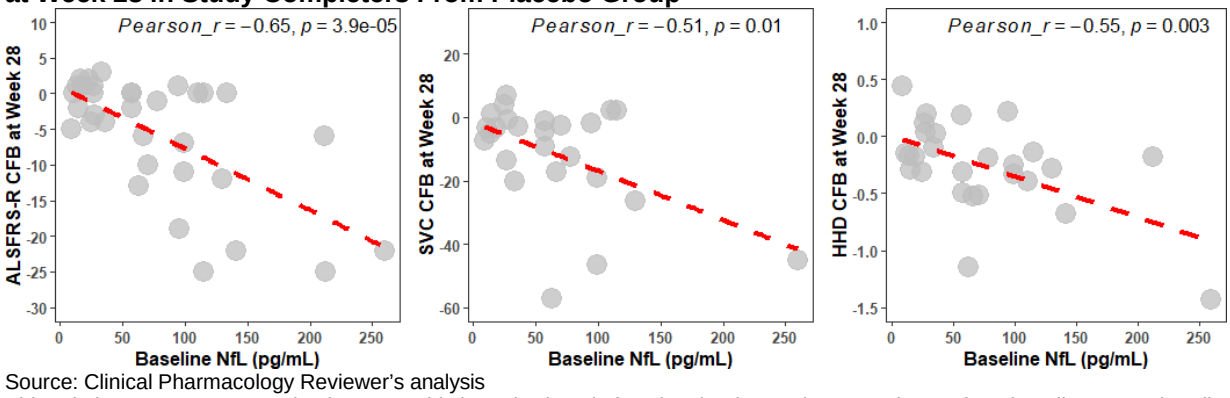
regression in several research studies. The hazard ratios for plasma NfL obtained from literature were used to calculate relative hazard risks, which suggested that subjects with higher plasma NfL had a higher risk of unfavorable clinical outcomes in all three studies.[26,27,29] Other studies have reported shortened survival for subjects with higher plasma NfL levels.[15,23] Overall, the literature suggests that higher levels of neurofilament are associated with higher risks of unfavorable clinical outcomes.

Refer to Section 14.5.1 for a detailed discussion of demonstrating the prognostic value of plasma NfL in ALS based on literature evidence.

Evidence From Placebo Arm in Tofersen Clinical Program

As part of the evaluation for use of NfL as a prognostic biomarker in ALS, the placebo data (n=33) from Study 101C were analyzed to identify prognostic factors associated with changes from baseline in clinical endpoints (ALSFRS-R total score, SVC, and HHD megascore) at Week 28. 9 shows the correlation between baseline plasma NfL and change from baseline in clinical endpoints at Week 28 in all study completers from the placebo group. This finding demonstrates that placebo subjects with higher baseline NfL experienced more decline across all clinical endpoints at Week 28, which is consistent with the meta-analysis findings.

Figure 9. Correlation Between Baseline Plasma NfL and Clinical Endpoint Change From Baseline at Week 28 in Study Completers From Placebo Group



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; HHD, handheld dynamometry; NfL, neurofilament light chain; SVC, slow vital capacity

Regression analysis was performed to identify additional prognostic factors other than plasma NfL that affect ALSFRS-R total score at Week 28. Table 16 lists the prognostic factors and various neurofilament metrics used in the analysis dataset. These variables were selected based on their availability in the dataset as well as potential clinical relevance.

[29] Benatar M, Zhang L, Wang L, et al. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. Neurology. 2020;95(1):e59-e69. doi:10.1212/WNL.0000000000009559

Table 16. Demographics, Disease Characteristics, and Neurofilament Metrics Used in the Analyses

A. List of Potential Prognostic Factors		
Demographics	**Disease Characteristics**	
Age	ALSFRS-R total score	Time from symptom onset
Sex	ALSFRS-R slope	Site of onset
Weight	Plasma NfL	Edaravone or Riluzole use
Height	Plasma pNfH	SOD1 protein
BMI	Slow vital capacity (SVC)	
B. Various Metrics of Neurofilaments Explored		
Baseline NfL (pg/mL)	NfL-time slope	
NfL change (pg/mL)	Log NfL (pg/mL)	
NfL change (%)	Log daily area under NfL-time curve (pg/mL)	
NfL ratio to baseline	Log linear-model-estimated area under NfL-time curve until Week 28 (pg·day/mL)	

Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; BMI, body mass index; NfL, neurofilament light chain; SOD1, superoxide dismutase 1

Two regression methods were used: linear regression and lasso regression. The findings of both methods suggested that baseline levels of plasma NfL were a significant predictor ($p<0.001$) for ALSFRS-R change from baseline (CFB) at Week 28, even after adjusting for multiple potential baseline prognostic factors and various transformations of NfL metrics. These analyses may be affected by the limited sample size (n=33). However, these results, along with the meta-analysis of the literature data outlined above, support the prognostic value of plasma NfL in ALS. Refer to Section 14.5.2 for detailed discussion on a model-based approach to identify prognostic factors that affect ALSFRS-R total scores based on evidence from the tofersen clinical program.

6.3.2.2.3. Relationship Between Reduction in Plasma NfL and Clinical Endpoints

Considering the prognostic value of plasma NfL levels in ALS, further analyses were conducted to evaluate the relationship between plasma NfL reduction with tofersen treatment and reduction in clinical decline.

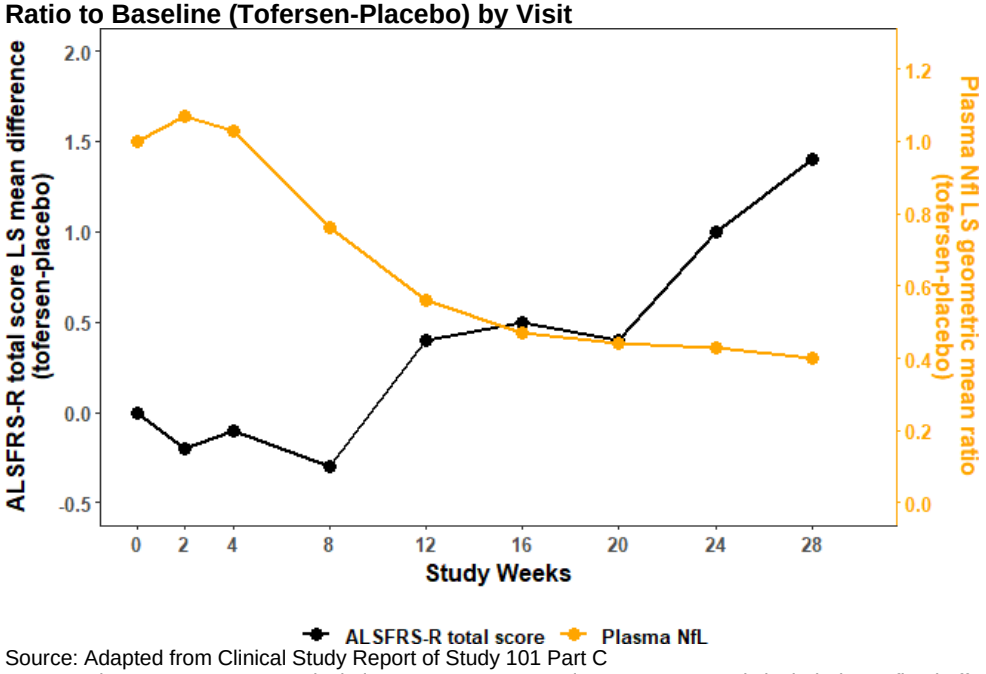
Longitudinal Changes in Plasma NfL and ALSFRS-R

Longitudinal changes in plasma NfL and ALSFRS-R suggested a potential relationship between the reductions in plasma NfL in the tofersen treatment group and reduction in decline of clinical endpoints.

This analysis focused on the entire (ITT) data set so as to provide the largest number of patients, and broadest range of NfL changes and ALSFRS-R changes to assess the relationship. Data from the ITT population (N=108) of Study 101C show that the mean NfL reductions in the tofersen treatment group began at Week 4 and peaked as early as Week 16. Beyond Week 16, the mean reductions in plasma NfL were consistent with those at Week 16. Although the changes in ALSFRS-R in the tofersen group relative to the placebo group were not statistically significant through Week 28, numerical differences were observed after Week 8 and continued through Week 28 (Figure 10). This could indicate that a treatment effect of slowing of disease progression may not become apparent until several weeks after treatment initiation.

To further evaluate the relationship between NfL reductions in the tofersen treatment group and a reduction in clinical decline, two analyses were conducted: (i) correlation analysis between plasma NfL reduction at Week 28 and ALSFRS-R CFB at Week 28; and (ii) causal inference analysis to quantify the impact of reductions in plasma NfL in the tofersen group at Week 16 on reduction in clinical decline of ALSFRS-R total score at Week 28. Given that mean plasma NfL values were consistent from Week 16 to Week 28, we expected that using NfL at Week 16 or Week 28 in the analyses will provide similar results.

Figure 10. ALSFRS-R Total Score LS Mean Difference (Tofersen-Placebo) and Plasma NfL LS Mean Ratio to Baseline (Tofersen-Placebo) by Visit



Source: Adapted from Clinical Study Report of Study 101 Part C
Note: For least squares mean calculation on ALSFRS-R total score, treatment is included as a fixed effect after adjusting for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone.
For least squares mean calculation on NfL, treatment is included as a fixed effect after adjusting for baseline disease duration since symptom onset, log baseline NfL, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; LS, least squares; NfL, neurofilament light chain

Correlation Analysis

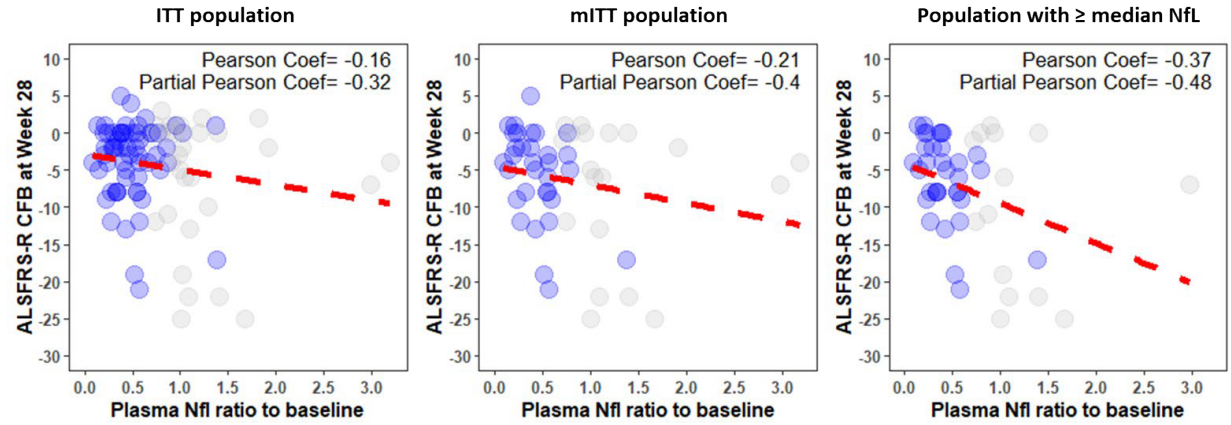
Correlation analysis demonstrated a relationship between reduction in NfL and ALSFRS-R CFB at Week 28. Figure 11A shows the relationship between plasma NfL reduction at Week 28 and ALSFRS-R CFB at Week 28 for the ITT population and in the mITT population (Figure 11A). In addition, a subgroup of subjects with baseline levels of NfL greater than or equal to the median was also evaluated. Correlation coefficients are provided with and without adjustment for other baseline prognostic variables. The prognostic variables were selected based on the findings from the regression analysis of tofersen clinical data and clinical relevance. The selected variables for this analysis were baseline NfL, baseline percent predicted SVC, time since symptom onset, sex, and weight. The results demonstrated that plasma NfL reduction was associated with reduction in clinical function decline of ALSFRS-R total score in both the ITT and mITT populations and in the higher median baseline NfL subgroup. The impact of NfL reduction on ALSFRS-R CFB at Week 28 was most prominent in the high baseline NfL

subgroup, as might be expected because higher baseline NfL predicts more rapid progression such that a treatment benefit, if present, may have been more apparent in that subgroup.

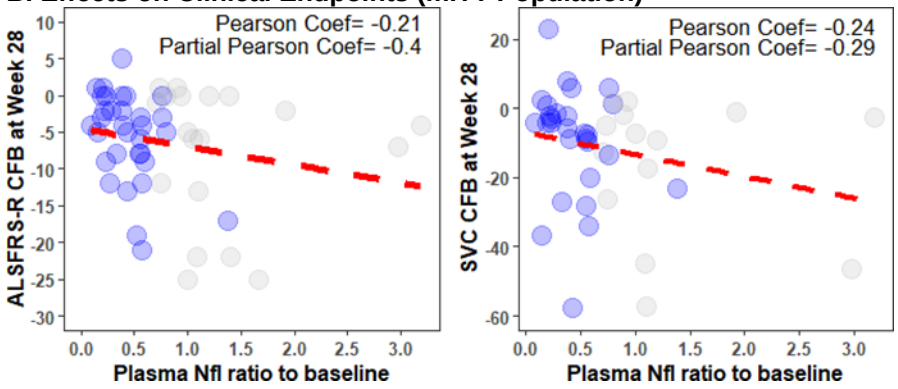
The impact of different clinical endpoints or NfL metrics on the correlations were evaluated using mITT population. Similar correlations were observed in the mITT population between plasma NfL and other clinical endpoints such as SVC (percent predicted) at Week 28 (Figure 11B). These findings were consistent not only for NfL ratio to baseline but also for other plasma NfL reduction metrics, such as percent reduction NfL, change from baseline in NfL, and absolute plasma NfL levels at Week 28 (Figure 11C).

Figure 11. Correlation Analysis of Plasma NfL Reduction With ALSFRS-R Score CFB at Week 28 Across Different Population (A), Clinical Endpoints (B), and Plasma NfL Reduction Metrics (C)

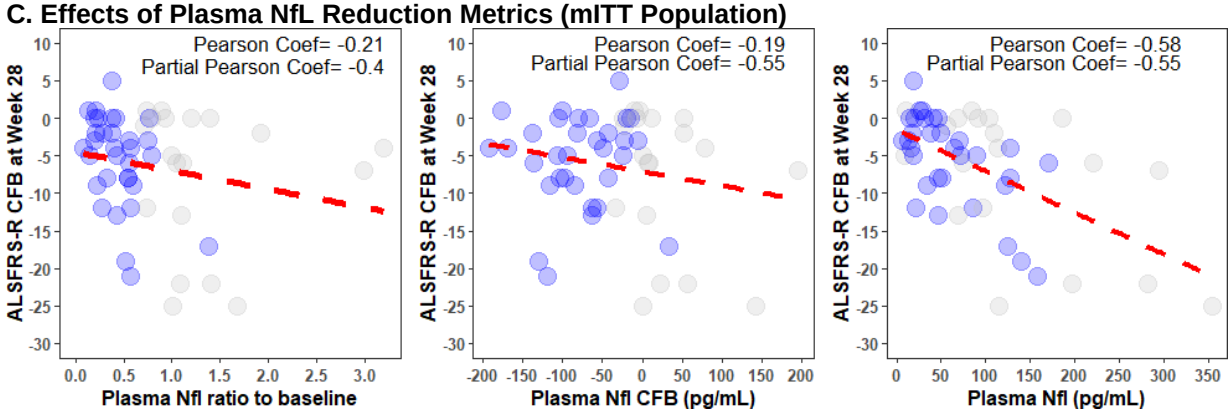
A. Effects of Different Populations



B. Effects on Clinical Endpoints (mITT Population)



C. Effects of Plasma NfL Reduction Metrics (mITT Population)



Source: Clinical Pharmacology Reviewer's analysis
mITT criteria: ALSFRS-R prerandomization slope (>0.2 to 0.9/month) and SOD1 mutation type. Partial Pearson correlation adjusted for NfL levels, SVC sex, time since symptom onset and weight. Blue and grey circles represent subjects from Treatment and Placebo group. Correlations in B. and C. are based on mITT population.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; ITT, Intention-to-treat; mITT, modified ITT; NfL, neurofilament light chain; SOD1, superoxide dismutase 1; SVC, slow vital capacity

Correlation analyses suggest that plasma NfL reduction appears to be associated with reduction in clinical decline across clinical endpoints, including ALSFRS-R, at Week 28.

The mITT population was intended to select subjects with faster disease progression; however, baseline imbalances in NfL were observed, and may be relevant given the strength of this covariate as a predictor of disease progression. A causal inference model was developed to assess progression considering differences in baseline NfL and other baseline characteristics by constructing a model-based matched control for each tofersen-treated participant. The intent of this model-derived matched control was to attempt to predict disease progression of patients in the treatment arm as if they had received placebo, so as to better assess the effect of tofersen, considering differences in expected rates of progression. These analyses must be considered as exploratory, given their post hoc nature and the limited size of the placebo group.

Causal Inference Analysis

The objective of the causal inference analysis was to evaluate the relationship between reduction in plasma NfL with tofersen at Day 113 (Week 16) and changes in clinical outcome measures (ALSFRS-R total score, percent predicted SVC, HHD megascore, ALSAQ-5 total score, and EQ-5D-5L utility score) at Day 197 (Week 28). Data from the ITT population (N=108) of Study 101C were used. The model partitioned the effect of tofersen on the change from baseline in the clinical endpoint at Week 28 into (i) natural disease progression, (ii) drug effect via the NfL pathway, and (iii) drug effect via a non-NfL pathway. Please refer to Section 14.5.3 for the model structure equations.

For ALSFRS-R total score, the model suggests that, at the mean baseline NfL level of 96.78 pg/mL, each 10 pg/mL reduction in plasma NfL at Week 16 is associated with an average 0.8-point reduction (p=0.0038) in worsening on ALSFRS-R at Week 28 (12; Table 17). The p-value assesses the strength of the relationship between plasma NfL reduction with tofersen treatment and ALSFRS-R CFB at Week 28 when adjusted for disease progression and drug effect via non-NfL pathways (with these components assessed based on changes from baseline in the placebo group). Note that this is not a p-value for the treatment effect for Study 101C (which was not statistically significant). Similar trends in the relationship of the reduction in plasma NfL

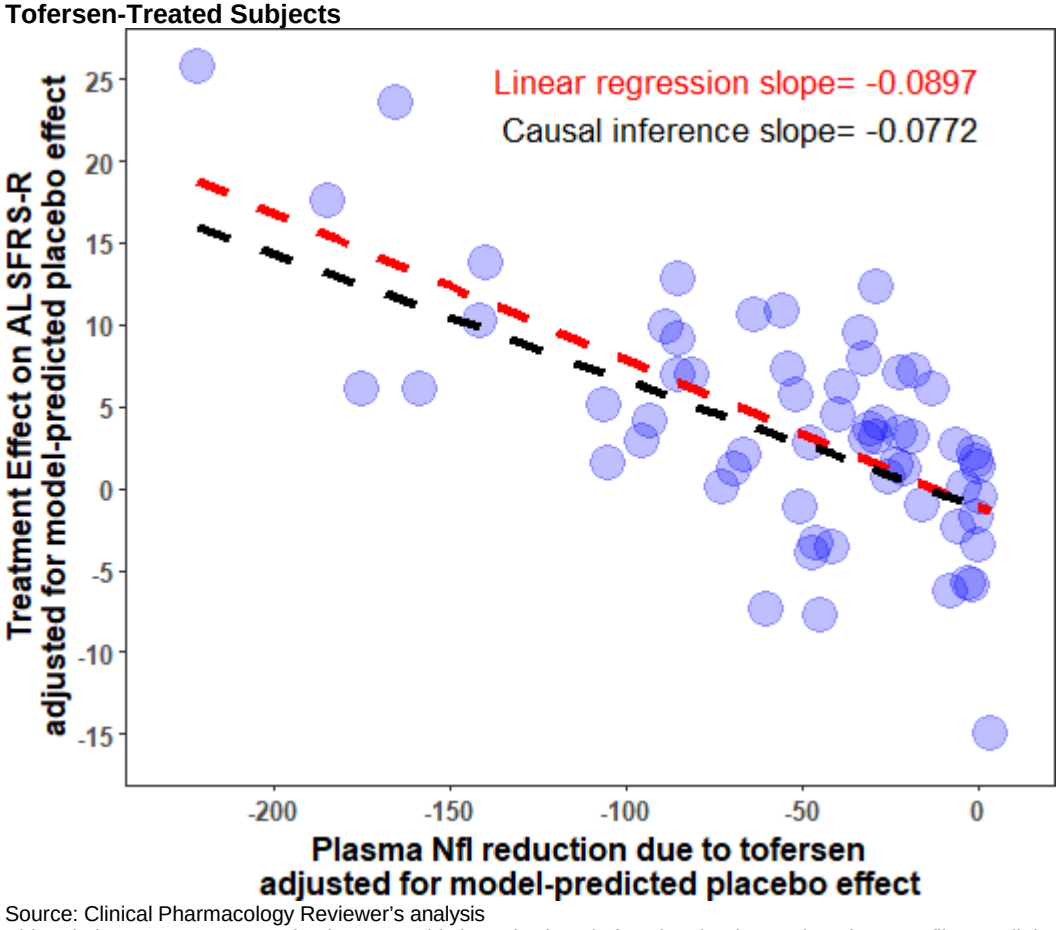
with tofersen treatment were observed for other clinical endpoints, including percent predicted SVC, HHD megascore, ALSAQ-5 total score, and EQ-5D-5L utility score (Table 17).

Table 17. Reduction in Worsening With Tofersen Per Unit NfL Reduction at the Sample Mean Baseline NfL of 96.78 pg/mL Across All Clinical Outcome Measures

Clinical outcome measure	Reduction in worsening with tofersen (vs. untreated) per 1 unit of NfL lowering at sample mean baseline NfL (96.78 pg/mL)
ALSFRS-R total score	0.0772 (p=0.0038)
SVC (percent-predicted)	0.1451 (p=0.0706)
HHD overall megascore	0.0029 (p=0.1303)
ALSAQ-5 total score	0.2194 (p=0.0056)
EQ-5D-5L utility score	0.0017 (p=0.0894)

Source: Summary of Clinical Pharmacology Studies, Section 2.7.2, p. 65, Table 9
Note: 1 unit of NfL corresponds to 1 pg/mL of NfL
Abbreviations: ALSAQ-5, 5-item amyotrophic lateral sclerosis assessment questionnaire; ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; EQ-5D-5L, European quality of life five-dimension five-level; HHD, handheld dynamometry; NfL, neurofilament light chain; SVC, slow vital capacity

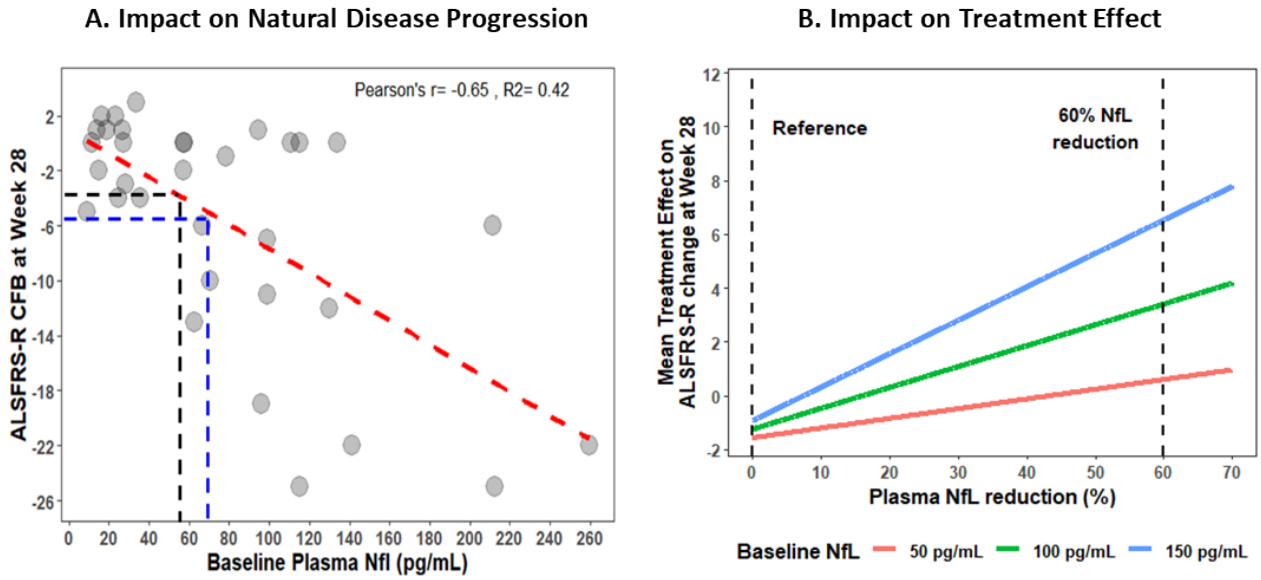
Figure 12. Relationship Between Plasma NfL Reduction Due to Tofersen and Treatment Effect on ALSFRS-R Changes From Baseline After Adjusting for Natural ALSFRS-R and NfL Progression in Tofersen-Treated Subjects



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

An advantage of the causal model is that it incorporates potential imbalances in influential baseline characteristics between the placebo group and the treatment group. One apparent difference between the treatment groups appears to be the baseline plasma NfL. The mean baseline plasma NfL levels in the treatment group were 10 pg/mL higher than placebo group (placebo: 57 pg/mL and treatment: 67 pg/mL) in the ITT population. The effects of differences in baseline NfL on natural disease progression are shown using placebo data (Figure 13A), which suggests that, without treatment, the enrolled patients in the tofersen treatment group might have had more rapid disease progression than did the placebo group without treatment. The causal model accounts for this difference in baseline NfL by predicting the NfL level and ALSFRS-R through the trajectory of the natural disease progression in the placebo group. The model predicts that if tofersen-treated subjects in Study 101C (n=72) were randomized to placebo, they would have experienced faster disease progression with an average of 3.83-point greater decline in the ALSFRS-R score over 28 weeks compared to subjects randomized to placebo.

Figure 13. Effect of Baseline NfL on (A) Disease Progression (ALSFRS-R Change at Week 28); and (B) the Relationship Between Plasma NfL Reduction and Treatment Effect on ALSFRS Change at Week 28



Source: Clinical Pharmacology Reviewer's analysis
Plot A: Red dashed line represents linear regressed line. Black and blue dashed line represents ALSFRS changes at Week 28 at geometric mean baseline NfL of Placebo and Treatment group from ITT population respectively
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; NfL, neurofilament light chain

These analyses suggest that the effect of plasma NfL reduction on ALSFRS-R CFB at Week 28 can be affected by baseline NfL, as shown by the causal inference model (Figure 13B). The model was used to predict tofersen effect at Week 28 in three typical subjects with baseline NfL levels of 50 pg/mL, 100 pg/mL, and 150 pg/mL and varying degrees of plasma NfL reduction. Overall, the results showed that reductions in plasma NfL with tofersen administration are associated with less decline in clinical function, or slowing of disease progression, and that this relationship is more pronounced in subjects with higher baseline NfL levels.

The limitations of this analysis must be recognized including the post hoc nature (with post hoc selection of key covariates in the model), and the small size of the placebo group in which natural

progression was assessed. In addition, although a small study, this was a randomized comparison, so correcting for a post hoc imbalance (i.e., plasma NfL) requires caution.

The focus of the analysis was to support the trend between NfL reduction and a reduction in ALSFRS-R decline. The model has some assumptions which could influence the results. Additional analyses were performed to evaluate some of these assumptions (Section 14.5.3), which suggested no apparent deviation from the model assumption. Overall, the causal inference model provides evidence that the extent of reduction in NfL with treatment is predictive of the magnitude of the clinical outcome.

6.3.2.3. Exploratory Evaluation of the Prognostic Value of NfL for Disease Progression Based on Study 101C and Study 102 Results

Based on the above findings on the value of plasma NfL in predicting disease progression, the review team conducted additional analyses to evaluate the impact of baseline NfL on disease progression in patients in Study 101C and evaluated the results of Study 102.

This evaluation focused on: a) the use of baseline NFL as a prognostic marker for disease progression, b) evaluation of the enrichment criteria to define a rapidly progressing population (mITT population), and c) evaluation of the long-term treatment effect of tofersen by comparing the data of subjects originally randomized to placebo (early-start group) to those originally randomized to placebo (delayed-start group) at Week 52.

6.3.2.3.1. Role of Baseline NfL in Explaining Heterogeneity and Imbalances in Disease Progression

ALS disease progression varies substantially across SOD1 mutation types based on literature findings and observations from Study 101C (i.e., a range of -4.2 to 0.86 points/month decline in the ALSFRS-R among subjects in the placebo group). Disease heterogeneity presents unique challenges and uncertainties for evaluating therapeutics in clinical studies of ALS.[30] To enrich a clinical study with patients who are expected to progress rapidly to advanced disease, the literature has reported predictive approaches based on baseline variables, including time from symptom onset to baseline, the ALSFRS-R score at baseline, and the slope of the ALSFRS-R score at baseline (calculated using a score of 48 the day prior to the day of symptom onset, also known as the prerandomization slope).[31] To predict survival time, several predictors—including progression rate (based on ALSFRSR-R change), bulbar versus non-bulbar onset, and diagnostic delay—were reported.[32] Biomarkers such as NFs, CHIT1, and CHI3L1 are reportedly associated

[30] Goyal NA, Berry JD, Windebank A, et al. Addressing heterogeneity in amyotrophic lateral sclerosis CLINICAL TRIALS. Muscle Nerve. 2020;62(2):156-166. doi:10.1002/mus.26801

[31] Taylor AA, Fournier C, Polak M, et al. Predicting disease progression in amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2016;3(11):866-875. Published 2016 Sep 7. doi:10.1002/acn3.348

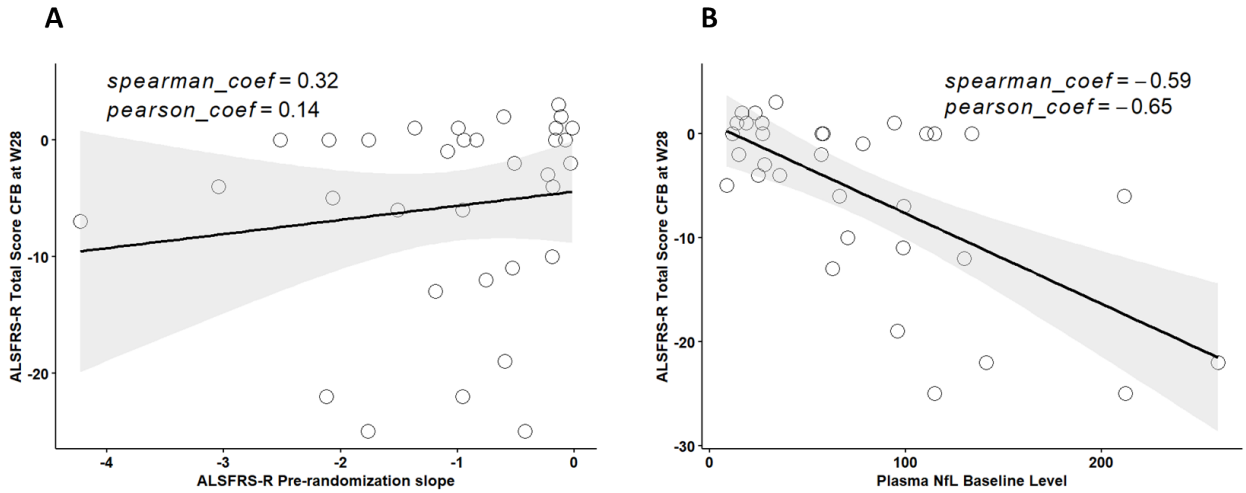
[32] Westeneng HJ, Debray TPA, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol. 2018;17(5):423-433. doi:10.1016/S1474-4422(18)30089-9

with disease progression and survival, and thus have potential as prognostic factors.[33,34,35] Among these biomarkers, NfL was consistently demonstrated to correlate with the rate of disease progression in patients with ALS and shows promise as a prognostic biomarker to aid patient stratification in clinical studies.[36]

In Study 101C, the mITT population (fast progressors) were selected with enrichment criteria based on prerandomization ALSFRS-R slope, SOD1 mutation type, and SVC cut-off value. NfL baseline level was not considered for patient enrichment at the time of study design, given that much of what is known about NfL has been reported since the design and initiation of the pivotal study. The review team conducted analyses to compare the prognostic values of prerandomization ALSFRS-R slope and baseline plasma NfL based on data from Study 101C.

Among the SOD1-ALS patients in the placebo group from Study 101C, baseline plasma NfL was more strongly correlated with ALSFRS-R progression, measured as change from baseline to Week 28 (N=33) or ALSFRS-R slope over 28 weeks (post-randomization slope, N=36) than was the prerandomization slope of ALSFRS-R score (slope between symptom onset and randomization) (Figure 14 and Figure 15).

Figure 14. Correlation Analysis of (A) Prerandomization Slope of ALSFRS-R Score or (B) NfL Baseline With ALSFRS-R Total Score Change From Baseline at Week 28 in Study 101C



Source: Clinical Pharmacology Reviewer's analysis

[33] Thompson AG, Gray E, Bampton A, Raciborska D, Talbot K, Turner MR. CSF chitinase proteins in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90(11):1215-1220. doi:10.1136/jnnp-2019-320442

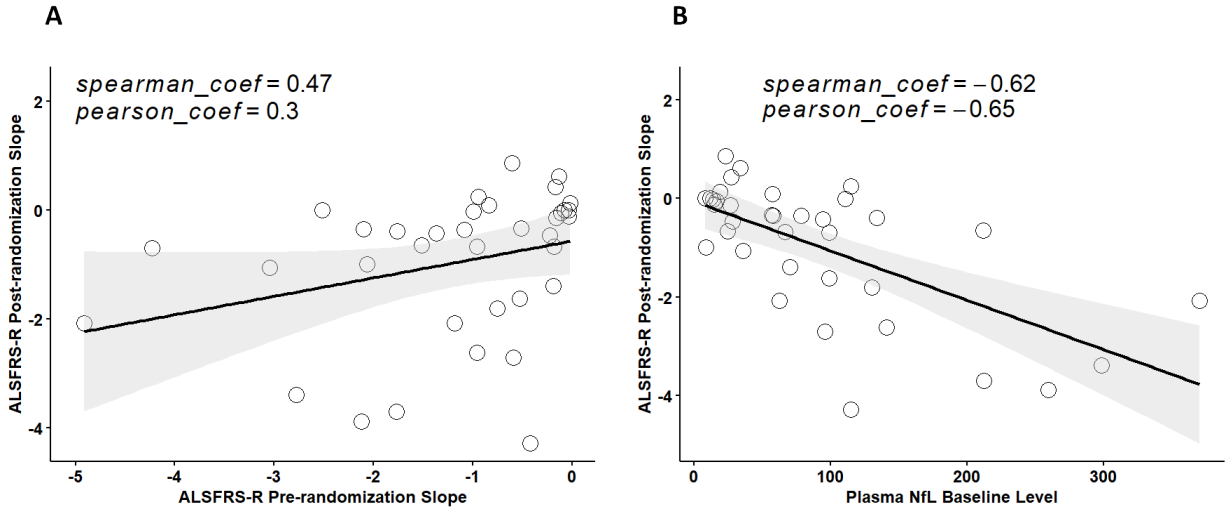
[34] Masrori P, De Schaepdryver M, Floeter MK, et al. Prognostic relationship of neurofilaments, CHIT1, YKL-40 and MCP-1 in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2022;93(6):681-682. doi:10.1136/jnnp-2021-327877

[35] Gaur N, Perner C, Witte OW, Grosskreutz J. The Chitinases as Biomarkers for Amyotrophic Lateral Sclerosis: Signals From the CNS and Beyond. Front Neurol. 2020;11:377. Published 2020 May 27. doi:10.3389/fneur.2020.00377

[36] Dreger M, Steinbach R, Otto M, Turner MR, Grosskreutz J. Cerebrospinal fluid biomarkers of disease activity and progression in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2022;93(4):422-435. doi:10.1136/jnnp-2021-327503

Solid line, regression line; shaded area, 95% confidence interval.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; NfL, neurofilament light chain

Figure 15. Correlation Analysis of (A) Prerandomization Slope of ALSFRS-R Score or (B) NfL Baseline With Postrandomization Slope of ALSFRS-R Total Score in Study 101C



Source: Clinical Pharmacology Reviewer's analysis
Solid line, regression line; shaded area, 95% confidence interval.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

Compared to the prerandomization slope, baseline plasma NfL correlated more strongly with the ALSFRS-R CFB at Week 28 and has acceptable within-subject variability when a single measurement at baseline was considered for predicting disease progression. Therefore, baseline plasma NfL appears to offer better prognostic value than prerandomization slope in predicting ALSFRS-R change in SOD1-ALS patients from Study 101C.

Given the prominence of baseline plasma NfL as a prognostic factor, it is also noteworthy that baseline NfL levels in the mITT population showed a trend of higher values in the tofersen group (25^{th} to 75^{th} percentiles: 94 to 183 pg/mL) compared to the placebo group (25^{th} to 75^{th} percentiles: 63 to 141 pg/mL). The geometric mean baseline plasma NfL was approximately 29 pg/mL (23%) higher in the tofersen group (122±83 [SD] pg/mL) compared to placebo (93±94 [SD] pg/mL). Because a higher NfL baseline level is associated with faster disease progression in ALS, the trend of higher NfL at baseline may imply a risk for faster disease progression in the tofersen treatment group compared to the placebo group. As predicted by the causal inference analyses, participants randomized to the tofersen group in the ITT population if they had not received treatment, would be expected to have had a greater decline over 28 weeks compared to the decline observed in placebo group (Section 6.3.2.2.3). This finding suggests that the imbalance of baseline plasma NfL in the mITT population may have influenced the study results.

Because the prespecified primary clinical endpoint was evaluated in the modified intent-to-treat (mITT) population, the selection of fast progressors to define the mITT population may not have been the optimal variable on which to base this population selection that was intended to identify individuals at risk of more rapid functional loss and also to reduce the heterogeneity of rates of progression, enhancing the ability to detect a treatment effect on ALSFRS-R.

The mITT population consisted of the subset (n=60) of participants who met the prognostic enrichment criteria for rapid disease progression based on their SOD1 mutation type and prerandomization ALSFRS-R slope (also referred to as the enriched or faster progressing/faster progressor subgroup, Table 18).

Table 18. Protocol-Defined Disease Progression Subgroups

Parameter	Faster-Progressing Subgroup (Enriched; mITT)	Slower-Progressing Subgroup (Other; Non-mITT)
Mutation type and prerandomization ALSFRS-R slope	Protocol-defined *SOD1* mutation historically associated with shorter survival[a] and ≥0.2 points/month prerandomization slope OR Another *SOD1* mutation and ≥0.9 points/month prerandomization slope	Another *SOD1* mutation and <0.9 points/month prerandomization slope
SVC cutoff	≥65% predicted	≥50% predicted

Source: Summary of Clinical Efficacy, Table 2
[a] p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; mITT, modified intent-to-treat; SOD1, superoxide dismutase 1; SVC, slow vital capacity

The placebo group of the enriched population (mITT) had a highly variable post-randomization slope of ALSFRS-R total score of −4.3 to 0.24 points/month. In addition, six patients (29%) in the enriched population (mITT) receiving placebo had no change or an increase of ALSFRS-R total score (improvement) at Week 28 compared to baseline.

When evaluating the disease progression rate within a prespecified SOD1 mutation, a wide range was noted for A5V carriers with a prerandomization slope ranging from 0.4 to 5.3 points/month (N=19, placebo and tofersen groups) and an in-study slope ranging from 0.3 to 4.2 points/month (N=6, placebo group only). These data suggest that the heterogeneity of the disease progression rate was not well-controlled in the mITT population when relying on mutation type and prerandomization slope.

In addition, the mITT population appeared to have a slower rate of decline in ALSFRS-R during the study compared to what was predicted or expected based on the prerandomization slope. The study design anticipated a slope of decline of −3.83 per month for the placebo subjects (i.e., 24.7-point decline over 28 weeks). The observed mean prerandomization slope was −1.8 (SD 1.2) and −1.7 (SD 1.6) for the placebo and tofersen groups, respectively. Comparing the in-study slope (rate of decline from Day 1 to Day 197 after randomization) to the prerandomization slope in the placebo group, the mITT and ITT populations had 22% and 17% slower rate of decline in-study, respectively.

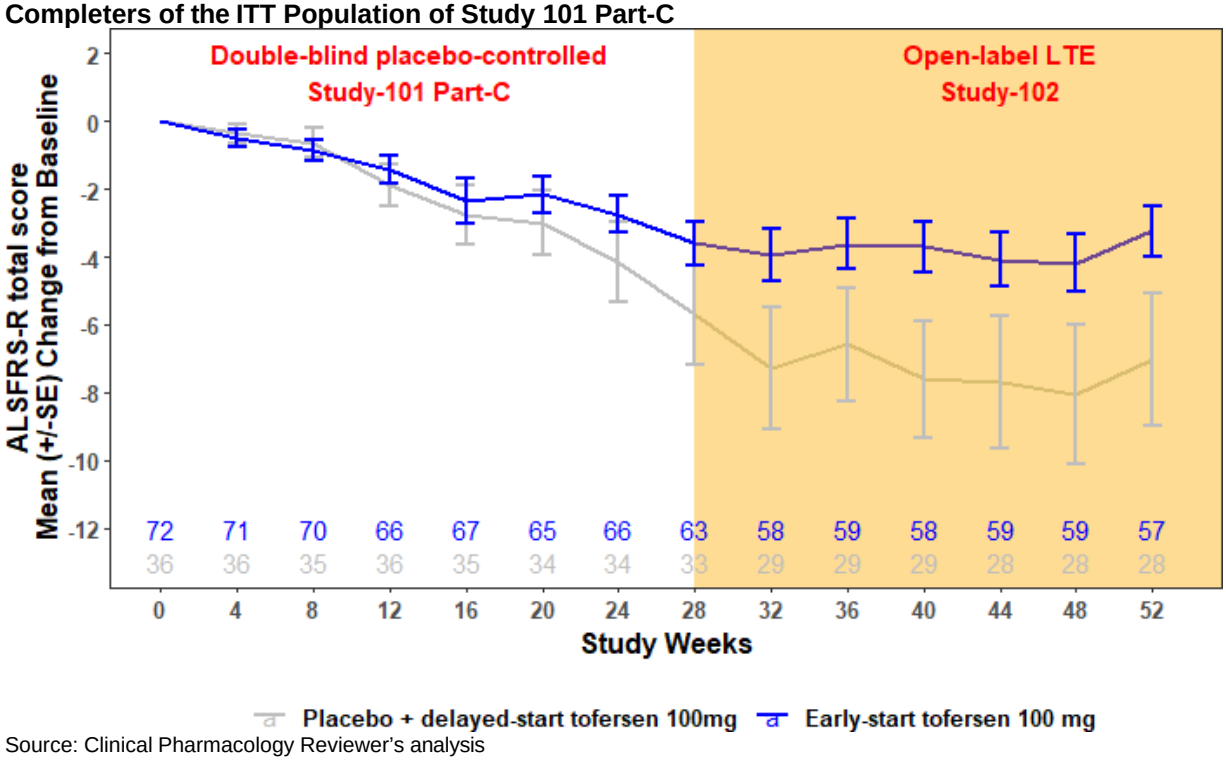
6.3.2.3.2. Evaluation of the Long-Term Treatment Effects

The total CSF SOD1 change from baseline profile following tofersen treatment showed a clear reduction of total SOD1 protein starting at Week 8. The total CSF SOD1 reached an approximate maximal reduction in the tofersen treatment group starting at Week 16. Thus, any potential treatment effect of tofersen on clinical function, a downstream effect of tofersen's biological effects on SOD1 protein, is likely to be delayed. Therefore, it is hypothesized that longer

treatment duration would offer a greater opportunity for tofersen to demonstrate a clinical benefit.

To explore the long-term treatment effect of tofersen, the Clinical Pharmacology review team conducted an independent, post hoc analysis to compare the ALSFRS-R changes at Week 52 from the integrated data from Study 101C and long-term extension Study 102 in the ITT population. When evaluating the long-term effect of tofersen, subjects in the early-start group (those who initiated tofersen in Study 101C) were compared with subjects in the placebo/delayed start group (i.e., those who had the opportunity to receive tofersen in Study 102 after 28 weeks on placebo) (16). Based on the ALSFRS-R total score, the early-start tofersen group showed numerically less decline in ALSFRS-R total score than the delayed-start group, which was consistent from Week 28 to Week 52. If one assumes that tofersen acts like a placebo, starting treatment 28 weeks earlier (or later) would not be anticipated to change the course of the disease or impact disease progression. In that case, the ALSFRS-R curves of the early-start group and the placebo/delayed-start group should overlap, as seen in the first 8 weeks. Nevertheless, the consistent separation on ALSFRS-R score between the two groups from Week 8 further supports the potential treatment effect of tofersen. We acknowledge the limitation that after Week 28, the study enters the open-label phase and all patients started to receive the same active treatment. However, as noted above, enrolled patients, site staff, and vendors were blinded to the initial treatment assignment even after entering the open-label phase so it is unlikely that the initial treatment assignment significantly affected the ALSFRS-R assessment in the open-label phase.

Figure 16. Longitudinal Change in Observed Mean (±SE) ALSFRS-R Over 52 Weeks in Study Completers of the ITT Population of Study 101 Part-C



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; ITT, intent-to-treat; LTE, long-term extension

A reduction in NfL was seen in patients who switched from placebo to active treatment in the OLE, with a magnitude of effect similar to that in Study 101C (Figure 6). Although the number

of patients was smaller due to the 2:1 randomization as well as some dropouts going into the OLE, a mean 44% reduction in NfL was seen in patients after switching to active treatment. These patients subsequently had a slowing of decline in the ALSFRS-R score (16). This provides additional support that a reduction in NfL in these patients may be predictive of clinical benefit.

The evaluation of whether an effect of tofersen on NfL in SOD1-ALS is reasonably likely to predict clinical benefit is multidisciplinary and involves important considerations related to: (1) the understanding of the disease pathology and the mechanism of action of tofersen, (2) statistical analyses to evaluate the prognostic value of plasma NfL levels in ALS and (3) the relationship between drug effects on NfL and on clinical endpoints. Below is summarized the evaluation of plasma NfL as a reasonably likely surrogate endpoint, including perspectives from the Clinical Pharmacology review team and the Statistical Review team.

Multidisciplinary Summary of NfL Analyses

Clinical Pharmacology Comments

The above clinical pharmacology analysis focused on evaluating plasma NfL as a reasonably likely surrogate endpoint for SOD1-ALS to provide support for accelerated approval. This was supported by:

1. The understanding of the pathophysiology of SOD1-ALS and the pharmacology of tofersen which provides mechanistic support that plasma NfL is a biomarker that is reasonably likely to predict clinical benefit;
2. The prognostic value of plasma NfL in ALS that was demonstrated by leveraging data from the literature and from Study 101C; and
3. The relationship between tofersen-driven NfL reduction and changes in clinical decline. This relationship was evaluated using longitudinal changes in NfL and ALSFRS-R total score, correlation analysis, and causal inference analysis. The effect of NfL reduction on the clinical endpoints from the causal inference analysis should be interpreted in the context of the model assumptions. Nevertheless, these analyses support the trend between tofersen-driven NfL reduction and reduction in clinical decline, and ensure no apparent deviation from some assumptions.

Overall, the above-mentioned evaluations and analyses collectively support plasma NfL as a biomarker that is reasonably likely to predict the clinical endpoint in SOD1-ALS.

Biostatistical Comments

The statistical review focuses on general statistical issues with evaluating candidate surrogate endpoints, and on the ability of analyses of NfL and clinical endpoint data from Study 101C (and its OLE, Study 102) to support NfL as a reasonably likely surrogate endpoint.

The Applicant reported extensive post hoc, exploratory analyses. Post hoc selection of timepoints, endpoints, and covariates risks introducing bias in the evaluation due to the data-driven nature of the analyses. Furthermore, it is challenging to assess whether a drug effect on a biomarker reasonably likely predicts a drug effect on a clinical outcome from a study that did not provide evidence of an effect on the clinical outcome.

The Applicant has provided support for the prognostic value of NfL in ALS, i.e., providing data from the literature showing that higher NfL levels correlate with higher risks of unfavorable outcomes. In addition, there is some correlation between changes in NfL and changes in ALSFRS-R in Study 101C. However, the magnitude of the correlation is small and may be influenced by potentially data-driven analysis choices such as endpoint selection, the scale for NfL, and selection of covariates in adjusted models.

Furthermore, it is important to emphasize that a correlation between a biomarker and clinical endpoint is necessary but not sufficient to support that a drug effect on the biomarker will reliably predict a drug effect on the clinical endpoint. Notably, even a strong correlation between the biomarker and the clinical endpoint in both the placebo and drug groups of a clinical study may not be sufficient. It is therefore often important to consider additional analyses and data sources that go beyond such correlations. See further discussion in Fleming, Thomas R., and John H. Powers, "Biomarkers and surrogate endpoints in clinical trials."

The Applicant has also conducted causal inference analyses to explore the relationship between tofersen effects on NfL and ALSFRS-R. Although the model may inform the relationship between changes in NfL and changes in clinical outcomes, it cannot conclusively establish a causal relationship between tofersen effects on NfL and ALSFRS-R. First, the model was developed after the unblinding of the study data and was likely driven by the observed data. Second, unlike an analysis based on a randomized comparison, the validity of the results depends on the form of the model, the variables included in the model, and the data used to fit the model. Third, the estimation of the uncertainty of the results depends on assumptions about the statistical error terms and missing data, which may not hold for the present model. For example:

- The analysis assumes that a natural NfL progression model based on only the placebo arm with 8.5% missing data is correct, with no error added to prediction for the active arm’s counterfactual placebo NfL within the causal model. This is despite the exponential transformation back to the original NfL scale, which might be less reliable and highly variable, especially for high baseline NfL. Therefore, the variability of the estimated causal effect is underestimated.
- The variances in the mITT and non-mITT population are assumed equal. However, the residual unexplained variance is higher for the mITT (fast progressors) than the non-mITT population as expected at the design stage (e.g., residual variance estimates are 26.6 and 4.7 for the mITT and non-mITT populations, respectively, for placebo in the subgroup analyses).
- The analysis may be confounded by missing data or death, which is assumed missing completely at random (i.e., not dependent on any variables or missing outcomes), and 12.5% of tofersen subjects and 8% of placebo subjects had missing values (including one death on tofersen).

It is also unclear whether the Applicant conducted model validation to assess how well their model(s) could predict the treatment effect on clinical outcomes. Model validation involves validation from independent data not used to build the model.

One alternative approach discussed in the statistical literature for assessment of surrogacy is to explore the extent to which the estimated treatment difference for the clinical endpoint, ALSFRS-R, may be explained by the treatment difference for the biomarker, NfL. Of note, in this application, such an approach may be greatly limited by the fact that the study did not

provide evidence of an effect on the clinical endpoint. On February 14, 2023, the Applicant submitted details of an extension of their causal model to the survival analyses. The review team has not fully reviewed those details, but they appear to have similar limitations as the causal model for ALSFRS-R and other functional endpoints, along with potential additional uncertainties due to the small numbers of survival endpoint events that have occurred.

The Biostatistics review team recognizes that the assessment of reasonably likely surrogacy is based on a multidisciplinary approach and, therefore, defers the decision to the Clinical Division.

Clinical Comments

Given the mechanistic evidence that tofersen reduces SOD1 protein, the intended target of the drug and a contributor to the pathophysiology of neuronal degeneration in patients with SOD1-ALS, and reduces NfL, a biomarker of neurodegeneration that is substantially elevated in patients with ALS, it is reasonable to consider NfL a surrogate endpoint that is reasonably likely to predict clinical benefit in SOD1-ALS.

This determination is further supported by evidence from the literature demonstrating the prognostic value of plasma NfL in predicting disease progression and survival in patients with ALS, as well as the observed correlation between the reduction in NfL and a slowing of decline on clinical outcomes, including the ALSFRS-R. The causal inference model, despite its statistical limitations outlined above, appears to support the ability of NfL to predict clinical benefit.

6.3.3. Conclusion

As part of the 21 CFR 314.510 Subpart H regulations, FDA may exercise its broad scientific judgment in applying the evidentiary approval standards to drugs for life-threatening and severely debilitating diseases, especially where there is no satisfactory alternative therapy. In addition, the accelerated approval regulations build upon this recognition by acknowledging that reliance on a surrogate endpoint "almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known." Together, these regulations recognize the importance of facilitating the development of, and access to, safe and effective treatment options for life-threatening and severely debilitating diseases with unmet medical needs. This approach has been reinforced by FDA's interactions with patients and their caregivers who describe their willingness to accept less certainty about effectiveness in return for earlier access to much-needed medicines.

Despite the notable limitations of a failed study and the many post hoc exploratory analyses that were conducted after Study 101C, the review team notes that SOD1-ALS is a very rare and devastating disease; therefore, it is of utmost importance that we give full consideration to all the available data. Given that tofersen appears to have a treatment effect, it is important to consider why Study 101C failed to detect a clinical benefit. The following factors were identified during the review that could have reduced the ability of the study to detect a drug effect with tofersen.

- Decline in both the placebo and treatment groups was much less than expected, leading to the study being greatly underpowered.

- As noted above, the mITT population was enriched for fast-progressors based on prerandomization slope and genetic mutation. However, the observed data on post-randomization slope/disease progression among placebo subjects suggested that the heterogeneity of the disease progression rate was not well-controlled in the mITT population when relying on mutation type and prerandomization slope.
- The imbalance of NfL baseline in the mITT population may have predicted faster progression in the tofersen arm, which would have placed a disadvantage for the tofersen group compared to the placebo and decreased the ability to detect a treatment effect if one is there.
- Additionally, a 28-week treatment duration may not have been sufficient to observe a treatment benefit, particularly given that tofersen-driven NfL reductions do not appear to peak until Week 16.

Accelerated approval may be granted for a product for a serious or life-threatening disease upon a determination that the product has an effect on a reasonably likely surrogate endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit. When granting accelerated approval, it is expected that there will be empirical evidence that the observed change in the biomarker after administration of the drug is likely to predict clinical benefit. This empirical evidence is disease specific, depends on the natural history of the disease, and the adequacy of the evidence to support use of the surrogate endpoint is based on the biologic plausibility of the relationship between the disease and the biomarker, and the magnitude of observed change in the biomarker that supports the relationship.

Plasma NfL has been evaluated as a reasonably likely surrogate endpoint for SOD1-ALS based on the following aspects:

- There is mechanistic evidence that tofersen reduces SOD1 protein, the intended target of the drug and known contributor to the pathophysiology of neuronal degeneration in patients with SOD1-ALS and also reduces NfL, a biomarker of neurodegeneration that is known to be substantially elevated in patients with ALS and predictive of disease progression.
- Evidence from the literature as well as clinical programs have demonstrated the prognostic value of plasma NfL in predicting both disease progression and survival in ALS.
- Additionally, there is an observed correlation between reduction in NfL and a slowing of decline on clinical outcomes such as the ALSFRS-R, and a causal inference model which, despite statistical limitations, appears to support the use of NfL as a biomarker reasonably likely to predict clinical benefit in patients with SOD1-ALS.

The Division has determined that the observed reduction in plasma NfL concentration is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit in patients with SOD1-ALS. Although the reduction in NfL plasma levels in tofersen-treated subjects was nominally statistically significant, the change is large, robust, and convincing. Additionally, reductions in SOD1 protein support the mechanism of tofersen and provide confirmatory evidence. Therefore, these data together provide substantial evidence of effectiveness of a treatment effect of tofersen on NfL in patients with SOD1-ALS to support accelerated approval. This determination also takes into account the severity, rarity, and prevalence of SOD1-ALS, and the significant unmet clinical need for effective treatments for this disease.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical toxicity studies submitted to the NDA consisted of single dose (rat) and repeat dose (mouse and monkey) general toxicity studies, as well a complete battery of genetic toxicology and reproductive and developmental toxicology studies. Primary toxicity in mouse consisted of a reduction in platelet count, for which an NOAEL was not established, in male and female CD1 mice administered 0, 6, 30, and 150 mg/kg tofersen by SC injection every 2 days for 26 weeks. These effects were also observed in recovery groups after an 8-week drug-free period. In monkeys, IT administration of 0, 4, 12, and 35 mg tofersen in male and female cynomolgus monkeys every other week for 9 months resulted in histologic findings of neuronal vacuolation at all doses; however, vacuolation was not accompanied by neurodegeneration and was not present in recovery groups. Additional findings in monkeys consisted of transient gait abnormalities and impairments of patellar and foot-grip reflexes in HDM and HDF. Based on neurological signs in the 9-month monkey study, the NOAEL for Q2W IT administration of tofersen was 12 mg (C_{max} 4840 ng/mL, $AUC_{0\text{-}24h}$ 30,000 µg·h/mL).

Reproductive and developmental toxicology studies indicated seminiferous tubule degeneration in mice administered tofersen prior to and during the mating period, for which the NOAEL was 10 mg/kg ($AUC_{0\text{-}last}$ 17,200 ng·h/mL). There were no effects on embryofetal development in CD1 mouse or NZW rabbit, or on pre- and postnatal development in CD1 mouse.

Tofersen was negative in a complete battery of genetic toxicology studies. The carcinogenic potential of tofersen is to be assessed postapproval.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Tofersen is an ASO inhibitor of SOD1 mRNA that is intended to reduce the levels of SOD1 protein in patients with SOD1-ALS.

Nusinersen is an approved single-stranded ASO for intrathecal administration. The prescribing information for nusinersen includes potential risks for thrombocytopenia and kidney toxicity. Other single-stranded ASOs that are FDA approved for intravenous or subcutaneous administration include mipomersen, inotersen, eteplirsen, golodirsen, vilpolarsen, and casimersen. Safety risks associated with systemically administered ASOs have included liver toxicity (mipomersen), thrombocytopenia (inotersen), and kidney toxicity (inotersen, golodirsen, eteplirsen, viltolarsen, casimersen). The prescribing information for nusinersen includes the risks for thrombocytopenia and kidney toxicity seen with systemically administered ASOs.

The Applicant speculates that tofersen's different chemical backbone structure, intrathecal route of administration, and lower systemic exposure may reduce these risks compared to prior ASOs. These potential risks are explored further in Sections 7.6 (hepatobiliary disorders, thrombocytopenia) and 7.7 (renal and urinary disorders).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. Tofersen is a new molecular entity. It is not approved in other regions of the world.

7.4. FDA Approach to the Safety Review

Clinical study data were independently analyzed using JMP software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. No major data quality or integrity issues were identified that would preclude a safety review of this BLA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in Studies 101C and 102 were reviewed and found to be acceptable. Treatment-emergent AEs (TEAEs) in Studies 101C and 102 were protocol-defined as having an onset date that is on or after start of study treatment, or that is worsened after the start of study treatment. All AEs in the reviewed studies were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4), which was reviewed and found to be acceptable.

Data from completed placebo-controlled Study 101C and from the ongoing open-label, long-term extension Study 102 formed the basis of the clinical safety evaluation, as well as additional supportive safety data from the single- and multiple-ascending-dose Studies 101A and 101B, respectively. Study 101C is the primary source of evidence of effectiveness, and the results of this study are presented individually in this review. Safety data from Study 101C will provide the primary description of safety, with Studies 101A, 101B, and 102 providing supporting data. The analyses include the data from the 120-day safety update.

A summary of the study designs can be found in Section 3.2 and Section 6.2.

7.5. Adequacy of the Clinical Safety Database

For chronically administered drugs, the International Conference on Harmonization (ICH) E-1 guidelines recommend having studied drug exposure in 1500 subjects overall, 300 to 600 subjects for 6 months, and 100 subjects for 1 year.

When compared to the ICH guidelines, the overall number of exposed subjects (147) is less than the usual recommendation. However, because SOD1-ALS is a serious, life-threatening, and rare disease, there is no minimum number of subjects that should be studied to establish clinical safety. The number of subjects exposed for ≥1 year exceeds the ICH recommendation.

Because SOD1-ALS is a rare, serious, and life-threatening illness, the overall subject exposure in the clinical development program is adequate.

Table 19. Duration of Exposure, Safety Population, Studies 233AS101 and 233AS102

Parameter	Tofersen 100 mg N=147 n (%)
Duration of treatment, weeks	
Mean (SD)	110.7 (57.7)
Median (Q1, Q3)	119.4 (59.4, 158)
Min, max	3.6, 212.4
Total exposure (person years)	312
Patients treated, by duration, n (%)	
≤12 weeks	4 (2.7)
>12 to ≤24 weeks	9 (6.1)
>24 to ≤36 weeks	11 (7.5)
>36 to ≤48 weeks	7 (4.8)
>48 to ≤60 weeks	6 (4.1)
>60 to ≤72 weeks	7 (4.8)
>72 to ≤84 weeks	4 (2.7)
>84 to ≤96 weeks	9 (6.1)
>96 to ≤108 weeks	8 (5.4)
>108 to ≤120 weeks	9 (6.1)
>120 to ≤132 weeks	10 (6.8)
>132 to ≤144 weeks	6 (4.1)
>144 to ≤156 weeks	18 (12.2)
>156 to ≤168 weeks	15 (10.2)
>168 to ≤180 weeks	6 (4.1)
>180 to ≤192 weeks	12 (8.2)
>192 to ≤204 weeks	3 (2.0)
>204 to ≤216 weeks	3 (2.0)

Source: adex.xpt and adsl.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Duration was 3.6 to 212.4 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Study 101C

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study 101C

Results of the FDA analysis of adverse events for the placebo-controlled Study 101C are shown in Table 20. The proportion of subjects experiencing AEs was 96% in the tofersen group and 94% in the placebo group. The proportion experiencing SAEs was 18% in the tofersen group and 14% in the placebo group. Permanent dose discontinuation due to AEs occurred in 6% of the tofersen group and 0% of the placebo group.

Table 20. Overview of Adverse Events, Safety Population, Study 233AS101 Part C

Event Category	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
SAE	13 (18.1)	5 (13.9)	4.2 (-10.2, 18.5)
SAEs with fatal outcome	1 (1.4)	0	1.4 (-1.3, 4.1)
Life-threatening SAEs	1 (1.4)	0	1.4 (-1.3, 4.1)
AE leading to permanent discontinuation of study drug	4 (5.6)	0	5.6 (0.3, 10.8)*
AE leading to dose modification of study drug	3 (4.2)	0	4.2 (-0.4, 8.8)
AE leading to interruption of study drug	3 (4.2)	0	4.2 (-0.4, 8.8)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE	69 (95.8)	34 (94.4)	1.4 (-7.4, 10.2)
Severe and worse	12 (16.7)	4 (11.1)	5.6 (-7.8, 19.0)
Moderate	32 (44.4)	15 (41.7)	2.8 (-17.0, 22.6)
Mild	25 (34.7)	15 (41.7)	-6.9 (-26.4, 12.6)

Source: adae.xpt; software: R
*, Rows in which the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as adverse events with an onset date and time on or after Day 1 or any pre-existing condition that worsened in severity after Day 1.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Study 101C

One subject (b) (6) in the tofersen group (1/72 subjects [1.4%]) died during the study from congestive heart failure. This death was likely related to the subject's medical history of coronary artery disease, two myocardial infarctions, hypertension, and type 2 diabetes mellitus. There were no deaths in the placebo group.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Study 101C

Results of the FDA analysis of serious adverse events for the placebo-controlled Study 101C are shown in Table 21. The proportion of subjects experiencing SAEs was 18% in the tofersen group and 14% in the placebo group. The only SAE that occurred at least 2% more frequently in the tofersen group was pneumonia aspiration (tofersen 3% versus placebo 0%). Aspiration pneumonia is common in the natural history of ALS.

Table 21. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 233AS101 Part C

System Organ Class Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Any SAE	13 (18.1)	5 (13.9)	4.2 (-10.2, 18.5)
Cardiac disorders (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Cardiac failure congestive	1 (1.4)	0	1.4 (-1.3, 4.1)

System Organ Class Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Fecaloma	1 (1.4)	0	1.4 (-1.3, 4.1)
General disorders and administration site conditions (SOC)	3 (4.2)	0	4.2 (-0.4, 8.8)
Hypothermia	1 (1.4)	0	1.4 (-1.3, 4.1)
Impaired self-care	1 (1.4)	0	1.4 (-1.3, 4.1)
Respiratory complication associated with device	1 (1.4)	0	1.4 (-1.3, 4.1)
Infections and infestations (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Myelitis	1 (1.4)	0	1.4 (-1.3, 4.1)
Injury, poisoning and procedural complications (SOC)	2 (2.8)	0	2.8 (-1.0, 6.6)
Fibula fracture	1 (1.4)	0	1.4 (-1.3, 4.1)
Meningitis chemical	1 (1.4)	0	1.4 (-1.3, 4.1)
Metabolism and nutrition disorders (SOC)	0	1 (2.8)	-2.8 (-8.1, 2.6)
Dehydration	0	1 (2.8)	-2.8 (-8.1, 2.6)
Nervous system disorders (SOC)	3 (4.2)	0	4.2 (-0.4, 8.8)
Loss of consciousness	1 (1.4)	0	1.4 (-1.3, 4.1)
Lumbar radiculopathy	1 (1.4)	0	1.4 (-1.3, 4.1)
Myelitis transverse	1 (1.4)	0	1.4 (-1.3, 4.1)
Respiratory, thoracic and mediastinal disorders (SOC)	5 (6.9)	4 (11.1)	-4.2 (-16.0, 7.7)
Pneumonia aspiration	2 (2.8)	0	2.8 (-1.0, 6.6)
Acute respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Aspiration	1 (1.4)	0	1.4 (-1.3, 4.1)
Pulmonary embolism	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Atelectasis	0	1 (2.8)	-2.8 (-8.1, 2.6)
Dyspnea	0	2 (5.6)	-5.6 (-13.0, 1.9)
Vascular disorders (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Deep vein thrombosis	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as untoward medical occurrences that, at any dose that results in death, are life-threatening, require hospitalization or prolongation of existing hospitalization, result in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or are congenital anomalies or birth defects.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

Table 22 shows SAEs grouped using the FDA Medical Query (Narrow). Grouped SAEs that occurred at least 2% more frequently in the tofersen group include thrombosis (6% tofersen versus 3% placebo), pneumonia (3% tofersen versus 0% placebo), and respiratory failure (3% tofersen versus 0% placebo). Respiratory failure is a common occurrence in the natural history of ALS and is further discussed in Section 7.7.5.

Table 22. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 233AS101 Part C

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombosis	4 (5.6)	1 (2.8)	2.8 (-4.8, 10.3)
Thrombosis venous	4 (5.6)	1 (2.8)	2.8 (-4.8, 10.3)
Cardiac disorders (SOC)			
Heart failure	1 (1.4)	0	1.4 (-1.3, 4.1)
General disorders and administration site conditions (SOC)			
Volume depletion	0	1 (2.8)	-2.8 (-8.1, 2.6)
Infections and infestations (SOC)			
Pneumonia	2 (2.8)	0	2.8 (-1.0, 6.6)
Musculoskeletal and connective tissue disorders (SOC)			
Fracture	1 (1.4)	0	1.4 (-1.3, 4.1)
Respiratory, thoracic and mediastinal disorders (SOC)			
Respiratory failure	2 (2.8)	0	2.8 (-1.0, 6.6)
Dyspnea	0	2 (5.6)	-5.6 (-13.0, 1.9)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA Medical Query. Those preferred terms are not shown or counted in this table. For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

The SAE of venous thrombosis occurred more frequently in the tofersen group (5.6%) than in the placebo group (2.8%). The SAE of pulmonary embolism also occurred more frequently in the tofersen group (4.2%) than in the placebo group (2.8%). The narratives for these subjects were reviewed and are summarized in Table 23. These SAEs were generally related to venous stasis and immobility related to ALS and prior existing conditions such as cancer and prior pulmonary embolus.

Table 23. Narrative Summaries of Pulmonary Embolus and Venous Thrombosis SAEs in Study 101C

Subject	Group	Comments
(b) (6)	Placebo	Pulmonary embolism, left lower extremity deep venous thrombosis
	Tofersen	DVT, resolved. Tofersen interrupted, subject continued in study. Increased DVT risk due to immobility following foot fracture. Prior history of stroke.
	Tofersen	SAE of pulmonary embolism: at greater risk due to decreased mobility secondary to ALS and prior DVT.
	Tofersen	SAE of pulmonary embolism: prior history of idiopathic pulmonary embolism and thyroid cancer.
	Tofersen	SAE of acute pulmonary embolism: pulmonary embolism was likely provoked by ALS, increased immobility, and family history of pulmonary embolism.

Source: FDA review of Adverse Events Narratives
Abbreviations: ALS, amyotrophic lateral sclerosis; DVT, deep vein thrombosis; SAE, serious adverse event

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 101C

Results of the FDA analysis of AEs leading to treatment discontinuation for the placebo-controlled Study 101C are shown in Table 24. The proportion of subjects experiencing AEs leading to treatment discontinuation was 6% in the tofersen group and 0% in the placebo group. These four AEs had frequencies of approximately 1% in the tofersen group and 0% in the placebo group. Myelitis is discussed in Section 7.7.1. Aseptic meningitis is discussed in Section 7.7.2. One subject (b) (6) in the tofersen group had an SAE of congestive heart failure that led to treatment discontinuation and death. This death was likely related to the subject's prior history of two prior myocardial infarctions, type 2 diabetes mellitus, hypercholesterolemia, and hypertension.

Table 24. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study 233AS101 Part C

System Organ Class Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Any AE leading to discontinuation	4 (5.6)	0	5.6 (0.3, 10.8) *
Cardiac disorders (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Cardiac failure congestive	1 (1.4)	0	1.4 (-1.3, 4.1)
Infections and infestations (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Myelitis	1 (1.4)	0	1.4 (-1.3, 4.1)
Injury, poisoning and procedural complications (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Meningitis chemical	1 (1.4)	0	1.4 (-1.3, 4.1)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.4)	0	1.4 (-1.3, 4.1)
Pulmonary embolism	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: adae.xpt; software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 25 shows AEs leading to treatment discontinuation grouped by FDA Medical Query (Narrow).

Table 25. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 233AS101 Part C

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombosis	1 (1.4)	0	1.4 (-1.3, 4.1)
Thrombosis venous	1 (1.4)	0	1.4 (-1.3, 4.1)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Cardiac disorders (SOC)			
Heart failure	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration is approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Study 101C

Results of the FDA analysis of TEAEs for the placebo-controlled Study 101C are shown in Table 26.

The proportion of subjects experiencing TEAEs was 96% in the tofersen group and 94% in the placebo group. Five TEAEs had risk difference 95% confidence intervals that did not include zero, indicating higher proportions in the tofersen group: back pain, pain, musculoskeletal stiffness, neuralgia, and CSF white blood cell count increased.

Table 26. Patients With Common Adverse Events Occurring at ≥3% Frequency, Safety Population, Study 233AS101 Part C

Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Any AE	69 (95.8)	34 (94.4)	1.4 (-7.4, 10.2)
Back pain	15 (20.8)	2 (5.6)	15.3 (3.3, 27.3) *
Fatigue	12 (16.7)	2 (5.6)	11.1 (-0.3, 22.5)
CSF white blood cell count increased	7 (9.7)	0	9.7 (2.9, 16.6) *
Pain	7 (9.7)	0	9.7 (2.9, 16.6) *
Pain in extremity	19 (26.4)	6 (16.7)	9.7 (-6.1, 25.6)
Arthralgia	10 (13.9)	2 (5.6)	8.3 (-2.6, 19.3)
Myalgia	10 (13.9)	2 (5.6)	8.3 (-2.6, 19.3)
CSF protein increased	6 (8.3)	1 (2.8)	5.6 (-2.8, 13.9)
Musculoskeletal stiffness	4 (5.6)	0	5.6 (0.3, 10.8) *
Neuralgia	4 (5.6)	0	5.6 (0.3, 10.8) *
Cough	5 (6.9)	1 (2.8)	4.2 (-3.8, 12.1)
Pleocytosis	3 (4.2)	0	4.2 (-0.4, 8.8)
Respiratory failure	3 (4.2)	0	4.2 (-0.4, 8.8)
Muscle contractions involuntary	4 (5.6)	1 (2.8)	2.8 (-4.8, 10.3)
Salivary hypersecretion	4 (5.6)	1 (2.8)	2.8 (-4.8, 10.3)
Contusion	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Decreased appetite	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Headache	33 (45.8)	16 (44.4)	1.4 (-18.5, 21.3)
Hypoesthesia	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Muscle spasms	5 (6.9)	2 (5.6)	1.4 (-8.1, 10.9)
Pruritus	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Pulmonary embolism	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)

Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Pyrexia	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Upper respiratory tract infection	5 (6.9)	2 (5.6)	1.4 (-8.1, 10.9)
Vomiting	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Ligament sprain	4 (5.6)	2 (5.6)	0 (-9.2, 9.2)
Musculoskeletal pain	4 (5.6)	2 (5.6)	0 (-9.2, 9.2)
Procedural pain	41 (56.9)	21 (58.3)	-1.4 (-21.1, 18.4)
Abdominal distension	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Anxiety	4 (5.6)	3 (8.3)	-2.8 (-13.2, 7.7)
Constipation	6 (8.3)	4 (11.1)	-2.8 (-14.9, 9.3)
Dizziness	4 (5.6)	3 (8.3)	-2.8 (-13.2, 7.7)
Oropharyngeal pain	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Procedural nausea	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Urinary tract infection	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Deep vein thrombosis	1 (1.4)	2 (5.6)	-4.2 (-12.1, 3.8)
Hypertension	1 (1.4)	2 (5.6)	-4.2 (-12.1, 3.8)
Insomnia	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Joint swelling	1 (1.4)	2 (5.6)	-4.2 (-12.1, 3.8)
Musculoskeletal procedural complication	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Nausea	9 (12.5)	6 (16.7)	-4.2 (-18.5, 10.2)
Post procedural complication	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Skin abrasion	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Vaccination complication	1 (1.4)	2 (5.6)	-4.2 (-12.1, 3.8)
Asthenia	0	2 (5.6)	-5.6 (-13.0, 1.9)
Choking	0	2 (5.6)	-5.6 (-13.0, 1.9)
Gastritis	0	2 (5.6)	-5.6 (-13.0, 1.9)
Muscular weakness	4 (5.6)	4 (11.1)	-5.6 (-17.1, 6.0)
Neck pain	4 (5.6)	4 (11.1)	-5.6 (-17.1, 6.0)
Nerve compression	0	2 (5.6)	-5.6 (-13.0, 1.9)
Type 2 diabetes mellitus	0	2 (5.6)	-5.6 (-13.0, 1.9)
Weight decreased	0	2 (5.6)	-5.6 (-13.0, 1.9)
Depression	1 (1.4)	3 (8.3)	-6.9 (-16.4, 2.5)
Dyspnea	4 (5.6)	5 (13.9)	-8.3 (-20.8, 4.1)
Paresthesia	6 (8.3)	6 (16.7)	-8.3 (-22.1, 5.4)
Skin laceration	0	3 (8.3)	-8.3 (-17.4, 0.7)
Diarrhea	1 (1.4)	5 (13.9)	-12.5 (-24.1, -0.9) *
Post lumbar puncture syndrome	13 (18.1)	11 (30.6)	-12.5 (-30.0, 5.0)
Nasopharyngitis	2 (2.8)	7 (19.4)	-16.7 (-30.1, -3.2) *
Fall	17 (23.6)	15 (41.7)	-18.1 (-36.9, 0.8)

Source: adae.xpt; software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was approximately 28 to 32 weeks.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; CSF, cerebrospinal fluid; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

Table 27 shows TEAEs grouped using the FDA Medical Query (Narrow). Two TEAEs had risk difference 95% confidence intervals that did not include zero, indicating higher proportions in the tofersen group: back pain and respiratory failure (discussed in Section 7.7.5).

Table 27. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 233AS101 Part C

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombosis	4 (5.6)	2 (5.6)	0 (-9.2, 9.2)
Thrombosis venous	4 (5.6)	2 (5.6)	0 (-9.2, 9.2)
Cardiac disorders (SOC)			
Arrhythmia	2 (2.8)	0	2.8 (-1.0, 6.6)
Cardiac conduction disturbance	1 (1.4)	0	1.4 (-1.3, 4.1)
Heart failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Tachycardia	1 (1.4)	0	1.4 (-1.3, 4.1)
Systemic hypertension	1 (1.4)	2 (5.6)	-4.2 (-12.1, 3.8)
Endocrine disorders (SOC)			
Hyperglycemia	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Gastrointestinal disorders (SOC)			
Vomiting	4 (5.6)	1 (2.8)	2.8 (-4.8, 10.3)
Dry mouth	1 (1.4)	0	1.4 (-1.3, 4.1)
Dyspepsia	1 (1.4)	0	1.4 (-1.3, 4.1)
Abdominal pain	2 (2.8)	1 (2.8)	0 (-6.6, 6.6)
Constipation	6 (8.3)	4 (11.1)	-2.8 (-14.9, 9.3)
Nausea	11 (15.3)	8 (22.2)	-6.9 (-22.9, 9.0)
Diarrhea	1 (1.4)	5 (13.9)	-12.5 (-24.1, -0.9) *
General disorders and administration site conditions (SOC)			
Fatigue	12 (16.7)	4 (11.1)	5.6 (-7.8, 19.0)
Decreased appetite	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Peripheral edema	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Pyrexia	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Local administration reaction	0	1 (2.8)	-2.8 (-8.1, 2.6)
Volume depletion	0	1 (2.8)	-2.8 (-8.1, 2.6)
Dizziness	5 (6.9)	4 (11.1)	-4.2 (-16.0, 7.7)
Fall	17 (23.6)	15 (41.7)	-18.1 (-36.9, 0.8)
Hepatobiliary disorders (SOC)			
Hepatic injury	1 (1.4)	0	1.4 (-1.3, 4.1)
Immune system disorders (SOC)			
Hypersensitivity	1 (1.4)	0	1.4 (-1.3, 4.1)
Infections and infestations (SOC)			
Bacterial infection	9 (12.5)	3 (8.3)	4.2 (-7.7, 16.0)
Pneumonia	2 (2.8)	0	2.8 (-1.0, 6.6)
Viral infection	3 (4.2)	2 (5.6)	-1.4 (-10.2, 7.4)
Fungal infection	2 (2.8)	2 (5.6)	-2.8 (-11.2, 5.6)
Nasopharyngitis	2 (2.8)	7 (19.4)	-16.7 (-30.1, -3.2) *
Musculoskeletal and connective tissue disorders (SOC)			
Back pain	17 (23.6)	3 (8.3)	15.3 (1.9, 28.6) *
Arthralgia	10 (13.9)	2 (5.6)	8.3 (-2.6, 19.3)
Myalgia	10 (13.9)	2 (5.6)	8.3 (-2.6, 19.3)
Fracture	1 (1.4)	0	1.4 (-1.3, 4.1)
Tendinopathy	0	1 (2.8)	-2.8 (-8.1, 2.6)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Nervous system disorders (SOC)			
Paresthesia	14 (19.4)	6 (16.7)	2.8 (-12.4, 18.0)
Confusional state	1 (1.4)	0	1.4 (-1.3, 4.1)
Dysgeusia	1 (1.4)	0	1.4 (-1.3, 4.1)
Tremor	1 (1.4)	0	1.4 (-1.3, 4.1)
Somnolence	0	1 (2.8)	-2.8 (-8.1, 2.6)
Syncope	0	1 (2.8)	-2.8 (-8.1, 2.6)
Headache	40 (55.6)	24 (66.7)	-11.1 (-30.3, 8.1)
Psychiatric disorders (SOC)			
Parasomnia	2 (2.8)	0	2.8 (-1.0, 6.6)
Anxiety	4 (5.6)	3 (8.3)	-2.8 (-13.2, 7.7)
Study agent abuse potential	0	1 (2.8)	-2.8 (-8.1, 2.6)
Insomnia	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Depression	2 (2.8)	3 (8.3)	-5.6 (-15.3, 4.2)
Renal and urinary disorders (SOC)			
Acute kidney injury	1 (1.4)	0	1.4 (-1.3, 4.1)
Renal and urinary tract infection	3 (4.2)	3 (8.3)	-4.2 (-14.3, 6.0)
Respiratory, thoracic and mediastinal disorders (SOC)			
Respiratory failure	4 (5.6)	0	5.6 (0.3, 10.8) *
Cough	5 (6.9)	1 (2.8)	4.2 (-3.8, 12.1)
Dyspnea	4 (5.6)	5 (13.9)	-8.3 (-20.8, 4.1)
Skin and subcutaneous tissue disorders (SOC)			
Alopecia	1 (1.4)	0	1.4 (-1.3, 4.1)
Pruritus	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Rash	3 (4.2)	1 (2.8)	1.4 (-5.7, 8.5)
Erythema	0	1 (2.8)	-2.8 (-8.1, 2.6)
Vascular disorders (SOC)			
Hemorrhage	7 (9.7)	2 (5.6)	4.2 (-6.0, 14.3)
Hypotension	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: adae.xpt; software: R
*, Rows in which the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

Thrombocytopenia is a potential antisense oligonucleotide class effect; therefore, analyses explored the risk of hemorrhage in the study. Hemorrhage occurred in 9.7% of the tofersen group and 5.6% of the placebo group. Adverse events of hemorrhage for the tofersen group and the placebo group are listed in Table 28. The events of hemorrhage consisted of contusions and epistaxis. There was no clinically significant difference in hemorrhage between the groups.

Table 28. Listing of Patients With Hemorrhage (Narrow FMQ), Safety Population, Study 233AS101 Part C

Study Arm	Patient ID	Sex	Age	Narrow FMQ	MedDRA Preferred Term	Verbatim Term	AE Onset Study Day	AE Stop Study Day	SAE	Leading to D/C	Investigator's Assessment of Relatedness	AE Outcome
Tofersen 100 mg	(b) (6)	F	58	Hemorrhage	Contusion	Bruising on knees and lower back	130		N	N	N	Not recovered/ Not resolved
Tofersen 100 mg		F	29	Hemorrhage	Contusion	Bruise on right upper arm due to fall	85	88	N	N	N	
Tofersen 100 mg		M	29	Hemorrhage	Epistaxis	Bloody nose (no etiology)	140	140	N	N	N	
Tofersen 100 mg		F	66	Hemorrhage	Epistaxis	Intermittent nosebleed	5	5	N	N	N	
Tofersen 100 mg		F	45	Hemorrhage	Contusion	Bruised head	161	170	N	N	N	
Tofersen 100 mg		M	39	Hemorrhage	Post procedural contusion	Bruises at LP site	139		N	N	N	Not recovered/ Not resolved
Tofersen 100 mg		M	23	Hemorrhage	Medical device site bruise	Cupping bruising upper back (shoulders)	53	59	N	N	N	
Placebo		M	47	Hemorrhage	Eye contusion	Black eye	134	145	N	N	N	
Placebo		M	47	Hemorrhage	Epistaxis	Nosebleed	171	171	N	N	N	
Placebo		M	64	Hemorrhage	Contusion	Right hand bruising S/P fall	125	142	N	N	N	

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is approximately 28 to 32 weeks.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; D/C, discontinuation; F, female; FMQ, FDA Medical Query; ID, identifier; LP, lumbar puncture; M, male; MedDRA, Medical Dictionary for Regulatory Activities; N, no; SAE, serious adverse event; S/P, status post

7.6.1.6. Laboratory Findings, Study 101C

Results of the FDA analysis of laboratory value abnormalities for Study 101C are shown in Table 29 and Table 30. The population consisted of all subjects who received tofersen 100 mg or placebo in Study 101C (pivotal placebo-controlled study). Overall, there were no clinically significant patterns or trends observed in abnormalities in blood chemistry. There were more cases of high chloride (2.8% tofersen versus 0% placebo) and low bicarbonate levels (22% tofersen versus 17% placebo) in the tofersen group, which could suggest metabolic acidosis. Respiratory insufficiency, common in ALS, can lead to metabolic acidosis. Analysis of renal function found no clinically significant difference between the tofersen and placebo groups, as discussed in Section 7.7.4. Hepatic assessments are discussed in Section 7.6.2.7.

Table 29. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study 233AS101 Part C

Laboratory Parameter	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	0/72 (0)	1/36 (2.8)	-2.8 (-8.1, 2.6)
Level 2 (<130)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (<125)	0/72 (0)	0/36 (0)	0 (0, 0)
Sodium, high (mEq/L)			
Level 1 (>150)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 2 (>155)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>160)	0/72 (0)	0/36 (0)	0 (0, 0)
Potassium, low (mEq/L)			
Level 1 (<3.6)	3/72 (4.2)	2/36 (5.6)	-1.4 (-10.2, 7.4)
Level 2 (<3.4)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (<3)	0/72 (0)	0/36 (0)	0 (0, 0)
Potassium, high (mEq/L)			
Level 1 (>5.5)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 2 (>6)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>6.5)	0/72 (0)	0/36 (0)	0 (0, 0)
Chloride, low (mEq/L)			
Level 1 (<95)	2/72 (2.8)	2/36 (5.6)	-2.8 (-11.2, 5.6)
Level 2 (<88)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (<80)	0/72 (0)	0/36 (0)	0 (0, 0)
Chloride, high (mEq/L)			
Level 1 (>108)	2/72 (2.8)	0/36 (0)	2.8 (-1.0, 6.6)
Level 2 (>112)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>115)	0/72 (0)	0/36 (0)	0 (0, 0)
Bicarbonate, low (mEq/L)			
Level 1 (<20)	13/72 (18.1)	5/36 (13.9)	4.2 (-10.2, 18.5)
Level 2 (<18)	3/72 (4.2)	1/36 (2.8)	1.4 (-5.7, 8.5)
Level 3 (<15)	0/72 (0)	0/36 (0)	0 (0, 0)
Bicarbonate, high (mEq/L)			
Level 3 (>30)	2/72 (2.8)	1/36 (2.8)	0 (-6.6, 6.6)
Glucose, low (mg/dL)			
Level 1 (<70)	9/72 (12.5)	3/36 (8.3)	4.2 (-7.7, 16.0)
Level 2 (<54)	0/72 (0)	1/36 (2.8)	-2.8 (-8.1, 2.6)
Level 3 (<40)	0/72 (0)	0/36 (0)	0 (0, 0)

Laboratory Parameter	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	2/72 (2.8)	5/36 (13.9)	-11.1 (-23.0, 0.8)
Level 3 (>250)	1/72 (1.4)	4/36 (11.1)	-9.7 (-20.3, 0.9)
Calcium, low (mg/dL)			
Level 1 (<8.4)	2/72 (2.8)	0/36 (0)	2.8 (-1.0, 6.6)
Level 2 (<8)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (<7.5)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Calcium, high (mg/dL)			
Level 1 (>10.5)	2/72 (2.8)	1/36 (2.8)	0 (-6.6, 6.6)
Level 2 (>11)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>12)	0/72 (0)	0/36 (0)	0 (0, 0)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	7/72 (9.7)	3/36 (8.3)	1.4 (-9.9, 12.7)
Level 2 (<2)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (<1.4)	0/72 (0)	0/36 (0)	0 (0, 0)
Protein, total, low (g/dL)			
Level 1 (<6)	3/72 (4.2)	1/36 (2.8)	1.4 (-5.7, 8.5)
Level 2 (<5.4)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (<5)	0/72 (0)	0/36 (0)	0 (0, 0)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 2 (<2.5)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (<2)	0/72 (0)	0/36 (0)	0 (0, 0)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	10/72 (13.9)	8/36 (22.2)	-8.3 (-24.1, 7.4)
Level 2 (>27)	4/72 (5.6)	6/36 (16.7)	-11.1 (-24.4, 2.2)
Level 3 (>31)	2/72 (2.8)	3/36 (8.3)	-5.6 (-15.3, 4.2)

Source: ad b.xpt; software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Thrombocytopenia leading to hemorrhage is a potential antisense oligonucleotide class effect; therefore, analyses explored other potential causes of bleeding. There was no clinically significant difference in coagulation parameters or platelet levels between the tofersen group and the placebo group, as seen in Table 30. Activated partial thromboplastin time >39.9 seconds occurred in 29% of the tofersen group and 36% of the placebo group.

Table 30. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study 233AS101 Part C

Laboratory Parameter	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
Complete blood count			
WBC, low (cells/µL)			
Level 1 (<3500)	1/72 (1.4)	1/36 (2.8)	-1.4 (-7.4, 4.6)
Level 2 (<3000)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (<1000)	0/72 (0)	0/36 (0)	0 (0, 0)
WBC, high (cells/µL)			
Level 1 (>10,800)	7/72 (9.7)	3/36 (8.3)	1.4 (-9.9, 12.7)
Level 2 (>13,000)	3/72 (4.2)	0/36 (0)	4.2 (-0.4, 8.8)
Level 3 (>15,000)	3/72 (4.2)	0/36 (0)	4.2 (-0.4, 8.8)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL decrease from baseline)	4/72 (5.6)	4/36 (11.1)	-5.6 (-17.1, 6.0)
Level 3 (>2 g/dL decrease from baseline)	1/72 (1.4)	2/36 (5.6)	-4.2 (-12.1, 3.8)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL increase from baseline)	0/72 (0)	4/36 (11.1)	-11.1 (-21.4, -0.8)
Level 3 (>3 g/dL increase from baseline)	0/72 (0)	1/36 (2.8)	-2.8 (-8.1, 2.6)
Platelets, low (cells/µL)			
Level 1 (<140,000)	3/72 (4.2)	1/36 (2.8)	1.4 (-5.7, 8.5)
Level 2 (<125,000)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (<100,000)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
WBC Differential			
Lymphocytes, low (cells/µL)			
Level 1 (<1000)	8/72 (11.1)	8/36 (22.2)	-11.1 (-26.5, 4.3)
Level 2 (<750)	1/72 (1.4)	2/36 (5.6)	-4.2 (-12.1, 3.8)
Level 3 (<500)	1/72 (1.4)	1/36 (2.8)	-1.4 (-7.4, 4.6)
Lymphocytes, high (cells/µL)			
Level 1 (>4000)	1/72 (1.4)	1/36 (2.8)	-1.4 (-7.4, 4.6)
Level 2 (>10,000)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (>20,000)	0/72 (0)	0/36 (0)	0 (0, 0)
Neutrophils, low (cells/µL)			
Level 1 (<2000)	8/72 (11.1)	3/36 (8.3)	2.8 (-8.8, 14.4)
Level 2 (<1000)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (<500)	0/72 (0)	0/36 (0)	0 (0, 0)
Eosinophils, high (cells/µL)			
Level 1 (>650)	2/72 (2.8)	1/36 (2.8)	0 (-6.6, 6.6)
Level 2 (>1500)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>5000)	0/72 (0)	0/36 (0)	0 (0, 0)
Coagulation studies			
PT, high (sec)			
Level 1 (>1.1× ULN)	14/72 (19.4)	6/36 (16.7)	2.8 (-12.4, 18.0)
Level 2 (>1.3× ULN)	3/72 (4.2)	0/36 (0)	4.2 (-0.4, 8.8)
Level 3 (>1.5× ULN)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
PTT, high (seconds)			
Level 1 (>1× ULN)	17/72 (23.6)	11/36 (30.6)	-6.9 (-24.9, 11.0)
Level 2 (>1.21× ULN)	3/72 (4.2)	4/36 (11.1)	-6.9 (-18.2, 4.3)
Level 3 (>1.41× ULN)	0/72 (0)	1/36 (2.8)	-2.8 (-8.1, 2.6)

Source: ad b.xpt; software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study 101C

Results of the FDA analysis of liver laboratory abnormalities for Study 101C are shown in Table 31 and Table 32. The population consisted of all subjects who received tofersen 100 mg or placebo in Study 101C (pivotal placebo-controlled study). There were no clinically significant patterns or trends observed in abnormalities in liver chemistry.

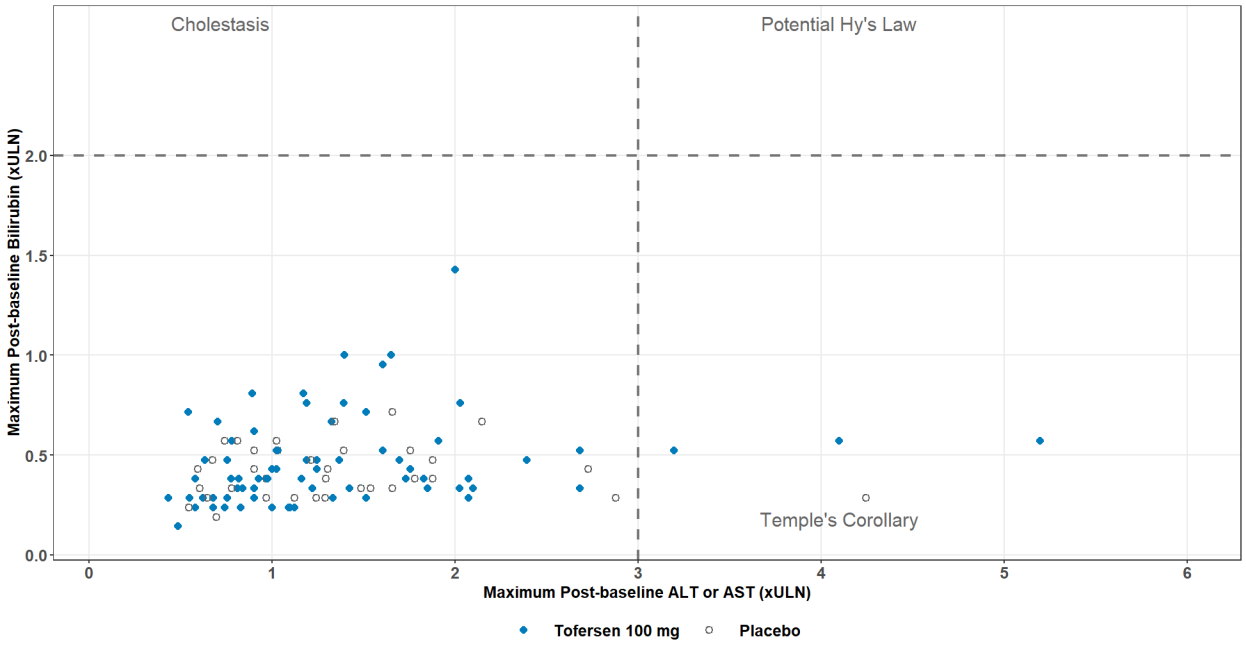
Table 31. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study 233AS101 Part C

Laboratory Parameter	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 2 (>2X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>3X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	3/72 (4.2)	1/36 (2.8)	1.4 (-5.7, 8.5)
Level 2 (>5X ULN)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 3 (>10X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	1/72 (1.4)	0/36 (0)	1.4 (-1.3, 4.1)
Level 2 (>5X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>10X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 2 (>2X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (>3X ULN)	0/72 (0)	0/36 (0)	0 (0, 0)

Source: ad b.xpt; software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot..” and “Cholestatic Drug-Induced Liver Injury Screening Plot..” and the tables “Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..” and “Patients in Each Quadrant for Cholestatic DILI Screening Plot…”
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Figure 17 and Table 32 show a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no Hy’s law cases.

Figure 17. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 233AS101 Part C



Source: ad b.xpt; software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN (ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 32. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Study 233AS101 Part C

Quadrant	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)
Potential Hy's law (right upper)	0/72 (0)	0/36 (0)
Cholestasis (left upper)	0/72 (0)	0/36 (0)
Temple's corollary (right lower)	3/72 (4.2)	1/36 (2.8)
Total	3/72 (4.2)	1/36 (2.8)

Source: ad b.xpt; software: R
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data

7.6.1.8. Vital Signs' Analyses, Study 101C

As seen in Table 33, Table 34 and Figure 18 to Figure 21, there were no clinically significant patterns or trends observed in abnormalities in vital signs (including diastolic and systolic blood pressure, pulse rate, respiratory rate, weight, and temperature) in Study 101C.

Table 33. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Study 233AS101 Part C

Systolic Blood Pressure (mm Hg)	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
<90	0/72 (0)	0/36 (0)	0 (0, 0)
≥90	72/72 (100)	36/36 (100)	0 (0, 0)
≥120	69/72 (95.8)	35/36 (97.2)	-1.4 (-8.5, 5.7)
≥140	38/72 (52.8)	18/36 (50.0)	2.8 (-17.2, 22.8)
≥160	10/72 (13.9)	3/36 (8.3)	5.6 (-6.5, 17.6)
≥180	1/72 (1.4)	1/36 (2.8)	-1.4 (-7.4, 4.6)

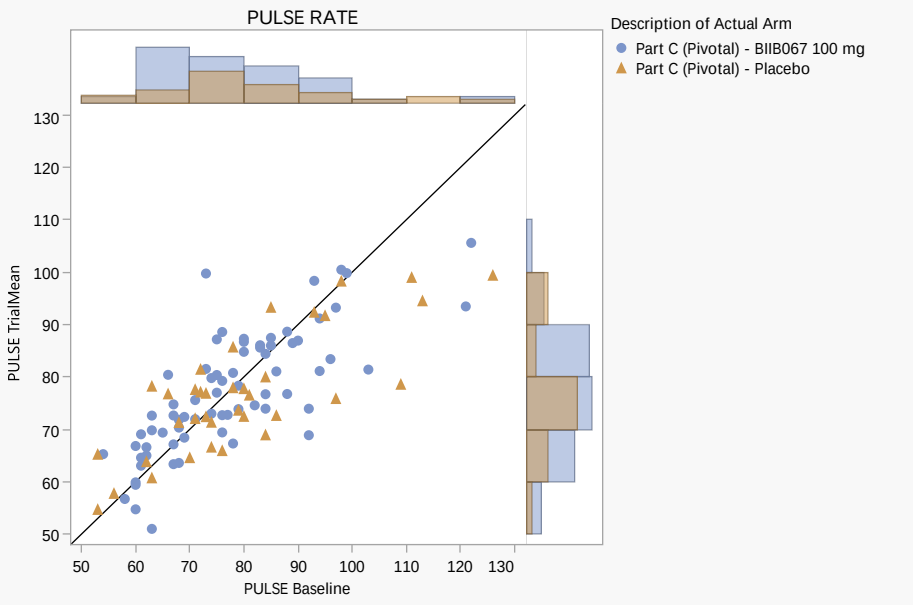
Source: advs.xpt; software: R
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 34. Percentages of Patients With Specific Hypotension Levels Postbaseline, Safety Population, Study 233AS101 Part C

Blood Pressure (mm Hg)	Tofersen 100 mg N=72 n/Nw (%)	Placebo N=36 n/Nw (%)	Risk Difference (%) (95% CI)
SBP <90	1/72 (1.4)	1/36 (2.8)	-1.4 (-7.4, 4.6)
DBP <60	19/72 (26.4)	10/36 (27.8)	-1.4 (-19.2, 16.4)

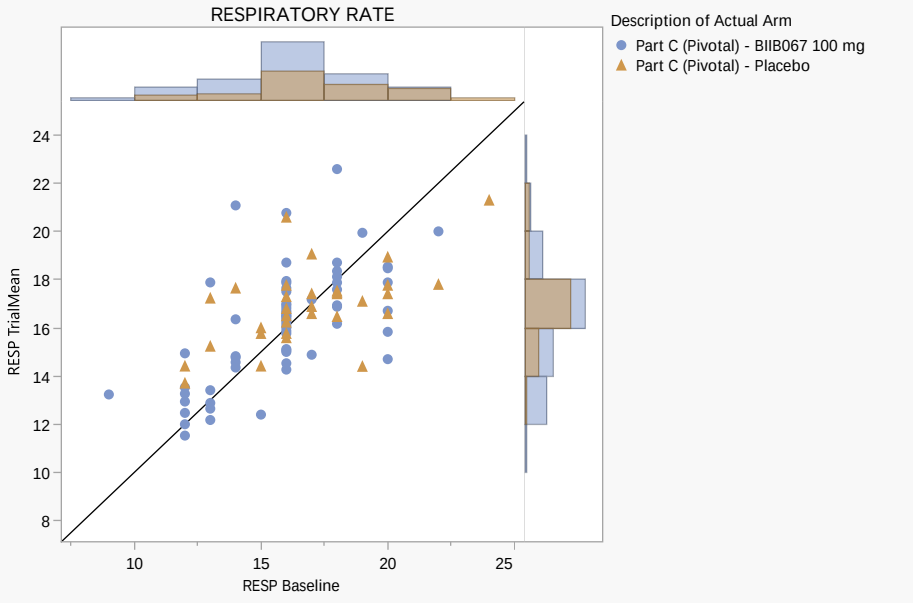
Source: advs.xpt; software: R
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SBP, systolic blood pressure

Figure 18. Shift Plot of Pulse Rate in Study 101C



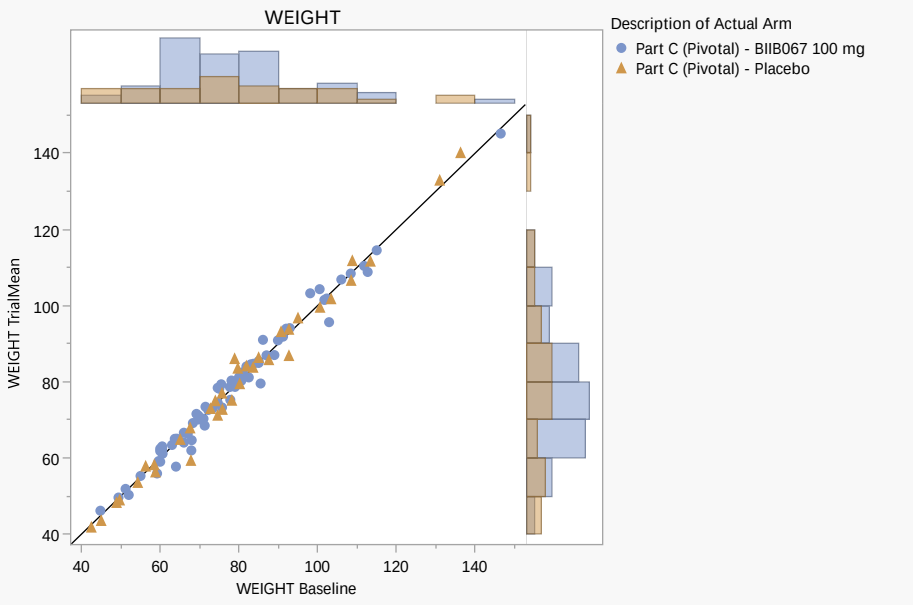
Source: FDA analysis

Figure 19. Shift Plot of Respiratory Rate in Study 101C



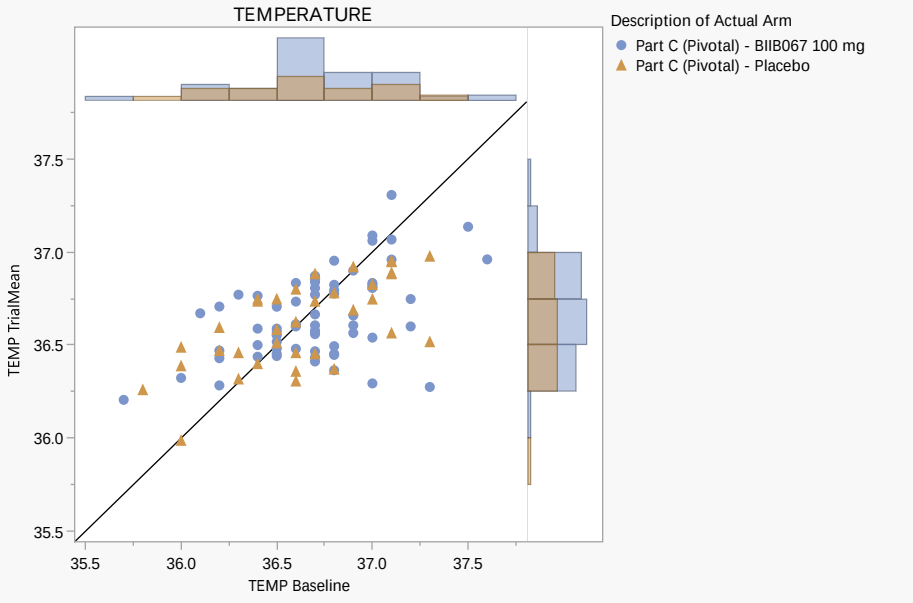
Source: FDA analysis
Abbreviations: RESP, respiratory

Figure 20. Shift Plot of Weight in Study 101C



Source: FDA analysis

Figure 21. Shift Plot of Temperature in Study 101C



Source: FDA analysis
Abbreviations: TEMP, temperature

7.6.1.9. Subgroup Analyses, Study 101C

Results of the FDA analysis of SAEs and AEs by demographic subgroup for Study 101C are shown in Table 35 and Table 36. The population consisted of all subjects who received tofersen 100 mg or placebo in Study 101C (pivotal placebo-controlled study).

Table 35. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Study 233AS101 Part C

Characteristic	Tofersen 100 mg N=72 n/N_s (%)	Placebo N=36 n/N_s (%)	Risk Difference (%) (95% CI)
Sex, n (%)			
Female	6/29 (20.7)	2/17 (11.8)	8.9 (-12.3, 30.2)
Male	7/43 (16.3)	3/19 (15.8)	0.5 (-19.3, 20.3)
Age group, years, n (%)			
18 to <35	3/10 (30.0)	0/2 (0)	30.0 (1.6, 58.4)
35 to <50	5/32 (15.6)	3/15 (20.0)	-4.4 (-28.2, 19.5)
50 to <65	3/21 (14.3)	1/14 (7.1)	7.1 (-13.0, 27.3)
≥65	2/9 (22.2)	1/5 (20.0)	2.2 (-42.1, 46.6)
Age group ≥75, years, n (%)			
≥75	0/1 (0)	0/0 (NA)	NA
Race, n (%)			
Asian	1/5 (20.0)	0/4 (0)	20.0 (-15.1, 55.1)
Black or African American	0/1 (0)	0/0 (NA)	NA
Not reported	4/21 (19.0)	1/7 (14.3)	4.8 (-26.1, 35.6)
Other	0/1 (0)	0/0 (NA)	NA
White	8/44 (18.2)	4/25 (16.0)	2.2 (-16.2, 20.5)
Ethnicity, n (%)			
Hispanic or Latino	1/4 (25.0)	0/1 (0)	25.0 (-17.4, 67.4)
Not Hispanic or Latino	8/47 (17.0)	4/28 (14.3)	2.7 (-14.1, 19.6)
Not reported	4/21 (19.0)	1/7 (14.3)	4.8 (-26.1, 35.6)

Source: adae.xpt; software: R
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each subgroup and were assigned to that group

Table 36. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study 233AS101 Part C

Characteristic	Tofersen 100 mg N=72 n/N_s (%)	Placebo N=36 n/N_s (%)	Risk Difference (%) (95% CI)
Sex, n (%)			
Female	28/29 (96.6)	17/17 (100)	-3.4 (-10.1, 3.2)
Male	41/43 (95.3)	17/19 (89.5)	5.9 (-9.3, 21.0)
Age group, years, n (%)			
18 to <35	10/10 (100)	2/2 (100)	0 (0, 0)
35 to <50	30/32 (93.8)	15/15 (100)	-6.2 (-14.6, 2.1)
50 to <65	20/21 (95.2)	14/14 (100)	-4.8 (-13.9, 4.3)
≥65	9/9 (100)	3/5 (60.0)	40.0 (-2.9, 82.9)
Age group ≥75, years, n (%)			
≥75	1/1 (100)	0/0 (NA)	NA
Race, n (%)			
Asian	5/5 (100)	4/4 (100)	0 (0, 0)
Black or African American	1/1 (100)	0/0 (NA)	NA
Not reported	20/21 (95.2)	7/7 (100)	-4.8 (-13.9, 4.3)
Other	1/1 (100)	0/0 (NA)	NA
White	42/44 (95.5)	23/25 (92.0)	3.5 (-8.8, 15.7)

Characteristic	Tofersen 100 mg N=72 n/N_s (%)	Placebo N=36 n/N_s (%)	Risk Difference (%) (95% CI)
Ethnicity, n (%)			
Hispanic or Latino	4/4 (100)	1/1 (100)	0 (0, 0)
Not Hispanic or Latino	45/47 (95.7)	26/28 (92.9)	2.9 (-8.3, 14.0)
Not reported	20/21 (95.2)	7/7 (100)	-4.8 (-13.9, 4.3)

Source: adae.xpt; software: R
Risk difference (with 95% confidence interval) between tofersen and placebo is shown.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

As seen in Table 35 and Table 36 based on the submission, there were no clinically significant differences in the proportions of subjects with AEs or with SAEs as a function of age or sex subgroup for Study 101C. There was also no clinically significant difference in the proportion of subjects with AEs as a function of race or ethnicity.

7.6.1.10. Exposure-Adjusted Analyses, Study 101C

Results of the FDA analysis of the exposure-adjusted incidence rate of SAEs and the key safety issues for the placebo-controlled Study 101C are shown in Table 37, Table 38, and Table 39. The analysis focused on myelitis, radiculitis, aseptic meningitis, CSF protein and white blood cell (WBC) count increased, papilledema, renal and urinary disorders, respiratory failure, hemorrhage, and hepatobiliary disorders.

Higher rates were observed in the tofersen group compared to placebo for renal and urinary disorders, respiratory failure, hemorrhage, hepatic steatosis, CSF protein and white blood cell increase, lumbar radiculopathy, chemical (aseptic) meningitis, myelitis, and transverse myelitis. Rates greater than 5 per 100 patient-years were observed in the tofersen group for glycosuria, micturition urgency, contusion, epistaxis, and CSF protein and WBC count increased.

Table 37. Exposure-Adjusted Analysis by System Organ Class and Preferred Term, Safety Population, Study 233AS101 Part C

System Organ Class Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Tofersen 100 mg PY=31 N=72 n (EAIR)	Placebo PY=16.2 N=32 n (EAIR)
Renal and urinary disorders (SOC)	6 (8.3)	1 (2.8)	6 (20.3)	1 (6.3)
Acute kidney injury	1 (1.4)	0	1 (3.3)	0 (0)
Glycosuria	2 (2.8)	0	2 (6.5)	0 (0)
Micturition urgency	2 (2.8)	0	2 (6.5)	0 (0)
Pollakiuria	1 (1.4)	1 (2.8)	1 (3.3)	1 (6.3)
Hepatobiliary disorders (SOC)	1 (1.4)	0	1 (3.2)	0 (0)
Hepatic steatosis	1 (1.4)	0	1 (3.2)	0 (0)

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Abbreviations: EAIR, exposure-adjusted incidence rate; N, number of patients in treatment arm; n, number of patients with adverse event; PY, patient years; SOC, system organ class

Table 38. Exposure-Adjusted Analysis by FDA Medical Query (Narrow) and Preferred Term, Safety Population, Study 233AS101 Part C

FMQ (Narrow) Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Tofersen 100 mg PY=31 N=72 n (EAIR)	Placebo PY=16.2 N=32 n (EAIR)
Respiratory failure (FMQ)	4 (5.6)	0	4 (12.9)	0
Acute respiratory failure	1 (1.4)	0	1 (3.2)	0
Hypoventilation	1 (1.4)	0	1 (3.2)	0
Oxygen saturation decreased	1 (1.4)	0	1 (3.3)	0
Respiratory failure	3 (4.2)	0	3 (9.8)	0
Hemorrhage (FMQ)	7 (9.7)	2 (5.6)	7 (23.6)	2 (12.5)
Contusion	3 (4.2)	1 (2.8)	3 (9.8)	1 (6.2)
Epistaxis	2 (2.8)	1 (2.8)	2 (6.6)	1 (6.2)
Eye contusion	0	1 (2.8)	0	1 (6.2)
Medical device site bruise	1 (1.4)	0	1 (3.3)	0
Post procedural contusion	1 (1.4)	0	1 (3.2)	0

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: EAIR, exposure-adjusted incidence rate; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; PY, patient years; SOC, system organ class

Table 39. Exposure-Adjusted Analysis by Preferred Term, Safety Population, Study 233AS101 Part C

Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Tofersen 100 mg PY=31 N=72 n (EAIR)	Placebo PY=16.2 N=32 n (EAIR)
CSF protein increased	6 (8.3)	1 (2.8)	6 (20.0)	1 (6.2)
CSF white blood cell count increased	7 (9.7)	0	7 (23.9)	0
Lumbar radiculopathy	1 (1.4)	0	1 (3.3)	0
Meningitis chemical	1 (1.4)	0	1 (3.2)	0
Myelitis	1 (1.4)	0	1 (3.2)	0
Myelitis transverse	1 (1.4)	0	1 (3.2)	0

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Coded as MedDRA preferred terms.
Abbreviations: CSF, cerebrospinal fluid; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; PY, patient years

7.6.2. Safety Results, Study 102

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 102

Results of the FDA analysis of adverse events for the open-label extension study 102 are shown in Table 40. The proportion of subjects experiencing AEs was 97% overall. The proportion experiencing SAEs was 37%. Permanent dose discontinuation due to AEs occurred in 17% of subjects.

Table 40. Overview of Adverse Events, Safety Population, Study 233AS102

Event Category	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
SAE	21 (33.3)	11 (34.4)	19 (43.2)	51 (36.7)
SAEs with fatal outcome	8 (12.7)	6 (18.8)	5 (11.4)	19 (13.7)
Life-threatening SAEs	3 (4.8)	0	2 (4.5)	5 (3.6)
AE leading to permanent discontinuation of study drug	9 (14.3)	6 (18.8)	8 (18.2)	23 (16.5)
AE leading to dose modification of study drug	10 (15.9)	6 (18.8)	6 (13.6)	22 (15.8)
AE leading to interruption of study drug	10 (15.9)	6 (18.8)	6 (13.6)	22 (15.8)
AE leading to reduction of study drug	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0
Other	0	0	0	0
Any AE	61 (96.8)	31 (96.9)	43 (97.7)	135 (97.1)
Severe and worse	21 (33.3)	12 (37.5)	17 (38.6)	50 (36.0)
Moderate	28 (44.4)	12 (37.5)	20 (45.5)	60 (43.2)
Mild	12 (19.0)	7 (21.9)	6 (13.6)	25 (18.0)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Study 102

Results of the FDA analysis of deaths for the open-label safety population of Study 102 are shown in Table 41 and Table 42. In the population of all subjects in the OLE Study 102 the proportion of deaths was 14%.

Table 41. Deaths, Safety Population, Study 233AS102

Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Any AE leading to death	8 (12.7)	6 (18.8)	5 (11.4)	19 (13.7)
Respiratory failure	4 (6.3)	5 (15.6)	2 (4.5)	11 (7.9)
Respiratory arrest	2 (3.2)	0	0	2 (1.4)
Septic shock	1 (1.6)	0	0	1 (0.7)
Sudden death	1 (1.6)	0	0	1 (0.7)
Amyotrophic lateral sclerosis	0	1 (3.1)	1 (2.3)	2 (1.4)
Cardiac arrest	0	1 (3.1)	0	1 (0.7)
Euthanasia	0	0	1 (2.3)	1 (0.7)
Pneumonia aspiration	0	0	1 (2.3)	1 (0.7)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
For patient-level data, see the table “List of Adverse Events Leading to Death…”
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

These deaths were consistent with the natural history of ALS (Table 42). Subject (b) (6) with sudden death had a medical history at the time of enrollment in Study 233AS102 that included hypertension, hyperlipidemia, coronary artery disease, stage III renal disease, and myocardial infarction. These comorbidities in addition to ALS likely contributed to the sudden death.

Table 42. Listing of All Individual Patient Deaths, Safety Population, Study 233AS102

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Part C tofersen 100 mg	(b) (6)	29	F	100 mg	108	260	Respiratory failure	Worsening respiratory failure due to ALS
Part C tofersen 100 mg		66	F	100 mg	309	378	Sudden death	Sudden unexpected death, unknown etiology
Part C tofersen 100 mg		40	M	100 mg	451	486	Respiratory arrest	Respiratory arrest
Part C tofersen 100 mg		61	F	100 mg	29	93	Respiratory failure	Respiratory failure secondary to ALS
Part C tofersen 100 mg		43	M	100 mg	252	299	Respiratory failure	Respiratory failure secondary to ALS
Part C tofersen 100 mg		48	M	100 mg	841	917	Septic shock	Septic shock
Part C tofersen 100 mg		71	M	100 mg	1	24	Respiratory arrest	Respiratory arrest due to ALS disease progression
Part C tofersen 100 mg		58	F	100 mg	141	170	Respiratory failure	Respiratory failure
Part C placebo		48	M	100 mg	198	203	Respiratory failure	Respiratory failure due to ALS
Part C placebo		65	M	100 mg	29	39	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Part C placebo		65	M	100 mg	29	39	Respiratory failure	Worsening respiratory failure in setting of ALS
Part C placebo		53	M	100 mg	281	296	Cardiac arrest	Cardiac arrest
Part C placebo		40	M	100 mg	197	230	Respiratory failure	Death due to respiratory insufficiency caused by ALS
Part C placebo		46	F	100 mg	225	236	Respiratory failure	Death due to respiratory failure
Part C placebo		53	M	100 mg	590	612	Respiratory failure	Respiratory insufficiency

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Part A/B all doses	(b) (6)	53	M	<100 mg	197	223	Pneumonia aspiration	Acute bronchopneumonia secondary to aspiration
Part A/B all doses		35	M	100 mg	259	267	Respiratory failure	Respiratory failure (secondary to amyotrophic lateral sclerosis)
Part A/B all doses		63	F	100 mg	1009	1116	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Part A/B all doses		60	M	100 mg	1291	1305	Respiratory failure	Respiratory failure secondary to motor neuron disease (unknown reason)
Part A/B all doses		54	M	100 mg	1150	1176	Euthanasia	Euthanasia

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Abbreviations: ALS, amyotrophic lateral sclerosis; F, female; ID, identifier; M, male

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study 102

Results of the FDA analysis of SAEs for the open-label safety population of Study 102 are shown in Table 43 and Table 44. In the population of all subjects in the OLE Study 102, the proportion of SAEs was 37%. SAEs that occurred in more than one subject were respiratory disorders (SOC) (18%), pneumonia aspiration (7%), dysphagia (5%), pneumonia (2%), intracranial pressure increased (2%), fall (2%), COVID-19 (1%), myelitis (1%), septic shock (1%), back pain (1%), ALS (1%), and nephrolithiasis (1%). Most of these SAEs are consistent with the natural history of ALS. Myelitis and intracranial pressure increased are discussed further in Section 7.7.

Table 43. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 233AS102

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Any SAE	21 (33.3)	11 (34.4)	19 (43.2)	51 (36.7)
Cardiac disorders (SOC)	1 (1.6)	1 (3.1)	1 (2.3)	3 (2.2)
Cardio-respiratory arrest	1 (1.6)	0	0	1 (0.7)
Cardiac arrest	0	1 (3.1)	0	1 (0.7)
Myopericarditis	0	0	1 (2.3)	1 (0.7)
Eye disorders (SOC)	0	1 (3.1)	0	1 (0.7)
Papilledema	0	1 (3.1)	0	1 (0.7)
Gastrointestinal disorders (SOC)	5 (7.9)	2 (6.2)	6 (13.6)	13 (9.4)
Dysphagia	4 (6.3)	0	3 (6.8)	7 (5.0)
Gastric ulcer perforation	1 (1.6)	0	0	1 (0.7)
Abdominal pain	0	1 (3.1)	0	1 (0.7)
Constipation	0	1 (3.1)	0	1 (0.7)
Fecaloma	0	0	1 (2.3)	1 (0.7)
Gastric perforation	0	0	1 (2.3)	1 (0.7)
Gastritis	0	0	1 (2.3)	1 (0.7)
Pancreatitis	0	0	1 (2.3)	1 (0.7)
General disorders and administration site conditions (SOC)	1 (1.6)	0	0	1 (0.7)
Sudden death	1 (1.6)	0	0	1 (0.7)
Hepatobiliary disorders (SOC)	1 (1.6)	0	0	1 (0.7)
Cholecystitis	1 (1.6)	0	0	1 (0.7)

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Infections and infestations (SOC)	9 (14.3)	7 (21.9)	4 (9.1)	20 (14.4)
Pneumonia aspiration	5 (7.9)	3 (9.4)	2 (4.5)	10 (7.2)
Septic shock	2 (3.2)	0	0	2 (1.4)
COVID-19	1 (1.6)	1 (3.1)	0	2 (1.4)
Pneumonia	1 (1.6)	2 (6.2)	0	3 (2.2)
Pneumonia pseudomonal	1 (1.6)	0	0	1 (0.7)
Pyelonephritis	1 (1.6)	0	0	1 (0.7)
Respiratory tract infection	1 (1.6)	0	0	1 (0.7)
Sepsis	1 (1.6)	0	0	1 (0.7)
Streptococcal bacteremia	1 (1.6)	0	0	1 (0.7)
COVID-19 pneumonia	0	0	1 (2.3)	1 (0.7)
Meningitis aseptic	0	1 (3.1)	0	1 (0.7)
Myelitis	0	0	1 (2.3)	1 (0.7)
Pneumonia bacterial	0	1 (3.1)	0	1 (0.7)
Urinary tract infection	0	1 (3.1)	0	1 (0.7)
Injury, poisoning and procedural complications (SOC)	1 (1.6)	0	3 (6.8)	4 (2.9)
Stoma site pain	1 (1.6)	0	0	1 (0.7)
Ankle fracture	0	0	1 (2.3)	1 (0.7)
Fall	0	0	3 (6.8)	3 (2.2)
Head injury	0	0	1 (2.3)	1 (0.7)
Skull fracture	0	0	1 (2.3)	1 (0.7)
Investigations (SOC)	0	0	1 (2.3)	1 (0.7)
Staphylococcus test positive	0	0	1 (2.3)	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (3.1)	1 (2.3)	2 (1.4)
Back pain	0	1 (3.1)	1 (2.3)	2 (1.4)
Muscular weakness	0	0	1 (2.3)	1 (0.7)

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Nervous system disorders (SOC)	2 (3.2)	3 (9.4)	6 (13.6)	11 (7.9)
Encephalopathy	1 (1.6)	0	0	1 (0.7)
Intracranial pressure increased	1 (1.6)	1 (3.1)	1 (2.3)	3 (2.2)
Amyotrophic lateral sclerosis	0	1 (3.1)	1 (2.3)	2 (1.4)
Headache	0	0	1 (2.3)	1 (0.7)
Migraine	0	0	1 (2.3)	1 (0.7)
Neurosarcoidosis	0	0	1 (2.3)	1 (0.7)
Radicular pain	0	1 (3.1)	0	1 (0.7)
Radiculopathy	0	0	1 (2.3)	1 (0.7)
Vocal cord paralysis	0	0	1 (2.3)	1 (0.7)
Psychiatric disorders (SOC)	1 (1.6)	0	0	1 (0.7)
Anxiety	1 (1.6)	0	0	1 (0.7)
Renal and urinary disorders (SOC)	1 (1.6)	1 (3.1)	1 (2.3)	3 (2.2)
Calculus urinary	1 (1.6)	0	0	1 (0.7)
Nephrolithiasis	0	1 (3.1)	1 (2.3)	2 (1.4)
Respiratory, thoracic and mediastinal disorders (SOC)	10 (15.9)	6 (18.8)	9 (20.5)	25 (18.0)
Respiratory failure	5 (7.9)	5 (15.6)	5 (11.4)	15 (10.8)
Acute respiratory failure	4 (6.3)	0	0	4 (2.9)
Respiratory arrest	2 (3.2)	0	0	2 (1.4)
Acute respiratory distress syndrome	1 (1.6)	0	0	1 (0.7)
Chronic respiratory failure	1 (1.6)	1 (3.1)	0	2 (1.4)
Pneumonitis aspiration	1 (1.6)	0	1 (2.3)	2 (1.4)
Pneumothorax	1 (1.6)	0	0	1 (0.7)
Pulmonary embolism	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Dyspnea	0	0	1 (2.3)	1 (0.7)
Respiratory distress	0	0	2 (4.5)	2 (1.4)

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Surgical and medical procedures (SOC)	0	1 (3.1)	1 (2.3)	2 (1.4)
Euthanasia	0	0	1 (2.3)	1 (0.7)
Gastrostomy	0	1 (3.1)	0	1 (0.7)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration was up to 360 weeks.
Abbreviations: COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 44 shows SAEs grouped using the FDA Medical Query (Narrow). Grouped SAEs that occurred in more than one subject were respiratory failure (14%), pneumonia (9%), bacterial infection (6%), thrombosis (3%), fall (2%), viral infection (2%), fracture (1%), back pain (1%), dyspnea (2%), and respiratory depression (1%).

Table 44. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 233AS102

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Blood and lymphatic system disorders (SOC)				
Thrombosis	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Thrombosis venous	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Gastrointestinal disorders (SOC)				
Abdominal pain	0	1 (3.1)	0	1 (0.7)
Constipation	0	1 (3.1)	0	1 (0.7)
Pancreatitis	0	0	1 (2.3)	1 (0.7)
General disorders and administration site conditions (SOC)				
Fall	0	0	3 (6.8)	3 (2.2)
Hepatobiliary disorders (SOC)				
Cholecystitis	1 (1.6)	0	0	1 (0.7)
Infections and infestations (SOC)				
Pneumonia	6 (9.5)	5 (15.6)	2 (4.5)	13 (9.4)
Bacterial infection	5 (7.9)	2 (6.2)	1 (2.3)	8 (5.8)
Viral infection	1 (1.6)	1 (3.1)	1 (2.3)	3 (2.2)
Musculoskeletal and connective tissue disorders (SOC)				
Back pain	0	1 (3.1)	1 (2.3)	2 (1.4)
Fracture	0	0	2 (4.5)	2 (1.4)
Nervous system disorders (SOC)				
Headache	0	0	2 (4.5)	2 (1.4)
Psychiatric disorders (SOC)				
Anxiety	1 (1.6)	0	0	1 (0.7)
Renal and urinary disorders (SOC)				
Renal and urinary tract infection	0	1 (3.1)	0	1 (0.7)

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)				
Respiratory failure	10 (15.9)	5 (15.6)	5 (11.4)	20 (14.4)
Respiratory depression	2 (3.2)	0	0	2 (1.4)
Dyspnea	0	0	3 (6.8)	3 (2.2)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration was up to 360 weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
For specific preferred terms under each FMQ, see the table “Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 102

Results of the FDA analysis of AEs leading to treatment discontinuation for the open-label safety population of Study 102 are shown in Table 45 and Table 46. The proportion of AEs leading to treatment discontinuation ins Study 102 was 17%.

The AEs leading to treatment discontinuation that occurred in more than one subject were respiratory failure (8%), respiratory arrest (1%), and ALS (1%).

Table 45. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study 233AS102

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Any AE leading to discontinuation	9 (14.3)	6 (18.8)	8 (18.2)	23 (16.5)
Cardiac disorders (SOC)	0	1 (3.1)	0	1 (0.7)
Cardiac arrest	0	1 (3.1)	0	1 (0.7)
Gastrointestinal disorders (SOC)	1 (1.6)	0	1 (2.3)	2 (1.4)
Salivary hypersecretion	1 (1.6)	0	0	1 (0.7)
Gastritis	0	0	1 (2.3)	1 (0.7)
Pancreatitis	0	0	1 (2.3)	1 (0.7)
General disorders and administration site conditions (SOC)	1 (1.6)	0	0	1 (0.7)
Sudden death	1 (1.6)	0	0	1 (0.7)
Infections and infestations (SOC)	1 (1.6)	0	1 (2.3)	2 (1.4)
Septic shock	1 (1.6)	0	0	1 (0.7)
Pneumonia aspiration	0	0	1 (2.3)	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	1 (1.6)	0	0	1 (0.7)
Muscular weakness	1 (1.6)	0	0	1 (0.7)
Nervous system disorders (SOC)	0	1 (3.1)	3 (6.8)	4 (2.9)
Amyotrophic lateral sclerosis	0	1 (3.1)	1 (2.3)	2 (1.4)
Neurosarcoidosis	0	0	1 (2.3)	1 (0.7)
Vocal cord paralysis	0	0	1 (2.3)	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	6 (9.5)	5 (15.6)	4 (9.1)	15 (10.8)
Respiratory failure	4 (6.3)	5 (15.6)	2 (4.5)	11 (7.9)
Respiratory arrest	2 (3.2)	0	0	2 (1.4)
Dyspnea	0	0	1 (2.3)	1 (0.7)
Pneumonitis aspiration	0	0	1 (2.3)	1 (0.7)

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Surgical and medical procedures (SOC)	0	0	1 (2.3)	1 (0.7)
Euthanasia	0	0	1 (2.3)	1 (0.7)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 46 for open-label Study 102 shows AEs leading to treatment discontinuation grouped using the FDA Medical Query (Narrow). Grouped treatment discontinuation AEs that occurred in more than one subject were respiratory failure (9%) and respiratory depression (1%).

Table 46. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 233AS102

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Gastrointestinal disorders (SOC)				
Pancreatitis	0	0	1 (2.3)	1 (0.7)
Infections and infestations (SOC)				
Pneumonia	0	0	1 (2.3)	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)				
Respiratory failure	6 (9.5)	5 (15.6)	2 (4.5)	13 (9.4)
Respiratory depression	2 (3.2)	0	0	2 (1.4)
Dyspnea	0	0	1 (2.3)	1 (0.7)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Study 102

Results of the FDA analysis of TEAEs for the Study 102 open-label safety population are shown in Table 47 and Table 48. The overall proportion of TEAEs in Study 102 was 97%.

Many of the TEAEs were consistent with the natural history of ALS and with the common adverse effects of lumbar puncture. Key TEAEs are further discussed in Section 7.7.

Table 47. Patients With Common Adverse Events Occurring in at Least 5% of Subjects in Any Arm, Safety Population, Study 233AS102

Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Any AE	61 (96.8)	31 (96.9)	43 (97.7)	135 (97.1)
Headache	33 (52.4)	16 (50.0)	29 (65.9)	78 (56.1)
Procedural pain	28 (44.4)	13 (40.6)	27 (61.4)	68 (48.9)
Back pain	21 (33.3)	10 (31.2)	22 (50.0)	53 (38.1)
COVID-19	17 (27.0)	5 (15.6)	8 (18.2)	30 (21.6)
Fall	17 (27.0)	17 (53.1)	26 (59.1)	60 (43.2)
Arthralgia	15 (23.8)	9 (28.1)	15 (34.1)	39 (28.1)
CSF protein increased	14 (22.2)	5 (15.6)	15 (34.1)	34 (24.5)
Pain in extremity	14 (22.2)	11 (34.4)	17 (38.6)	42 (30.2)
Myalgia	13 (20.6)	3 (9.4)	8 (18.2)	24 (17.3)
CSF white blood cell count increased	12 (19.0)	2 (6.2)	9 (20.5)	23 (16.5)
Fatigue	12 (19.0)	9 (28.1)	12 (27.3)	33 (23.7)
Post lumbar puncture syndrome	12 (19.0)	5 (15.6)	13 (29.5)	30 (21.6)
Muscle spasms	10 (15.9)	5 (15.6)	9 (20.5)	24 (17.3)
Nausea	10 (15.9)	4 (12.5)	14 (31.8)	28 (20.1)
Constipation	9 (14.3)	7 (21.9)	7 (15.9)	23 (16.5)
Dyspnea	9 (14.3)	3 (9.4)	5 (11.4)	17 (12.2)
Salivary hypersecretion	9 (14.3)	1 (3.1)	2 (4.5)	12 (8.6)
Dizziness	8 (12.7)	5 (15.6)	12 (27.3)	25 (18.0)
Dysphagia	7 (11.1)	1 (3.1)	5 (11.4)	13 (9.4)
Muscular weakness	7 (11.1)	5 (15.6)	4 (9.1)	16 (11.5)
Pyrexia	7 (11.1)	7 (21.9)	9 (20.5)	23 (16.5)
Contusion	6 (9.5)	6 (18.8)	12 (27.3)	24 (17.3)
Pneumonia aspiration	6 (9.5)	4 (12.5)	2 (4.5)	12 (8.6)
Respiratory failure	6 (9.5)	5 (15.6)	6 (13.6)	17 (12.2)
Chills	5 (7.9)	0	3 (6.8)	8 (5.8)
Nasopharyngitis	5 (7.9)	5 (15.6)	12 (27.3)	22 (15.8)
Pain	5 (7.9)	3 (9.4)	2 (4.5)	10 (7.2)
Paresthesia	5 (7.9)	1 (3.1)	4 (9.1)	10 (7.2)
Pleocytosis	5 (7.9)	3 (9.4)	4 (9.1)	12 (8.6)
Rash	5 (7.9)	1 (3.1)	6 (13.6)	12 (8.6)
Abdominal pain	4 (6.3)	1 (3.1)	3 (6.8)	8 (5.8)
Acute respiratory failure	4 (6.3)	1 (3.1)	0	5 (3.6)
Anxiety	4 (6.3)	1 (3.1)	3 (6.8)	8 (5.8)
CSF glucose increased	4 (6.3)	0	3 (6.8)	7 (5.0)
Gastroesophageal reflux disease	4 (6.3)	0	1 (2.3)	5 (3.6)
Upper respiratory tract infection	4 (6.3)	0	7 (15.9)	11 (7.9)
Vaccination site pain	4 (6.3)	0	1 (2.3)	5 (3.6)
Alanine aminotransferase increased	3 (4.8)	2 (6.2)	2 (4.5)	7 (5.0)
Cough	3 (4.8)	2 (6.2)	4 (9.1)	9 (6.5)
Dysarthria	3 (4.8)	2 (6.2)	0	5 (3.6)
Insomnia	3 (4.8)	1 (3.1)	3 (6.8)	7 (5.0)
Intracranial pressure increased	3 (4.8)	2 (6.2)	1 (2.3)	6 (4.3)
Joint swelling	3 (4.8)	3 (9.4)	2 (4.5)	8 (5.8)
Muscle spasticity	3 (4.8)	2 (6.2)	2 (4.5)	7 (5.0)
Musculoskeletal stiffness	3 (4.8)	1 (3.1)	4 (9.1)	8 (5.8)
Neck pain	3 (4.8)	3 (9.4)	5 (11.4)	11 (7.9)

Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Oropharyngeal pain	3 (4.8)	0	5 (11.4)	8 (5.8)
Peripheral swelling	3 (4.8)	2 (6.2)	5 (11.4)	10 (7.2)
Pneumonia	3 (4.8)	4 (12.5)	4 (9.1)	11 (7.9)
Urinary tract infection	3 (4.8)	4 (12.5)	9 (20.5)	16 (11.5)
Abdominal distension	2 (3.2)	2 (6.2)	1 (2.3)	5 (3.6)
Abdominal pain upper	2 (3.2)	2 (6.2)	3 (6.8)	7 (5.0)
Balance disorder	2 (3.2)	0	3 (6.8)	5 (3.6)
Blood urine present	2 (3.2)	0	3 (6.8)	5 (3.6)
Depression	2 (3.2)	0	5 (11.4)	7 (5.0)
Gastroenteritis viral	2 (3.2)	0	4 (9.1)	6 (4.3)
Hepatic steatosis	2 (3.2)	2 (6.2)	0	4 (2.9)
Immunization reaction	2 (3.2)	1 (3.1)	4 (9.1)	7 (5.0)
Migraine	2 (3.2)	1 (3.1)	4 (9.1)	7 (5.0)
Muscle contractions involuntary	2 (3.2)	2 (6.2)	2 (4.5)	6 (4.3)
Muscle strain	2 (3.2)	1 (3.1)	4 (9.1)	7 (5.0)
Musculoskeletal chest pain	2 (3.2)	2 (6.2)	2 (4.5)	6 (4.3)
Musculoskeletal pain	2 (3.2)	1 (3.1)	4 (9.1)	7 (5.0)
Nasal congestion	2 (3.2)	0	4 (9.1)	6 (4.3)
Oral candidiasis	2 (3.2)	2 (6.2)	0	4 (2.9)
Pollakiuria	2 (3.2)	1 (3.1)	5 (11.4)	8 (5.8)
Post procedural contusion	2 (3.2)	3 (9.4)	1 (2.3)	6 (4.3)
Sinusitis	2 (3.2)	2 (6.2)	2 (4.5)	6 (4.3)
Skin abrasion	2 (3.2)	1 (3.1)	4 (9.1)	7 (5.0)
Vertigo	2 (3.2)	0	4 (9.1)	6 (4.3)
Abdominal discomfort	1 (1.6)	0	4 (9.1)	5 (3.6)
Blood glucose increased	1 (1.6)	1 (3.1)	5 (11.4)	7 (5.0)
Cystitis	1 (1.6)	2 (6.2)	0	3 (2.2)
Decreased appetite	1 (1.6)	3 (9.4)	0	4 (2.9)
Diarrhea	1 (1.6)	9 (28.1)	6 (13.6)	16 (11.5)
Hypertension	1 (1.6)	0	5 (11.4)	6 (4.3)
Hypoesthesia	1 (1.6)	4 (12.5)	5 (11.4)	10 (7.2)
Lower respiratory tract infection	1 (1.6)	0	3 (6.8)	4 (2.9)
Oedema peripheral	1 (1.6)	1 (3.1)	6 (13.6)	8 (5.8)
Papilledema	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Post procedural swelling	1 (1.6)	0	3 (6.8)	4 (2.9)
Pulmonary embolism	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Rhinitis	1 (1.6)	2 (6.2)	0	3 (2.2)
Sensory disturbance	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Skin laceration	1 (1.6)	1 (3.1)	3 (6.8)	5 (3.6)
Tooth infection	1 (1.6)	0	3 (6.8)	4 (2.9)
Toothache	1 (1.6)	0	4 (9.1)	5 (3.6)
Tremor	1 (1.6)	2 (6.2)	4 (9.1)	7 (5.0)
Viral infection	1 (1.6)	0	4 (9.1)	5 (3.6)
Vomiting	1 (1.6)	1 (3.1)	6 (13.6)	8 (5.8)
Blister	0	1 (3.1)	3 (6.8)	4 (2.9)
Bronchitis	0	1 (3.1)	5 (11.4)	6 (4.3)
Cellulitis	0	0	4 (9.1)	4 (2.9)
Diplopia	0	2 (6.2)	0	2 (1.4)
Dysuria	0	2 (6.2)	1 (2.3)	3 (2.2)

Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Hematuria	0	0	3 (6.8)	3 (2.2)
Head injury	0	2 (6.2)	1 (2.3)	3 (2.2)
Influenza	0	1 (3.1)	3 (6.8)	4 (2.9)
Micturition urgency	0	0	3 (6.8)	3 (2.2)
Oral herpes	0	0	3 (6.8)	3 (2.2)
Post procedural complication	0	0	3 (6.8)	3 (2.2)
Radicular pain	0	1 (3.1)	3 (6.8)	4 (2.9)
Traumatic lumbar puncture	0	0	3 (6.8)	3 (2.2)
Urticaria	0	2 (6.2)	0	2 (1.4)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; CSF, cerebrospinal fluid; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; n, number of patients with adverse event

Table 48 shows TEAEs grouped using the FDA Medical Query (Narrow). The SOCs with proportions of at least 10% were gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, respiratory disorders, skin disorders, and vascular disorders.

Table 48. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Occurring in at Least 5% of Subjects in Any Group, Safety Population, Study 233AS102

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Blood and lymphatic system disorders (SOC)				
Anemia	2 (3.2)	2 (6.2)	1 (2.3)	5 (3.6)
Thrombosis	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Thrombosis venous	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)
Cardiac disorders (SOC)				
Arrhythmia	2 (3.2)	3 (9.4)	1 (2.3)	6 (4.3)
Systemic hypertension	2 (3.2)	1 (3.1)	5 (11.4)	8 (5.8)
Ear and labyrinth disorders (SOC)				
Vertigo	2 (3.2)	0	4 (9.1)	6 (4.3)

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Endocrine disorders (SOC)				
Hyperglycemia	2 (3.2)	1 (3.1)	5 (11.4)	8 (5.8)
Gastrointestinal disorders (SOC)				
Nausea	11 (17.5)	4 (12.5)	15 (34.1)	30 (21.6)
Constipation	9 (14.3)	7 (21.9)	7 (15.9)	23 (16.5)
Abdominal pain	7 (11.1)	3 (9.4)	10 (22.7)	20 (14.4)
Dyspepsia	3 (4.8)	3 (9.4)	5 (11.4)	11 (7.9)
Diarrhea	2 (3.2)	10 (31.2)	6 (13.6)	18 (12.9)
Vomiting	1 (1.6)	1 (3.1)	6 (13.6)	8 (5.8)
General disorders and administration site conditions (SOC)				
Fall	17 (27.0)	17 (53.1)	26 (59.1)	60 (43.2)
Dizziness	12 (19.0)	6 (18.8)	19 (43.2)	37 (26.6)
Fatigue	12 (19.0)	9 (28.1)	13 (29.5)	34 (24.5)
Pyrexia	7 (11.1)	7 (21.9)	9 (20.5)	23 (16.5)
Local administration reaction	5 (7.9)	1 (3.1)	6 (13.6)	12 (8.6)
Peripheral edema	3 (4.8)	3 (9.4)	9 (20.5)	15 (10.8)
Decreased appetite	1 (1.6)	3 (9.4)	0	4 (2.9)
Hepatobiliary disorders (SOC)				
Hepatic injury	3 (4.8)	2 (6.2)	2 (4.5)	7 (5.0)
Infections and infestations (SOC)				
Viral infection	19 (30.2)	8 (25.0)	18 (40.9)	45 (32.4)
Bacterial infection	11 (17.5)	9 (28.1)	16 (36.4)	36 (25.9)
Nasopharyngitis	7 (11.1)	6 (18.8)	14 (31.8)	27 (19.4)
Pneumonia	7 (11.1)	7 (21.9)	6 (13.6)	20 (14.4)
Fungal infection	5 (7.9)	2 (6.2)	6 (13.6)	13 (9.4)
Purulent material	1 (1.6)	2 (6.2)	3 (6.8)	6 (4.3)
Metabolism and nutrition disorders (SOC)				
Lipid disorder	2 (3.2)	2 (6.2)	2 (4.5)	6 (4.3)
Musculoskeletal and connective tissue disorders (SOC)				
Back pain	21 (33.3)	10 (31.2)	23 (52.3)	54 (38.8)
Arthralgia	15 (23.8)	9 (28.1)	15 (34.1)	39 (28.1)
Myalgia	14 (22.2)	3 (9.4)	9 (20.5)	26 (18.7)
Fracture	3 (4.8)	1 (3.1)	5 (11.4)	9 (6.5)
Tendinopathy	1 (1.6)	0	3 (6.8)	4 (2.9)
Nervous system disorders (SOC)				
Headache	38 (60.3)	19 (59.4)	32 (72.7)	89 (64.0)
Paresthesia	7 (11.1)	4 (12.5)	9 (20.5)	20 (14.4)
Tremor	1 (1.6)	3 (9.4)	5 (11.4)	9 (6.5)
Psychiatric disorders (SOC)				
Anxiety	5 (7.9)	1 (3.1)	6 (13.6)	12 (8.6)
Depression	5 (7.9)	1 (3.1)	5 (11.4)	11 (7.9)
Insomnia	3 (4.8)	2 (6.2)	3 (6.8)	8 (5.8)
Renal and urinary disorders (SOC)				
Renal and urinary tract infection	4 (6.3)	6 (18.8)	9 (20.5)	19 (13.7)
Reproductive system and breast disorders (SOC)				
Abnormal uterine bleeding	0	0	3 (6.8)	3 (2.2)

System Organ Class FMQ (Narrow)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)				
Respiratory failure	13 (20.6)	7 (21.9)	6 (13.6)	26 (18.7)
Dyspnea	10 (15.9)	4 (12.5)	7 (15.9)	21 (15.1)
Cough	4 (6.3)	2 (6.2)	5 (11.4)	11 (7.9)
Skin and subcutaneous tissue disorders (SOC)				
Rash	7 (11.1)	5 (15.6)	7 (15.9)	19 (13.7)
Pruritus	3 (4.8)	2 (6.2)	1 (2.3)	6 (4.3)
Urticaria	0	2 (6.2)	0	2 (1.4)
Vascular disorders (SOC)				
Hemorrhage	14 (22.2)	10 (31.2)	19 (43.2)	43 (30.9)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in the open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was up to 360 weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.2.6. Laboratory Findings, Study 102

Results of the FDA analysis of laboratory value abnormalities for the Study 102 open-label safety population are shown in Table 49. Overall, there were no clinically significant patterns or trends observed in abnormalities in blood chemistry. There were cases of low bicarbonate levels (56%) which could suggest metabolic acidosis. Respiratory insufficiency, common in ALS, can lead to metabolic acidosis. Analysis of renal function found no clinically significant difference between the tofersen and placebo groups, as discussed in Section 7.7.4. Hepatic assessments are discussed in Section 7.6.1.7.

Table 49. Patients With One or More Chemistry Analyte Value With Elevated or Low Values Meeting Specified Levels, Safety Population, Study 233AS102

Laboratory Parameter	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
Sodium, low (mEq/L)				
Level 1 (<132)	2/62 (3.2)	0/32 (0)	4/44 (9.1)	6/138 (4.3)
Level 2 (<130)	2/62 (3.2)	0/32 (0)	2/44 (4.5)	4/138 (2.9)
Level 3 (<125)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Sodium, high (mEq/L)				
Level 1 (>150)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 2 (>155)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (>160)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Potassium, low (mEq/L)				
Level 1 (<3.6)	4/62 (6.5)	7/32 (21.9)	6/44 (13.6)	17/138 (12.3)
Level 2 (<3.4)	1/62 (1.6)	2/32 (6.2)	1/44 (2.3)	4/138 (2.9)
Level 3 (<3)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Potassium, high (mEq/L)				
Level 1 (>5.5)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 2 (>6)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (>6.5)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Chloride, low (mEq/L)				
Level 1 (<95)	8/62 (12.9)	3/32 (9.4)	8/44 (18.2)	19/138 (13.8)
Level 2 (<88)	1/62 (1.6)	0/32 (0)	1/44 (2.3)	2/138 (1.4)
Level 3 (<80)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Chloride, high (mEq/L)				
Level 1 (>108)	4/62 (6.5)	1/32 (3.1)	4/44 (9.1)	9/138 (6.5)
Level 2 (>112)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (>115)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Bicarbonate, low (mEq/L)				
Level 1 (<20)	19/62 (30.6)	12/32 (37.5)	23/44 (52.3)	54/138 (39.1)
Level 2 (<18)	5/62 (8.1)	6/32 (18.8)	10/44 (22.7)	21/138 (15.2)
Level 3 (<15)	0/62 (0)	1/32 (3.1)	1/44 (2.3)	2/138 (1.4)
Bicarbonate, high (mEq/L)				
Level 3 (>30)	4/62 (6.5)	4/32 (12.5)	2/44 (4.5)	10/138 (7.2)
Glucose, low (mg/dL)				
Level 1 (<70)	9/62 (14.5)	2/32 (6.2)	12/44 (27.3)	23/138 (16.7)
Level 2 (<54)	1/62 (1.6)	0/32 (0)	1/44 (2.3)	2/138 (1.4)
Level 3 (<40)	1/62 (1.6)	0/32 (0)	0/44 (0)	1/138 (0.7)
Glucose, random, high (mg/dL)				
Level 2 (≥200)	3/62 (4.8)	5/32 (15.6)	4/44 (9.1)	12/138 (8.7)
Level 3 (>250)	2/62 (3.2)	4/32 (12.5)	3/44 (6.8)	9/138 (6.5)
Calcium, low (mg/dL)				
Level 1 (<8.4)	2/62 (3.2)	0/32 (0)	0/44 (0)	2/138 (1.4)
Level 2 (<8)	2/62 (3.2)	0/32 (0)	0/44 (0)	2/138 (1.4)
Level 3 (<7.5)	1/62 (1.6)	0/32 (0)	0/44 (0)	1/138 (0.7)
Calcium, high (mg/dL)				
Level 1 (>10.5)	4/62 (6.5)	3/32 (9.4)	6/44 (13.6)	13/138 (9.4)
Level 2 (>11)	0/62 (0)	1/32 (3.1)	0/44 (0)	1/138 (0.7)
Level 3 (>12)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)

Laboratory Parameter	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
Phosphate, low (mg/dL)				
Level 1 (<2.5)	5/62 (8.1)	3/32 (9.4)	7/44 (15.9)	15/138 (10.9)
Level 2 (<2)	1/62 (1.6)	0/32 (0)	2/44 (4.5)	3/138 (2.2)
Level 3 (<1.4)	1/62 (1.6)	0/32 (0)	0/44 (0)	1/138 (0.7)
Protein, total, low (g/dL)				
Level 1 (<6)	6/62 (9.7)	2/32 (6.2)	6/44 (13.6)	14/138 (10.1)
Level 2 (<5.4)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (<5)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Albumin, low (g/dL)				
Level 1 (<3.1)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 2 (<2.5)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (<2)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Blood urea nitrogen, high (mg/dL)				
Level 1 (>23)	12/62 (19.4)	11/32 (34.4)	8/44 (18.2)	31/138 (22.5)
Level 2 (>27)	5/62 (8.1)	6/32 (18.8)	2/44 (4.5)	13/138 (9.4)
Level 3 (>31)	1/62 (1.6)	2/32 (6.2)	0/44 (0)	3/138 (2.2)

Source: ad b.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was up to 360 weeks.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study 102

Results of the FDA analysis of liver laboratory abnormalities for the open-label Study 102 are shown in Table 50 and Table 51. There were no clinically significant patterns or trends observed in abnormalities in liver chemistry.

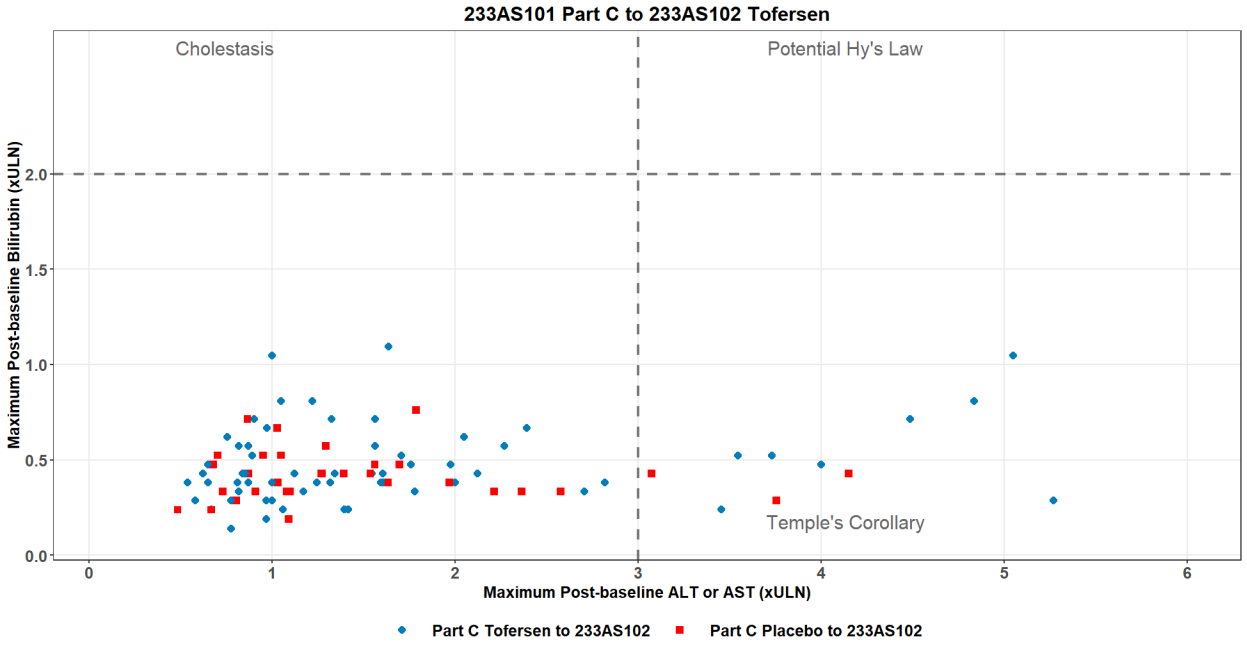
Table 50. Patients With One or More Liver Biochemistry Analyte Value Exceeding Specified Levels, Safety Population, Study 233AS102

Laboratory Parameter	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
Alkaline phosphatase, high (U/L)				
Level 1 (>1.5× ULN)	2/62 (3.2)	1/32 (3.1)	0/44 (0)	3/138 (2.2)
Level 2 (>2× ULN)	1/62 (1.6)	0/32 (0)	0/44 (0)	1/138 (0.7)
Level 3 (>3× ULN)	1/62 (1.6)	0/32 (0)	0/44 (0)	1/138 (0.7)
Alanine aminotransferase, high (U/L)				
Level 1 (>3× ULN)	7/62 (11.3)	3/32 (9.4)	4/44 (9.1)	14/138 (10.1)
Level 2 (>5× ULN)	2/62 (3.2)	0/32 (0)	3/44 (6.8)	5/138 (3.6)
Level 3 (>10× ULN)	0/62 (0)	0/32 (0)	1/44 (2.3)	1/138 (0.7)
Aspartate aminotransferase, high (U/L)				
Level 1 (>3× ULN)	3/62 (4.8)	1/32 (3.1)	3/44 (6.8)	7/138 (5.1)
Level 2 (>5× ULN)	0/62 (0)	0/32 (0)	2/44 (4.5)	2/138 (1.4)
Level 3 (>10× ULN)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Bilirubin, total, high (mg/dL)				
Level 1 (>1.5× ULN)	0/62 (0)	0/32 (0)	1/44 (2.3)	1/138 (0.7)
Level 2 (>2× ULN)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Level 3 (>3× ULN)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)

Source: ad b.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was up to 360 weeks.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot..” and “Cholestatic Drug-Induced Liver Injury Screening Plot..” and the tables “Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..” and “Patients in Each Quadrant for Cholestatic DILI Screening Plot…”
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Figure 22 and Table 51 show a screening assessment for potential cases of serious DILI. There were no Hy’s law cases.

Figure 22. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 233AS102



Source: ad b.xpt; software: R
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 51. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Study 233AS102

Quadrant	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
Potential Hy's law (right upper)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Cholestasis (left upper)	0/62 (0)	0/32 (0)	0/44 (0)	0/138 (0)
Temple's corollary (right lower)	8/62 (12.9)	3/32 (9.4)	4/44 (9.1)	15/138 (10.9)
Total	8/62 (12.9)	3/32 (9.4)	4/44 (9.1)	15/138 (10.9)

Source: ad b.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data

7.6.2.8. Vital Signs Analyses, Study 102

There were no clinically significant patterns or trends observed in abnormalities in vital signs (including diastolic and systolic blood pressure, pulse rate, respiratory rate, weight, and temperature) in Study 102.

Table 52. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Study 233AS102

Systolic Blood Pressure (mm Hg)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
<90	0/63 (0)	0/32 (0)	0/44 (0)	0/139 (0)
≥90	63/63 (100)	32/32 (100)	44/44 (100)	139/139 (100)
≥120	61/63 (96.8)	32/32 (100)	43/44 (97.7)	136/139 (97.8)
≥140	36/63 (57.1)	19/32 (59.4)	36/44 (81.8)	91/139 (65.5)
≥160	14/63 (22.2)	2/32 (6.2)	12/44 (27.3)	28/139 (20.1)
≥180	2/63 (3.2)	0/32 (0)	2/44 (4.5)	4/139 (2.9)

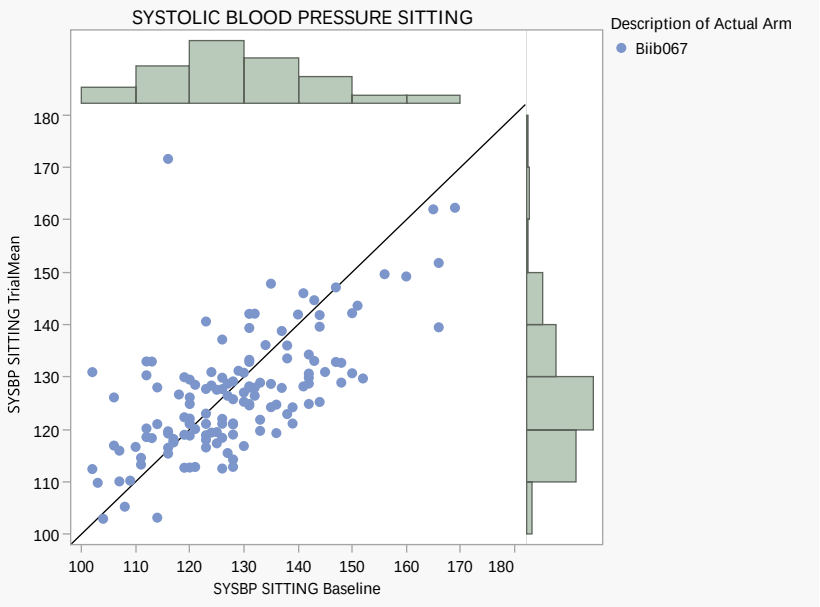
Source: advs.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 53**. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Study 233AS102**

Diastolic Blood Pressure (mm Hg)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_w (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_w (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_w (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_w (%)
<60	0/63 (0)	0/32 (0)	0/44 (0)	0/139 (0)
≥60	63/63 (100)	32/32 (100)	44/44 (100)	139/139 (100)
≥90	40/63 (63.5)	21/32 (65.6)	34/44 (77.3)	95/139 (68.3)
≥110	2/63 (3.2)	2/32 (6.2)	4/44 (9.1)	8/139 (5.8)
≥120	0/63 (0)	0/32 (0)	0/44 (0)	0/139 (0)

Source: advs.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

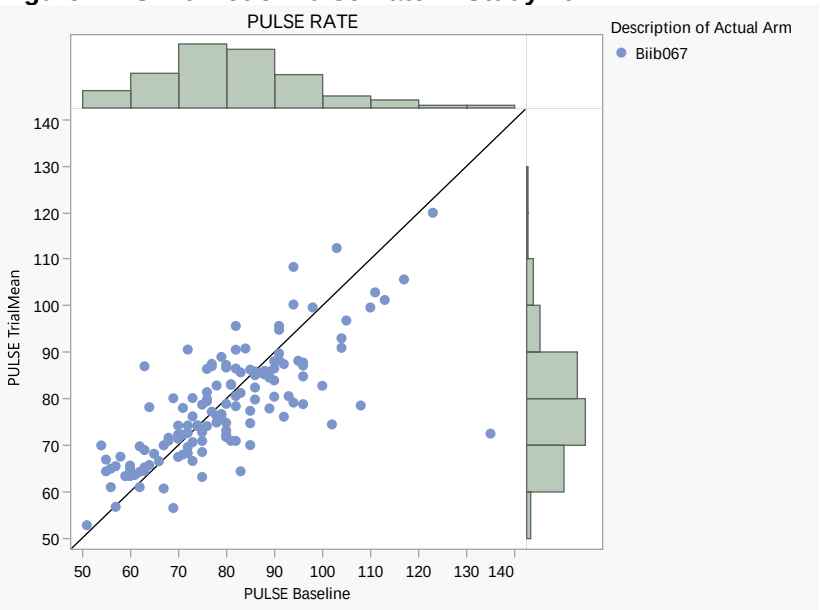
Figure 23. Shift Plot of Systolic Blood Pressure in Study 102



Source: FDA analysis
Abbreviation: SYSBP, systolic blood pressure

The outlier (subject (b) (6)) with a baseline systolic blood pressure of 116 and a study mean of 172 experienced sudden death on study Day 378. This subject had a medical history at the time of enrollment in Study 233AS102 that included hypertension, hyperlipidemia, coronary artery disease, stage III renal disease, and myocardial infarction. These comorbidities likely contributed to the worsening hypertension during the study and the sudden death.

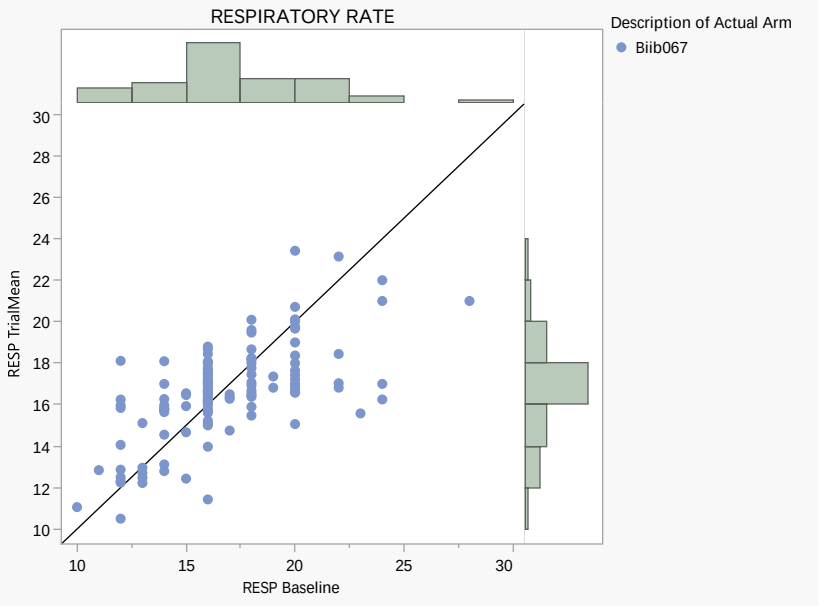
Figure 24. Shift Plot of Pulse Rate in Study 102



Source: FDA analysis

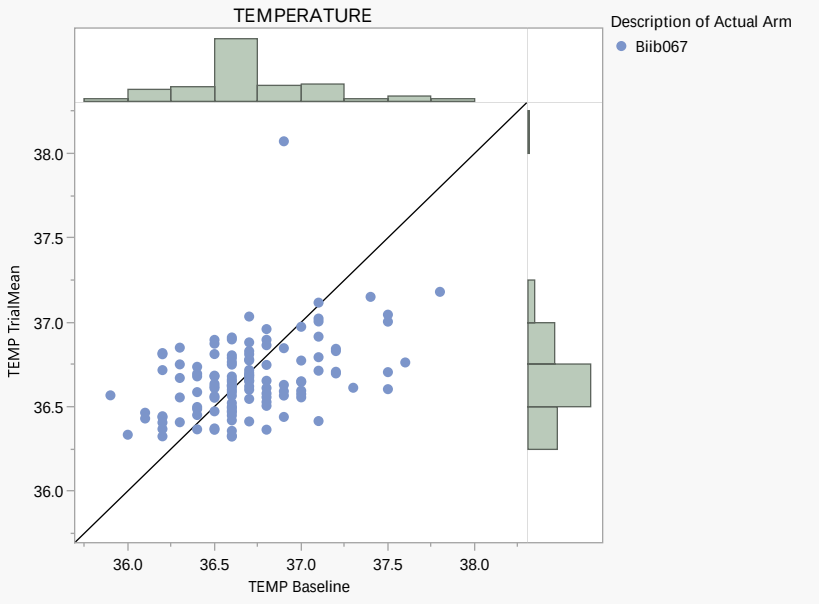
The outlier (subject (b) (6)) in the bottom right of Figure 24 with an elevated baseline pulse rate of approximately 135 had AEs at baseline of agitation, constipation, and sleep disorder. Agitation could have resulted in the elevated baseline pulse rate.

Figure 25. Shift Plot of Respiratory Rate in Study 102



Source: FDA analysis
Abbreviation: RESP, respiratory

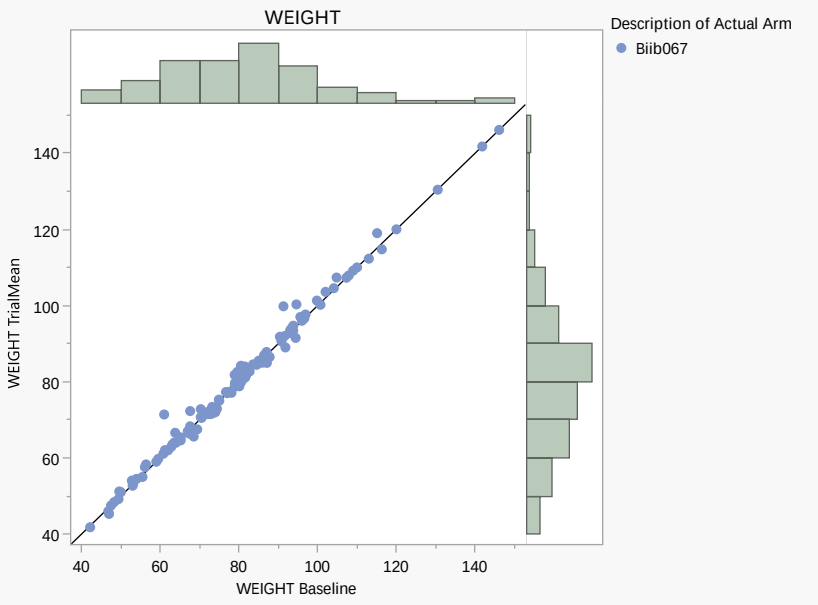
Figure 26. Shift Plot of Temperature in Study 102



Source: FDA analysis
Abbreviation: TEMP, temperature

The outlier (subject (b) (6)) with a baseline temperature of approximately 37° and a mean above 38° had four temperature measurements in Fahrenheit that were erroneously labeled as Celsius, incorrectly driving up the mean.

Figure 27. Shift Plot of Weight in Study 102



Source: FDA analysis

7.6.2.9. Subgroup Analyses, Study 102

Results of the FDA analysis of SAEs and AEs by demographic subgroup for the OLE Study 102 are shown in Table 54 and Table 55.

Table 54. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Study 233AS102

Characteristic	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_s (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_s (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_s (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_s (%)
Sex, n (%)				
Female	8/24 (33.3)	3/15 (20.0)	10/19 (52.6)	21/58 (36.2)
Male	13/39 (33.3)	8/17 (47.1)	9/25 (36.0)	30/81 (37.0)
Age group, years, n (%)				
18 to <35	3/7 (42.9)	0/1 (0)	1/5 (20.0)	4/13 (30.8)
35 to <50	12/29 (41.4)	4/12 (33.3)	6/16 (37.5)	22/57 (38.6)
50 to <65	3/20 (15.0)	4/13 (30.8)	10/19 (52.6)	17/52 (32.7)
≥65	3/7 (42.9)	3/6 (50.0)	2/4 (50.0)	8/17 (47.1)
Age group ≥75, years, n (%)				
≥75	0/0 (NA)	0/0 (NA)	0/1 (0)	0/1 (0)

Characteristic	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_s (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_s (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_s (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_s (%)
Race, n (%)				
Asian	1/4 (25.0)	0/4 (0)	1/1 (100)	2/9 (22.2)
Black or African American	0/1 (0)	0/0 (NA)	0/0 (NA)	0/1 (0)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/0 (NA)	0/1 (0)	0/1 (0)
Not reported	5/20 (25.0)	1/6 (16.7)	9/18 (50.0)	15/44 (34.1)
Other	1/1 (100)	0/0 (NA)	1/1 (100)	2/2 (100)
White	14/37 (37.8)	10/22 (45.5)	8/23 (34.8)	32/82 (39.0)
Ethnicity, n (%)				
Hispanic or Latino	1/3 (33.3)	0/1 (0)	0/0 (NA)	1/4 (25.0)
Not Hispanic or Latino	15/40 (37.5)	10/25 (40.0)	10/26 (38.5)	35/91 (38.5)
Not reported	5/20 (25.0)	1/6 (16.7)	9/18 (50.0)	15/44 (34.1)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 55. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study 233AS102

Characteristic	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_s (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_s (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_s (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_s (%)
Sex, n (%)				
Female	24/24 (100)	15/15 (100)	19/19 (100)	58/58 (100)
Male	37/39 (94.9)	16/17 (94.1)	24/25 (96.0)	77/81 (95.1)
Age group, years, n (%)				
18 to <35	7/7 (100)	1/1 (100)	5/5 (100)	13/13 (100)
35 to <50	29/29 (100)	12/12 (100)	15/16 (93.8)	56/57 (98.2)
50 to <65	18/20 (90.0)	13/13 (100)	19/19 (100)	50/52 (96.2)
≥65	7/7 (100)	5/6 (83.3)	4/4 (100)	16/17 (94.1)
Age group ≥75, years, n (%)				
≥75	0/0 (NA)	0/0 (NA)	1/1 (100)	1/1 (100)

Characteristic	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n/N_s (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n/N_s (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n/N_s (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n/N_s (%)
Race, n (%)				
Asian	4/4 (100)	4/4 (100)	1/1 (100)	9/9 (100)
Black or African American	1/1 (100)	0/0 (NA)	0/0 (NA)	1/1 (100)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/0 (NA)	1/1 (100)	1/1 (100)
Not reported	18/20 (90.0)	6/6 (100)	18/18 (100)	42/44 (95.5)
Other	1/1 (100)	0/0 (NA)	1/1 (100)	2/2 (100)
White	37/37 (100)	21/22 (95.5)	22/23 (95.7)	80/82 (97.6)
Ethnicity, n (%)				
Hispanic or Latino	3/3 (100)	1/1 (100)	0/0 (NA)	4/4 (100)
Not Hispanic or Latino	40/40 (100)	24/25 (96.0)	25/26 (96.2)	89/91 (97.8)
Not reported	18/20 (90.0)	6/6 (100)	18/18 (100)	42/44 (95.5)

Source: adae.xpt; software: R
"233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen" refers to the patients previously treated with tofersen 100 mg in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part C Placebo to 233AS102 Tofersen" refers to the patients who received placebo in Study 233AS101 Part C prior to receiving tofersen in open-label Study 233AS102.
"233AS101 Part A/B All Doses to 233AS102 Tofersen" refers to the patients previously treated with tofersen 10, 20, 40, 60, or 100 mg, or placebo in Studies 233AS101 Part A or B prior to receiving tofersen in open-label Study 233AS102.
"Total 233AS101 Part A, B, and C to 233AS102 Tofersen" refers to all patients who received tofersen in open-label Study 233AS102 after completing Part A, B, or C of Study 233AS101.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

There were no clinically significant differences in the proportions of subjects with AEs or with SAEs as a function of age or sex subgroup in Study 102. The proportions of SAEs were highest in the other (100%), white (39%), not reported (34%), and Asian (22%) race groups, but the differences in subgroup sizes and the small numbers of subjects in the black (n=1), Native Hawaiian (n=1), and other (n=2) groups make this comparison uninterpretable.

7.6.2.10. Exposure-Adjusted Analyses, Study 102

Results of the FDA analysis of the exposure-adjusted incidence rate of SAEs and the key safety issues for the open-label extension study 102 are shown in Table 56. The analysis focused on myelitis, radiculitis, aseptic meningitis, CSF protein and WBC increased, papilledema, renal and urinary disorders, respiratory failure, hemorrhage, and hepatobiliary disorders.

Rates greater than 5 per 100 patient-years were observed in the total population for contusion, respiratory failure, and CSF protein and WBC count increased.

Table 56. Exposure-Adjusted Analysis by System Organ Class and Preferred Term, Safety Population, Study 233AS102

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen PY=107.1 N=63 n (EAIR)	233AS101 Part C Placebo to 233AS102 Tofersen PY=39.1 N=32 n (EAIR)	233AS101 Part A/B All Doses to 233AS102 Tofersen PY=134.4 N=44 n (EAIR)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen PY=280.6 N=139 n (EAIR)
Hepatobiliary disorders (SOC)	2 (3.2)	2 (6.2)	2 (4.5)	6 (4.3)	2 (1.9)	2 (5.2)	2 (1.5)	6 (2.2)
Cholecystitis	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Cholelithiasis	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Hepatic function abnormal	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Hepatic steatosis	2 (3.2)	2 (6.2)	0	4 (2.9)	2 (1.9)	2 (5.2)	0	4 (1.4)
Hypertransaminasemia	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Renal and urinary disorders (SOC)	9 (14.3)	4 (12.5)	15 (34.1)	28 (20.1)	9 (9.1)	4 (10.9)	15 (13.8)	28 (11.5)
Acute kidney injury	2 (3.2)	1 (3.1)	0	3 (2.2)	2 (1.9)	1 (2.6)	0	3 (1.1)
Bladder dysfunction	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Bladder spasm	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Calculus urinary	1 (1.6)	0	1 (2.3)	2 (1.4)	1 (0.9)	0	1 (0.8)	2 (0.7)
Chromaturia	1 (1.6)	0	0	1 (0.7)	1 (1.0)	0	0	1 (0.4)
Dysuria	0	2 (6.2)	1 (2.3)	3 (2.2)	0	2 (5.4)	1 (0.8)	3 (1.1)
Hematuria	0	0	3 (6.8)	3 (2.2)	0	0	3 (2.3)	3 (1.1)
Micturition urgency	0	0	3 (6.8)	3 (2.2)	0	0	3 (2.3)	3 (1.1)
Nephrolithiasis	2 (3.2)	1 (3.1)	2 (4.5)	5 (3.6)	2 (1.9)	1 (2.6)	2 (1.5)	5 (1.8)
Neurogenic bladder	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Pollakiuria	2 (3.2)	1 (3.1)	5 (11.4)	8 (5.8)	2 (1.9)	1 (2.6)	5 (3.9)	8 (2.9)
Renal cyst	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Urinary hesitation	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Urinary incontinence	0	0	2 (4.5)	2 (1.4)	0	0	2 (1.5)	2 (0.7)
Urinary retention	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Abbreviations: EAIR, exposure-adjusted incidence rate; N, number of patients in treatment arm; n, number of patients with adverse event; PY, patient years; SOC, system organ class

Table 57. Exposure-Adjusted Analysis by FDA Medical Query (Narrow) and Preferred Term, Safety Population, Study 233AS102

FMQ (Narrow) Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen PY=107.1 N=63 n (EAIR)	233AS101 Part C Placebo to 233AS102 Tofersen PY=39.1 N=32 n (EAIR)	233AS101 Part A/B All Doses to 233AS102 Tofersen PY=134.4 N=44 n (EAIR)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen PY=280.6 N=139 n (EAIR)
Hemorrhage (FMQ)	14 (22.2)	10 (31.2)	19 (43.2)	43 (30.9)	14 (14.9)	10 (32.7)	19 (19.6)	43 (19.4)
Blood loss anemia	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Blood urine present	2 (3.2)	0	3 (6.8)	5 (3.6)	2 (1.9)	0	3 (2.3)	5 (1.8)
Bone contusion	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Cerebral hemorrhage	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Contusion	6 (9.5)	6 (18.8)	12 (27.3)	24 (17.3)	6 (5.8)	6 (18.7)	12 (10.9)	24 (9.8)
Epistaxis	0	0	2 (4.5)	2 (1.4)	0	0	2 (1.5)	2 (0.7)
Eye contusion	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Hematoma	0	0	2 (4.5)	2 (1.4)	0	0	2 (1.5)	2 (0.7)
Hematuria	0	0	3 (6.8)	3 (2.2)	0	0	3 (2.3)	3 (1.1)
Infusion site bruising	1 (1.6)	0	1 (2.3)	2 (1.4)	1 (0.9)	0	1 (0.7)	2 (0.7)
Infusion site hematoma	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Injection site bruising	1 (1.6)	0	0	1 (0.7)	1 (1.0)	0	0	1 (0.4)
Petechiae	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Post procedural contusion	2 (3.2)	3 (9.4)	1 (2.3)	6 (4.3)	2 (1.9)	3 (7.9)	1 (0.7)	6 (2.2)
Post procedural hematuria	0	1 (3.1)	0	1 (0.7)	0	1 (2.6)	0	1 (0.4)
Post procedural hemorrhage	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Vaginal hemorrhage	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Vessel puncture site hematoma	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Respiratory failure (FMQ)	13 (20.6)	7 (21.9)	6 (13.6)	26 (18.7)	13 (12.6)	7 (18.4)	6 (4.8)	26 (9.7)
Acute respiratory distress syndrome	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Acute respiratory failure	4 (6.3)	1 (3.1)	0	5 (3.6)	4 (3.8)	1 (2.6)	0	5 (1.8)
Cardio-respiratory arrest	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Chronic respiratory failure	1 (1.6)	1 (3.1)	0	2 (1.4)	1 (0.9)	1 (2.6)	0	2 (0.7)
Hypercapnia	2 (3.2)	0	0	2 (1.4)	2 (1.9)	0	0	2 (0.7)
Hypopnea	0	1 (3.1)	0	1 (0.7)	0	1 (2.6)	0	1 (0.4)
Hypoxia	1 (1.6)	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.4)
Oxygen saturation decreased	1 (1.6)	1 (3.1)	0	2 (1.4)	1 (0.9)	1 (2.6)	0	2 (0.7)
Respiratory acidosis	1 (1.6)	1 (3.1)	0	2 (1.4)	1 (0.9)	1 (2.6)	0	2 (0.7)

FMQ (Narrow) Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen PY=107.1 N=63 n (EAIR)	233AS101 Part C Placebo to 233AS102 Tofersen PY=39.1 N=32 n (EAIR)	233AS101 Part A/B All Doses to 233AS102 Tofersen PY=134.4 N=44 n (EAIR)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen PY=280.6 N=139 n (EAIR)
Respiratory arrest	2 (3.2)	0	0	2 (1.4)	2 (1.9)	0	0	2 (0.7)
Respiratory failure	6 (9.5)	5 (15.6)	6 (13.6)	17 (12.2)	6 (5.6)	5 (12.7)	6 (4.7)	17 (6.2)
Sleep apnea syndrome	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: EAIR, exposure-adjusted incidence rate; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; PY, patient years; SOC, system organ class

Table 58. Exposure-Adjusted Analysis by Preferred Term, Safety Population, Study 233AS102

Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen PY=107.1 N=63 n (EAIR)	233AS101 Part C Placebo to 233AS102 Tofersen PY=39.1 N=32 n (EAIR)	233AS101 Part A/B All Doses to 233AS102 Tofersen PY=134.4 N=44 n (EAIR)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen PY=280.6 N=139 n (EAIR)
CSF protein increased	14 (22.2)	5 (15.6)	15 (34.1)	34 (24.5)	14 (17.0)	5 (15.4)	15 (15.7)	34 (16.2)
CSF white blood cell count increased	12 (19.0)	2 (6.2)	9 (20.5)	23 (16.5)	12 (13.7)	2 (5.4)	9 (8.2)	23 (9.8)
Lumbar radiculopathy	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.7)	1 (0.4)
Meningitis aseptic	0	1 (3.1)	1 (2.3)	2 (1.4)	0	1 (2.6)	1 (0.8)	2 (0.7)
Meningitis chemical	1 (1.6)	0	1 (2.3)	2 (1.4)	1 (0.9)	0	1 (0.7)	2 (0.7)
Myelitis	0	0	1 (2.3)	1 (0.7)	0	0	1 (0.8)	1 (0.4)
Papilledema	1 (1.6)	2 (6.2)	1 (2.3)	4 (2.9)	1 (0.9)	2 (5.3)	1 (0.8)	4 (1.4)

Source: adae.xpt; software: R
Patient-years represents the total time at risk among the subjects in the analysis population, which is calculated as the time from first dose to event +1 or from time from first dose to last dose +1 if the patient did not experience the event.
Exposure-adjusted incidence rate is calculated as number of subjects divided by the total time at risk and is displayed as EAIR per 100 patient-years.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Coded as MedDRA preferred terms.
Abbreviations: CSF, cerebrospinal fluid; EAIR, exposure-adjusted incidence rate; MedDRA, medical dictionary of regulatory activities; N, number of patients in treatment arm; n, number of patients with adverse event; PY, patient years

7.6.3. Safety Results, Pooled Analyses, Studies 101 and 102

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of adverse events for the pooled safety population are shown in Table 59. In the pooled population of all subjects who received tofersen 100mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102, the proportion of subjects experiencing AEs was 99% and the proportion experiencing SAEs was 40%. Dose interruption of tofersen due to AEs occurred in 15% of subjects.

Table 59. Overview of Adverse Events, Safety Population, Studies 233AS101 and 233AS102

Event Category	Tofersen 100 mg N=147 n (%)
SAE	59 (40.1)
SAEs with fatal outcome	19 (12.9)
Life-threatening SAEs	6 (4.1)
AE leading to permanent discontinuation of study drug	26 (17.7)
AE leading to dose modification of study drug	22 (15.0)
AE leading to interruption of study drug	22 (15.0)
AE leading to reduction of study drug	0
AE leading to dose delay of study drug	0
Other	0
Any AE	145 (98.6)
Severe and worse	58 (39.5)
Moderate	67 (45.6)
Mild	20 (13.6)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Duration is 3.6 to 212.4 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.3.2. Deaths, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of deaths for the pooled safety population are shown in Table 60 and Table 61. In the pooled population of all subjects who received tofersen 100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102, the proportion of deaths was 13%.

Table 60. Deaths, Safety Population, Studies 233AS101 and 233AS102

Preferred Term	Tofersen 100 mg N=147 n (%)
Any AE leading to death	19 (12.9)
Respiratory failure	11 (7.5)
Amyotrophic lateral sclerosis	2 (1.4)
Respiratory arrest	2 (1.4)
Cardiac arrest	1 (0.7)
Cardiac failure congestive	1 (0.7)
Euthanasia	1 (0.7)
Septic shock	1 (0.7)
Sudden death	1 (0.7)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Duration was 3.6 to 212.4 weeks.
For patient-level data, see the table “List of Adverse Events Leading to Death…”
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

These deaths were consistent with the natural history of ALS, as seen in Table 61.

Table 61. All Individual Patient Deaths, Safety Population, Studies 233AS101 and 233AS102

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Tofersen 100 mg	(b) (6)	47	M	100 mg	400	400	Respiratory failure	Respiratory failure due to ALS
Tofersen 100 mg		29	F	100 mg	453	453	Respiratory failure	Worsening respiratory failure due to ALS
Tofersen 100 mg		64	M	100 mg	237	237	Respiratory failure	Worsening respiratory failure in setting of ALS
Tofersen 100 mg		64	M	100 mg	237	237	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Tofersen 100 mg		66	F	100 mg	575	575	Sudden death	Sudden unexpected death, unknown etiology
Tofersen 100 mg		34	M	100 mg	463	463	Respiratory failure	Respiratory failure (secondary to amyotrophic lateral sclerosis)
Tofersen 100 mg		40	M	100 mg	694	694	Respiratory arrest	Respiratory arrest
Tofersen 100 mg		61	F	100 mg	288	288	Respiratory failure	Respiratory failure secondary to ALS
Tofersen 100 mg		52	M	100 mg	491	491	Cardiac arrest	Cardiac arrest
Tofersen 100 mg		42	M	100 mg	496	496	Respiratory failure	Respiratory failure secondary to ALS
Tofersen 100 mg		39	M	100 mg	425	425	Respiratory failure	Death due to respiratory insufficiency caused by ALS
Tofersen 100 mg		62	F	100 mg	1340	1340	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Tofersen 100 mg		47	M	100 mg	1113	1113	Septic shock	Septic shock
Tofersen 100 mg		70	M	100 mg	220	220	Respiratory arrest	Respiratory arrest due to ALS disease progression
Tofersen 100 mg		63	M	100 mg	114	114	Cardiac failure congestive	Congestive heart failure resulting in death
Tofersen 100 mg		46	F	100 mg	433	433	Respiratory failure	Death due to respiratory failure
Tofersen 100 mg		59	M	100 mg	1600	1600	Respiratory failure	Respiratory failure secondary to motor neuron disease (unknown reason)

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Tofersen 100 mg	(b) (6)	53	M	100 mg	1433	1433	Euthanasia	Euthanasia
Tofersen 100 mg		53	M	100 mg	808	808	Respiratory failure	Respiratory insufficiency
Tofersen 100 mg		57	F	100 mg	365	365	Respiratory failure	Respiratory failure

Source: adae.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was 3.6 to 212.4 weeks.
Abbreviations: F, female; ID, identifier; M, male

7.6.3.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of SAEs for the pooled safety population are shown in Table 62 and Table 63. In the pooled population of all subjects who received tofersen 100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102, the proportion of SAEs was 40%. The SAEs that occurred in more than one subject were respiratory disorders (SOC) (19%), pneumonia aspiration (7%), dysphagia (5%), pneumonia (2%), intracranial pressure increased (2%), fall (2%), COVID-19 (1%), myelitis (1%), septic shock (1%), back pain (1%), ALS (1%), nephrolithiasis (1%), and fecaloma (1%). Most of these SAEs are consistent with the natural history of ALS. Myelitis and intracranial pressure increased are discussed further in Section 7.7.

Table 62. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Studies 233AS101 and 233AS102

System Organ Class Preferred Term	Tofersen 100 mg N=147 n (%)
Any SAE	59 (40.1)
Cardiac disorders (SOC)	4 (2.7)
Cardiac arrest	1 (0.7)
Cardiac failure congestive	1 (0.7)
Cardio-respiratory arrest	1 (0.7)
Myopericarditis	1 (0.7)
Eye disorders (SOC)	1 (0.7)
Papilledema	1 (0.7)
Gastrointestinal disorders (SOC)	14 (9.5)
Dysphagia	7 (4.8)
Fecaloma	2 (1.4)
Abdominal pain	1 (0.7)
Constipation	1 (0.7)
Gastric perforation	1 (0.7)
Gastric ulcer perforation	1 (0.7)
Gastritis	1 (0.7)
Pancreatitis	1 (0.7)
General disorders and administration site conditions (SOC)	4 (2.7)
Hypothermia	1 (0.7)
Impaired self-care	1 (0.7)
Respiratory complication associated with device	1 (0.7)
Sudden death	1 (0.7)
Hepatobiliary disorders (SOC)	1 (0.7)
Cholecystitis	1 (0.7)

System Organ Class Preferred Term	Tofersen 100 mg N=147 n (%)
Infections and infestations (SOC)	21 (14.3)
Pneumonia aspiration	10 (6.8)
Pneumonia	3 (2.0)
COVID-19	2 (1.4)
Myelitis	2 (1.4)
Septic shock	2 (1.4)
COVID-19 pneumonia	1 (0.7)
Meningitis aseptic	1 (0.7)
Pneumonia bacterial	1 (0.7)
Pneumonia pseudomonal	1 (0.7)
Pyelonephritis	1 (0.7)
Respiratory tract infection	1 (0.7)
Sepsis	1 (0.7)
Streptococcal bacteremia	1 (0.7)
Urinary tract infection	1 (0.7)
Injury, poisoning and procedural complications (SOC)	6 (4.1)
Fall	3 (2.0)
Ankle fracture	1 (0.7)
Fibula fracture	1 (0.7)
Head injury	1 (0.7)
Meningitis chemical	1 (0.7)
Skull fracture	1 (0.7)
Stoma site pain	1 (0.7)
Investigations (SOC)	1 (0.7)
Staphylococcus test positive	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	2 (1.4)
Back pain	2 (1.4)
Muscular weakness	1 (0.7)
Nervous system disorders (SOC)	13 (8.8)
Intracranial pressure increased	3 (2.0)
Amyotrophic lateral sclerosis	2 (1.4)
Encephalopathy	1 (0.7)
Headache	1 (0.7)
Loss of consciousness	1 (0.7)
Lumbar radiculopathy	1 (0.7)
Myelitis transverse	1 (0.7)
Neurosarcoidosis	1 (0.7)
Radicular pain	1 (0.7)
Radiculopathy	1 (0.7)
Vocal cord paralysis	1 (0.7)
Psychiatric disorders (SOC)	1 (0.7)
Anxiety	1 (0.7)
Renal and urinary disorders (SOC)	3 (2.0)
Nephrolithiasis	2 (1.4)
Calculus urinary	1 (0.7)

System Organ Class Preferred Term	Tofersen 100 mg N=147 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	28 (19.0)
Respiratory failure	16 (10.9)
Pulmonary embolism	6 (4.1)
Acute respiratory failure	5 (3.4)
Pneumonitis aspiration	4 (2.7)
Chronic respiratory failure	2 (1.4)
Respiratory arrest	2 (1.4)
Respiratory distress	2 (1.4)
Acute respiratory distress syndrome	1 (0.7)
Aspiration	1 (0.7)
Pneumothorax	1 (0.7)
Surgical and medical procedures (SOC)	2 (1.4)
Euthanasia	1 (0.7)
Gastrostomy	1 (0.7)
Vascular disorders (SOC)	1 (0.7)
Deep vein thrombosis	1 (0.7)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in the open-label extension Study 233AS102.
Duration was 3.6 to 212.4 weeks.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

Table 63 shows SAEs grouped using the FDA Medical Query (Narrow). The grouped SAEs that occurred in more than one subject were respiratory failure (15%), pneumonia (9%), bacterial infection (5%), thrombosis (5%), fall (2%), viral infection (2%), fracture (2%), back pain (1%), dyspnea (1%), and respiratory depression (1%).

Table 63. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies 233AS101 and 233AS102

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Blood and lymphatic system disorders (SOC)	
Thrombosis	7 (4.8)
Thrombosis venous	7 (4.8)
Cardiac disorders (SOC)	
Heart failure	1 (0.7)
Gastrointestinal disorders (SOC)	
Abdominal pain	1 (0.7)
Constipation	1 (0.7)
Pancreatitis	1 (0.7)
General disorders and administration site conditions (SOC)	
Fall	3 (2.0)
Hepatobiliary disorders (SOC)	
Cholecystitis	1 (0.7)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Infections and infestations (SOC)	
Pneumonia	13 (8.8)
Bacterial infection	8 (5.4)
Viral infection	3 (2.0)
Musculoskeletal and connective tissue disorders (SOC)	
Fracture	3 (2.0)
Back pain	2 (1.4)
Nervous system disorders (SOC)	
Headache	1 (0.7)
Psychiatric disorders (SOC)	
Anxiety	1 (0.7)
Renal and urinary disorders (SOC)	
Renal and urinary tract infection	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	
Respiratory failure	22 (15.0)
Dyspnea	2 (1.4)
Respiratory depression	2 (1.4)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration was 3.6 to 212.4 weeks.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. For specific preferred terms under each FMQ, see the table “Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.3.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of AEs leading to treatment discontinuation for the pooled safety population are shown in Table 64 and Table 65. In the pooled population of all subjects who received tofersen 100mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102, the proportion of AEs leading to treatment discontinuation was 18%.

As seen in Table 64, the AEs leading to treatment discontinuation that occurred in more than one subject were respiratory failure (8%), respiratory arrest (1%), and ALS (1%).

Table 64. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Studies 233AS101 and 233AS102

System Organ Class Preferred Term	Tofersen 100 mg N=147 n (%)
Any AE leading to discontinuation	26 (17.7)
Cardiac disorders (SOC)	2 (1.4)
Cardiac arrest	1 (0.7)
Cardiac failure congestive	1 (0.7)
Gastrointestinal disorders (SOC)	2 (1.4)
Gastritis	1 (0.7)
Pancreatitis	1 (0.7)
Salivary hypersecretion	1 (0.7)
General disorders and administration site conditions (SOC)	1 (0.7)
Sudden death	1 (0.7)
Infections and infestations (SOC)	2 (1.4)
Myelitis	1 (0.7)
Septic shock	1 (0.7)
Injury, poisoning and procedural complications (SOC)	1 (0.7)
Meningitis chemical	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.7)
Muscular weakness	1 (0.7)
Nervous system disorders (SOC)	4 (2.7)
Amyotrophic lateral sclerosis	2 (1.4)
Neurosarcoidosis	1 (0.7)
Vocal cord paralysis	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	16 (10.9)
Respiratory failure	11 (7.5)
Respiratory arrest	2 (1.4)
Dyspnea	1 (0.7)
Pneumonitis aspiration	1 (0.7)
Pulmonary embolism	1 (0.7)
Surgical and medical procedures (SOC)	1 (0.7)
Euthanasia	1 (0.7)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Duration was 3.6 to 212.4 weeks.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 65 shows AEs leading to treatment discontinuation grouped using the FDA Medical Query (Narrow). The grouped treatment discontinuation AEs that occurred in more than one subject were respiratory failure (9%) and respiratory depression (1%).

Table 65. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies 233AS101 and 233AS102

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Blood and lymphatic system disorders (SOC)	
Thrombosis	1 (0.7)
Thrombosis venous	1 (0.7)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Cardiac disorders (SOC)	
Heart failure	1 (0.7)
Gastrointestinal disorders (SOC)	
Pancreatitis	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	
Respiratory failure	13 (8.8)
Respiratory depression	2 (1.4)
Dyspnea	1 (0.7)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was 3.6 to 212.4 weeks.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

7.6.3.5. Treatment-Emergent Adverse Events, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of TEAEs for the pooled safety population are shown in Table 66 and Table 67. In the pooled population of all subjects who received tofersen 100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102, the proportion of TEAEs was 99%.

Many TEAEs were consistent with the natural history of ALS and with the common adverse effects of lumbar puncture. Key TEAEs are further discussed in Section 7.7.

Table 66. Patients With Common Adverse Events Occurring at ≥2.5% Frequency, Safety Population, Studies 233AS101 and 233AS102

Preferred Term	Tofersen 100 mg N=147 n (%)
Any AE	145 (98.6)
Headache	90 (61.2)
Procedural pain	84 (57.1)
Fall	66 (44.9)
Back pain	62 (42.2)
Pain in extremity	58 (39.5)
Arthralgia	47 (32.0)
Fatigue	39 (26.5)
CSF protein increased	36 (24.5)
Nausea	34 (23.1)
Post lumbar puncture syndrome	34 (23.1)
COVID-19	31 (21.1)
Myalgia	28 (19.0)
Muscle spasms	27 (18.4)
Constipation	26 (17.7)

Preferred Term	Tofersen 100 mg N=147 n (%)
Dizziness	26 (17.7)
Contusion	24 (16.3)
CSF white blood cell count increased	24 (16.3)
Nasopharyngitis	24 (16.3)
Pyrexia	23 (15.6)
Respiratory failure	20 (13.6)
Dyspnea	19 (12.9)
Muscular weakness	19 (12.9)
Urinary tract infection	17 (11.6)
Diarrhea	16 (10.9)
Pain	15 (10.2)
Salivary hypersecretion	15 (10.2)
Upper respiratory tract infection	15 (10.2)
Dysphagia	14 (9.5)
Paresthesia	14 (9.5)
Rash	14 (9.5)
Cough	13 (8.8)
Pleocytosis	13 (8.8)
Anxiety	12 (8.2)
Hypoesthesia	12 (8.2)
Neck pain	12 (8.2)
Pneumonia aspiration	12 (8.2)
Peripheral swelling	11 (7.5)
Insomnia	10 (6.8)
Musculoskeletal pain	10 (6.8)
Oropharyngeal pain	10 (6.8)
Skin abrasion	10 (6.8)
Abdominal pain	9 (6.1)
Joint swelling	9 (6.1)
Ligament sprain	9 (6.1)
Oedema peripheral	9 (6.1)
Pneumonia	9 (6.1)
Vomiting	9 (6.1)
Alanine aminotransferase increased	8 (5.4)
Chills	8 (5.4)
Decreased appetite	8 (5.4)
Depression	8 (5.4)
Immunization reaction	8 (5.4)
Muscle contractions involuntary	8 (5.4)
Muscle spasticity	8 (5.4)
Muscle strain	8 (5.4)
Musculoskeletal stiffness	8 (5.4)
Abdominal pain upper	7 (4.8)
Blood glucose increased	7 (4.8)
Hypertension	7 (4.8)
Migraine	7 (4.8)
Neuralgia	7 (4.8)
Procedural nausea	7 (4.8)
Pruritus	7 (4.8)
Abdominal distension	6 (4.1)
Acute respiratory failure	6 (4.1)
Bronchitis	6 (4.1)
CSF glucose increased	6 (4.1)

Preferred Term	Tofersen 100 mg N=147 n (%)
Dysarthria	6 (4.1)
Flank pain	6 (4.1)
Intracranial pressure increased	6 (4.1)
Nasal congestion	6 (4.1)
Pollakiuria	6 (4.1)
Post procedural complication	6 (4.1)
Pulmonary embolism	6 (4.1)
Sinusitis	6 (4.1)
Skin laceration	6 (4.1)
Tremor	6 (4.1)
Aspartate aminotransferase increased	5 (3.4)
Balance disorder	5 (3.4)
Blood urine present	5 (3.4)
Burning sensation	5 (3.4)
CSF white blood cell count positive	5 (3.4)
Gastroenteritis viral	5 (3.4)
Hepatic enzyme increased	5 (3.4)
Hepatic steatosis	5 (3.4)
Influenza	5 (3.4)
Laryngospasm	5 (3.4)
Limb discomfort	5 (3.4)
Micturition urgency	5 (3.4)
Musculoskeletal chest pain	5 (3.4)
Nephrolithiasis	5 (3.4)
Oral candidiasis	5 (3.4)
Post procedural contusion	5 (3.4)
Stoma site pain	5 (3.4)
Vaccination site pain	5 (3.4)
Vertigo	5 (3.4)
Viral infection	5 (3.4)
Weight decreased	5 (3.4)
Abdominal discomfort	4 (2.7)
Acute kidney injury	4 (2.7)
Blister	4 (2.7)
Cellulitis	4 (2.7)
Ear discomfort	4 (2.7)
Epistaxis	4 (2.7)
Erythema	4 (2.7)
Gastroesophageal reflux disease	4 (2.7)
Head injury	4 (2.7)
Influenza-like illness	4 (2.7)
Muscle tightness	4 (2.7)
Muscle twitching	4 (2.7)
Papilledema	4 (2.7)
Pneumonitis aspiration	4 (2.7)
Post procedural swelling	4 (2.7)
Respiratory distress	4 (2.7)
Seasonal allergy	4 (2.7)
Sensory disturbance	4 (2.7)
Tachycardia	4 (2.7)
Tooth infection	4 (2.7)
Toothache	4 (2.7)
Vision blurred	4 (2.7)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was 3.6 to 212.4 weeks.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; CSF, cerebrospinal fluid; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

Since the NDA submission, the Applicant has identified pyrexia as a new nonserious adverse drug reaction (ADR) for tofersen. The AE of pyrexia occurred in 4% of the tofersen group and 3% of the placebo group and does not appear to be clinically significantly different between the groups in the placebo-controlled study. Pyrexia occurred in 16% of subjects in the OLE Study 102. Across all clinical studies, there were 83 events of pyrexia in 33 participants. All events were nonserious and mild to moderate in severity, and none were treatment limiting. However, the Applicant received reports from investigators of positive rechallenge experiences in Study 102.

Four subjects in Study 102 receiving tofersen 100 mg experienced 3 to 16 events that the investigators assessed as related to tofersen. There were no confounders identified; events occurred 0 to 2 days after tofersen administration and resolved. ADAs were positive in two of four participants with recurrent pyrexia, with titers of 1:6,400 and 1:102,400. The Applicant concluded that pyrexia should be included as a nonserious ADR of tofersen due to the plausible relationship between tofersen and pyrexia given the existence of a positive rechallenge and the timing of the event relative to that of drug exposure.

Table 67 shows TEAEs grouped using the FDA Medical Query (Narrow). The SOCs with proportions of at least 10% were gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, respiratory disorders, skin disorders, and vascular disorders.

Table 67. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Studies 233AS101 and 233AS102

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Blood and lymphatic system disorders (SOC)	
Thrombosis	7 (4.8)
Thrombosis venous	7 (4.8)
Anemia	5 (3.4)
Cardiac disorders (SOC)	
Systemic hypertension	9 (6.1)
Arrhythmia	7 (4.8)
Tachycardia	4 (2.7)
Cardiac conduction disturbance	2 (1.4)
Heart failure	2 (1.4)
Palpitations	1 (0.7)
Ear and labyrinth disorders (SOC)	
Vertigo	5 (3.4)
Endocrine disorders (SOC)	
Hyperglycemia	9 (6.1)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Eye disorders (SOC)	
Glaucoma	1 (0.7)
Gastrointestinal disorders (SOC)	
Nausea	38 (25.9)
Constipation	26 (17.7)
Abdominal pain	19 (12.9)
Diarrhea	18 (12.2)
Dyspepsia	11 (7.5)
Vomiting	10 (6.8)
Dry mouth	1 (0.7)
Pancreatitis	1 (0.7)
General disorders and administration site conditions (SOC)	
Fall	66 (44.9)
Fatigue	40 (27.2)
Dizziness	39 (26.5)
Pyrexia	23 (15.6)
Peripheral edema	17 (11.6)
Local administration reaction	11 (7.5)
Decreased appetite	8 (5.4)
Volume depletion	1 (0.7)
Hepatobiliary disorders (SOC)	
Hepatic injury	8 (5.4)
Cholecystitis	1 (0.7)
Immune system disorders (SOC)	
Hypersensitivity	2 (1.4)
Infections and infestations (SOC)	
Viral infection	44 (29.9)
Bacterial infection	41 (27.9)
Nasopharyngitis	29 (19.7)
Pneumonia	18 (12.2)
Fungal infection	13 (8.8)
Purulent material	4 (2.7)
Metabolism and nutrition disorders (SOC)	
Lipid disorder	6 (4.1)
Musculoskeletal and connective tissue disorders (SOC)	
Back pain	68 (46.3)
Arthralgia	47 (32.0)
Myalgia	30 (20.4)
Fracture	9 (6.1)
Tendinopathy	4 (2.7)
Osteoporosis	2 (1.4)
Rhabdomyolysis	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	
Malignancy	2 (1.4)
Nervous system disorders (SOC)	
Headache	101 (68.7)
Paresthesia	30 (20.4)
Tremor	8 (5.4)
Confusional state	2 (1.4)
Stroke TIA	2 (1.4)
Syncope	2 (1.4)
Dysgeusia	1 (0.7)

System Organ Class FMQ (Narrow)	Tofersen 100 mg N=147 n (%)
Somnolence	1 (0.7)
Psychiatric disorders (SOC)	
Anxiety	16 (10.9)
Depression	13 (8.8)
Insomnia	11 (7.5)
Parasomnia	3 (2.0)
Self-harm	2 (1.4)
Arthritis	1 (0.7)
Irritability	1 (0.7)
Study agent abuse potential	1 (0.7)
Renal and urinary disorders (SOC)	
Renal and urinary tract infection	21 (14.3)
Acute kidney injury	4 (2.7)
Urinary retention	3 (2.0)
Reproductive system and breast disorders (SOC)	
Abnormal uterine bleeding	3 (2.0)
Erectile dysfunction	2 (1.4)
Sexual dysfunction	2 (1.4)
Excessive menstrual bleeding	1 (0.7)
Gynecomastia	1 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	
Respiratory failure	30 (20.4)
Dyspnea	23 (15.6)
Cough	16 (10.9)
Respiratory depression	2 (1.4)
Pneumonitis	1 (0.7)
Skin and subcutaneous tissue disorders (SOC)	
Rash	22 (15.0)
Pruritus	8 (5.4)
Erythema	5 (3.4)
Urticaria	2 (1.4)
Alopecia	1 (0.7)
Vascular disorders (SOC)	
Hemorrhage	43 (29.3)
Hypotension	3 (2.0)

Source: adae.xpt; software: R
Treatment-emergent adverse events defined as any adverse event with an onset date and time that is on or after Day 1 or any pre-existing condition that has worsened in severity after Day 1.
Duration was 3.6 to 212.4 weeks.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

7.6.3.6. Laboratory Findings, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of laboratory value abnormalities for the pooled safety population are shown in Table 68. The pooled population consisted of all subjects who received tofersen

100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102. There were no clinically significant patterns or trends observed in abnormalities in blood chemistry. Assessments of renal and urinary disorders are discussed in Section 7.7.4. Hepatic assessments are discussed in Section 7.6.1.7.

Table 68. Patients With One or More Chemistry Analyte Value With Elevated or Low Values Meeting Specified Levels, Safety Population, Studies 233AS101 and 233AS102

Laboratory Parameter	Tofersen 100 mg N=147 n/N_w (%)
Sodium, low (mEq/L)	
Level 1 (<132)	6/147 (4.1)
Level 2 (<130)	4/147 (2.7)
Level 3 (<125)	0/147 (0)
Sodium, high (mEq/L)	
Level 1 (>150)	0/147 (0)
Level 2 (>155)	0/147 (0)
Level 3 (>160)	0/147 (0)
Potassium, low (mEq/L)	
Level 1 (<3.6)	19/147 (12.9)
Level 2 (<3.4)	6/147 (4.1)
Level 3 (<3)	0/147 (0)
Potassium, high (mEq/L)	
Level 1 (>5.5)	0/147 (0)
Level 2 (>6)	0/147 (0)
Level 3 (>6.5)	0/147 (0)
Chloride, low (mEq/L)	
Level 1 (<95)	19/147 (12.9)
Level 2 (<88)	3/147 (2.0)
Level 3 (<80)	0/147 (0)
Chloride, high (mEq/L)	
Level 1 (>108)	11/147 (7.5)
Level 2 (>112)	0/147 (0)
Level 3 (>115)	0/147 (0)
Bicarbonate, low (mEq/L)	
Level 1 (<20)	54/147 (36.7)
Level 2 (<18)	19/147 (12.9)
Level 3 (<15)	2/147 (1.4)
Bicarbonate, high (mEq/L)	
Level 3 (>30)	13/147 (8.8)
Glucose, low (mg/dL)	
Level 1 (<70)	24/147 (16.3)
Level 2 (<54)	1/147 (0.7)
Level 3 (<40)	1/147 (0.7)
Glucose, random, high (mg/dL)	
Level 2 (≥200)	11/147 (7.5)
Level 3 (>250)	8/147 (5.4)
Calcium, low (mg/dL)	
Level 1 (<8.4)	5/147 (3.4)
Level 2 (<8)	4/147 (2.7)
Level 3 (<7.5)	2/147 (1.4)
Calcium, high (mg/dL)	
Level 1 (>10.5)	12/147 (8.2)
Level 2 (>11)	1/147 (0.7)

Laboratory Parameter	Tofersen 100 mg N=147 n/N_w (%)
Level 3 (>12)	0/147 (0)
Phosphate, low (mg/dL)	
Level 1 (<2.5)	20/147 (13.6)
Level 2 (<2)	4/147 (2.7)
Level 3 (<1.4)	1/147 (0.7)
Protein, total, low (g/dL)	
Level 1 (<6)	16/147 (10.9)
Level 2 (<5.4)	1/147 (0.7)
Level 3 (<5)	0/147 (0)
Albumin, low (g/dL)	
Level 1 (<3.1)	0/147 (0)
Level 2 (<2.5)	0/147 (0)
Level 3 (<2)	0/147 (0)
Blood urea nitrogen, high (mg/dL)	
Level 1 (>23)	35/147 (23.8)
Level 2 (>27)	16/147 (10.9)
Level 3 (>31)	4/147 (2.7)

Source: ad b.xpt; software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other laboratory values. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Levels 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was 3.6 to 212.4 weeks.
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in open-label extension study 233AS102.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

7.6.3.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of liver laboratory abnormalities for the pooled safety population are shown in Table 69 and Table 70. The pooled population consisted of all subjects who received tofersen 100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102.

Table 69. Patients With One or More Liver Biochemistry Analyte Value Exceeding Specified Levels, Safety Population, Studies 233AS101 and 233AS102

Laboratory Parameter	Tofersen 100 mg N=147 n/N_w (%)
Alkaline phosphatase, high (U/L)	
Level 1 (>1.5× ULN)	4/147 (2.7)
Level 2 (>2× ULN)	1/147 (0.7)
Level 3 (>3× ULN)	1/147 (0.7)
Alanine aminotransferase, high (U/L)	
Level 1 (>3× ULN)	16/147 (10.9)
Level 2 (>5× ULN)	6/147 (4.1)
Level 3 (>10× ULN)	1/147 (0.7)
Aspartate aminotransferase, high (U/L)	
Level 1 (>3× ULN)	8/147 (5.4)
Level 2 (>5× ULN)	2/147 (1.4)

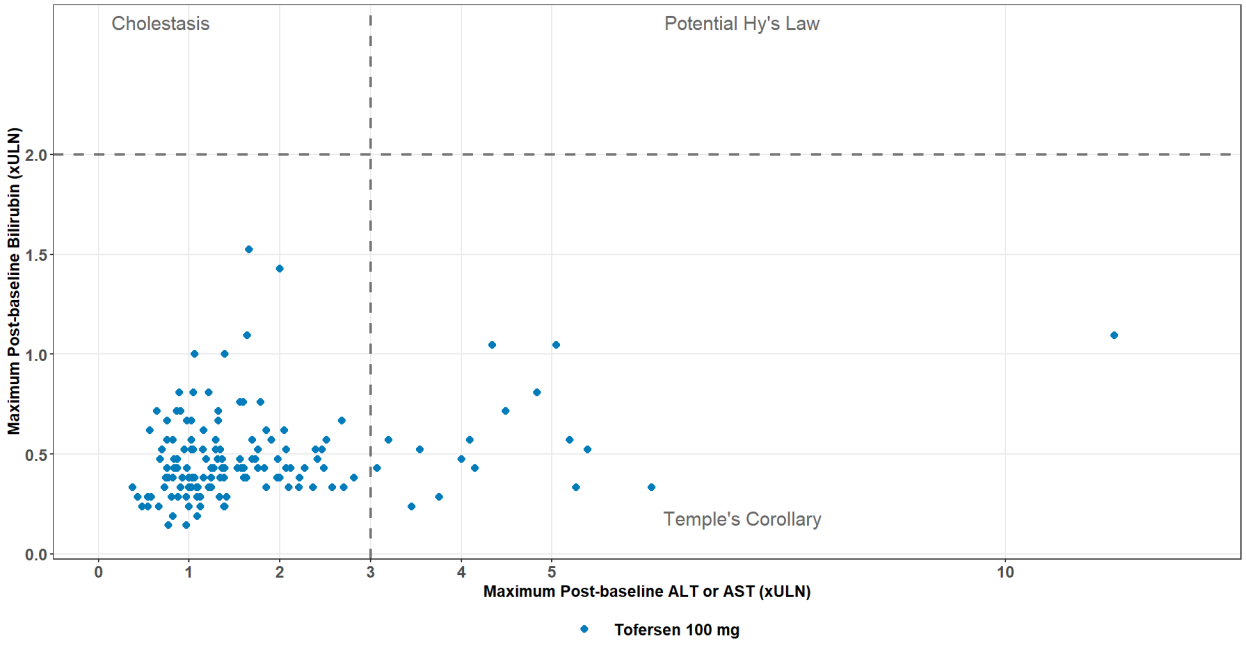
Laboratory Parameter	Tofersen 100 mg N=147 n/N_w (%)
Level 3 (>10× ULN)	0/147 (0)
Bilirubin, total, high (mg/dL)	
Level 1 (>1.5× ULN)	1/147 (0.7)
Level 2 (>2× ULN)	0/147 (0)
Level 3 (>3× ULN)	0/147 (0)

Source: ad b.xpt; software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was 3.6 to 212.4 weeks.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot.." and "Cholestatic Drug-Induced Liver Injury Screening Plot.." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot.." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot…"
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or Part C, or further enrolled in open-label extension study 233AS102.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

There was one AE of blood alkaline phosphatase increased in subject [redacted] (b) (6) who received tofersen 100 mg in Studies 101 and 102. This subject also had SAEs of pulmonary embolism and cholecystitis with cholelithiasis. This AE was assessed as moderate in severity. No action was taken with study treatment as a result of the event. The subject continued in the study.

Figure 28 and Table 70 show a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no Hy's law cases.

Figure 28. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Studies 233AS101 and 233AS102



Source: ad b.xpt; software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 70. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Studies 233AS101 and 233AS102

Quadrant	Tofersen 100 mg N=147 n/N_w (%)
Potential Hy's law (right upper)	0/147 (0)
Cholestasis (left upper)	0/147 (0)
Temple's corollary (right lower)	17/147 (11.6)
Total	17/147 (11.6)

Source: ad b.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in the open-label extension Study 233AS102.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data

7.6.3.8. Vital Signs, Pooled Analyses, Studies 101 and 102

No clinically significant patterns or trends were observed in abnormalities in vital signs (including diastolic and systolic blood pressure, pulse rate, respiratory rate, weight, and temperature) in Studies 101 and 102.

Table 71. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Studies 233AS101 and 233AS102

Systolic Blood Pressure (mm Hg)	Tofersen 100 mg N=147 n/N_w (%)
<90	0/147 (0)
≥90	147/147 (100)
≥120	145/147 (98.6)
≥140	100/147 (68.0)
≥160	29/147 (19.7)
≥180	4/147 (2.7)

Source: advs.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in the open-label extension Study 233AS102.
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 72. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Studies 233AS101 and 233AS102

Blood Pressure (mm Hg)	Tofersen 100 mg N=147 n/N_w (%)
SBP <90	5/147 (3.4)
DBP <60	42/147 (28.6)

Source: advs.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in the open-label extension Study 233AS102.
Abbreviations: DBP, diastolic blood pressure; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SBP, systolic blood pressure

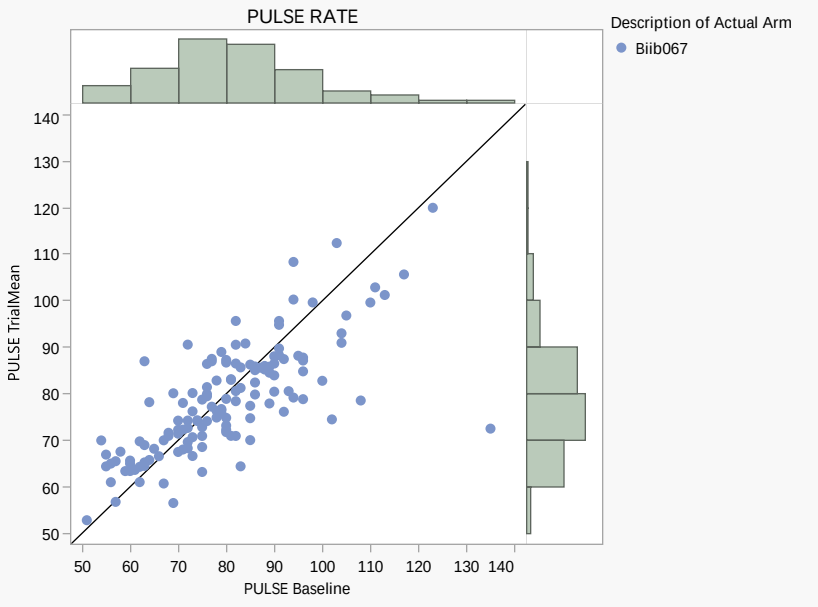
Table 73. Mean Change From Baseline in Systolic Blood Pressure

233AS101 and 233AS102 ISS: Vital signs change from baseline by visit - safety population
Page: 161 of 255
Systolic Blood Pressure (mmHg)

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72)	placebo (N=36)	tofersen 100 mg (N=104)	Total tofersen 100 mg (N=147)	Total tofersen all doses (N=166)
Week 28: Pre-dose					
n	58	31	84	121	115
Mean (SD)	1.1 (13.59)	-4.7 (11.14)	-0.5 (14.51)	-0.7 (13.93)	-0.7 (13.71)
Median	0.0	-5.0	0.0	0.0	0.0
Q1, Q3	-7.0, 9.0	-13.0, 5.0	-8.5, 8.0	-8.0, 7.0	-8.0, 7.0
Min, Max	-42, 35	-34, 15	-45, 35	-45, 35	-45, 35

Source: Integrated Summary of Safety Appendix 4.5, Outputs 1 to 3
Abbreviations: Q1, first quartile; Q3, third quartile

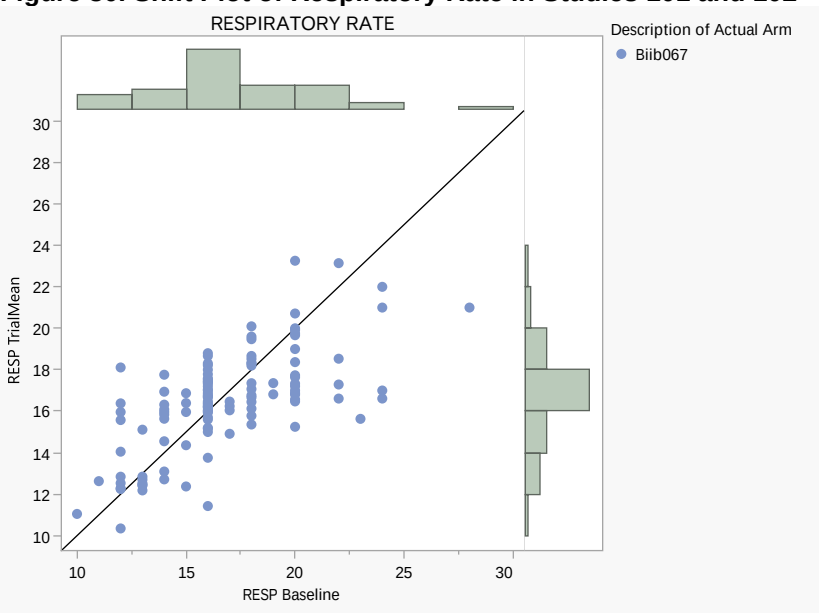
Figure 29. Shift Plot of Pulse Rate in Studies 101 and 102



Source: FDA Analysis

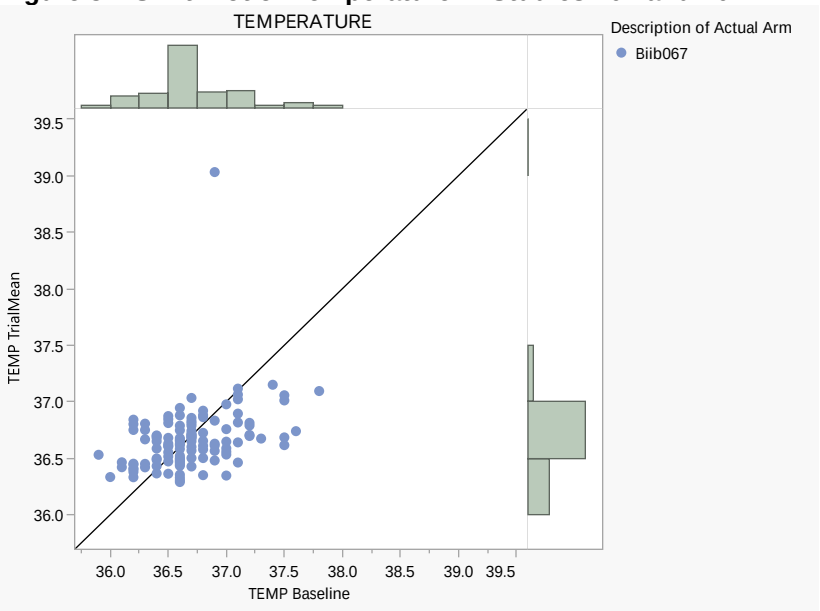
The outlier (subject (b) (6)) in the bottom right Figure 29 with an elevated baseline pulse rate of approximately 135 had AEs at baseline of agitation, constipation, and sleep disorder. Agitation could have resulted in the elevated baseline pulse rate.

Figure 30. Shift Plot of Respiratory Rate in Studies 101 and 102



Source: FDA analysis
Abbreviation: RESP, respiratory

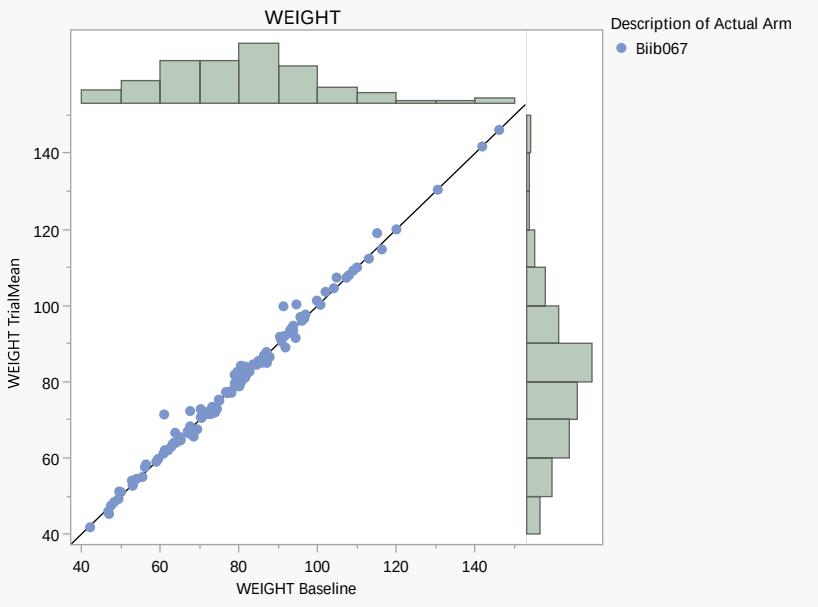
Figure 31. Shift Plot of Temperature in Studies 101 and 102



Source: FDA analysis
Abbreviation: TEMP, temperature

The outlier (subject (b) (6)) with a baseline temperature of approximately 37° and a mean above 39° had four temperature measurements in Fahrenheit that were erroneously labeled as Celsius, incorrectly driving up the mean.

Figure 32. Shift Plot of Weight in Studies 101 and 102



Source: FDA analysis

7.6.3.9. Subgroups, Pooled Analyses, Studies 101 and 102

Results of the FDA analysis of SAEs and AEs by demographic subgroup for the pooled safety population are shown in Table 74 and Table 75. The pooled population consisted of all subjects who received tofersen 100 mg in Study 101B (phase 2 multiple-ascending-dose study), Study 101C (pivotal placebo-controlled study), and the OLE Study 102.

Table 74. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Studies 233AS101 and 233AS102

Characteristic	Tofersen 100 mg N=147 n/N_s (%)
Sex, n (%)	
Female	27/65 (41.5)
Male	32/82 (39.0)
Age group, years, n (%)	
18 to <35	7/16 (43.8)
35 to <50	25/60 (41.7)
50 to <65	19/52 (36.5)
≥65	8/19 (42.1)
Age group ≥75, years, n (%)	
≥75	0/2 (0)
Race, n (%)	
Asian	3/10 (30.0)
Black or African American	0/1 (0)
Native Hawaiian or Other Pacific Islander	0/1 (0)
Not reported	18/45 (40.0)
Other	2/2 (100)
White	36/88 (40.9)

Characteristic	Tofersen 100 mg N=147 n/N_s (%)
Ethnicity, n (%)	
Hispanic or Latino	2/5 (40.0)
Not Hispanic or Latino	39/97 (40.2)
Not reported	18/45 (40.0)

Source: adae.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in the open-label extension Study 233AS102.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 75. Overview of Adverse Events by Demographic Subgroup, Safety Population, Studies 233AS101 and 233AS102

Characteristic	Tofersen 100 mg N=147 n/N_s (%)
Sex, n (%)	
Female	65/65 (100)
Male	80/82 (97.6)
Age group, years, n (%)	
18 to <35	16/16 (100)
35 to <50	60/60 (100)
50 to <65	51/52 (98.1)
≥65	18/19 (94.7)
Age group ≥75, years, n (%)	
≥75	2/2 (100)
Race, n (%)	
Asian	10/10 (100)
Black or African American	1/1 (100)
Native Hawaiian or Other Pacific Islander	1/1 (100)
Not reported	44/45 (97.8)
Other	2/2 (100)
White	87/88 (98.9)
Ethnicity, n (%)	
Hispanic or Latino	5/5 (100)
Not Hispanic or Latino	96/97 (99.0)
Not reported	44/45 (97.8)

Source: adae.xpt; software: R
The total number of patients (N=147) reflects patients treated with 100 mg of tofersen in Study 233AS101 Part B or C, or further enrolled in the open-label extension Study 233AS102.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

As seen in Table 74 and Table 75 based on the submission, there were no clinically significant differences in the proportions of subjects with AEs or with SAEs as a function of age or sex subgroup for the pooled Studies 101 and 102. There was also no clinically significant difference in the proportion of subjects with AEs as a function of race or ethnicity. The proportions of SAEs were highest in the other (100%), white (41%), not reported (40%), and Asian (30%) race groups, but the differences in subgroup sizes and the small numbers of subjects in the black (n=1), Native Hawaiian (n=1), and other (n=2) groups make this comparison uninterpretable.

7.7. Key Safety Review Issues

7.7.1. Myelitis and Radiculitis

Issue

Five subjects receiving tofersen in Studies 101C, 102, and the expanded-access program experienced an SAE of myelitis.

Two subjects receiving tofersen in Studies 101C and 102 experienced an SAE of radiculitis.

No subject receiving placebo in Study 101C experienced SAEs of myelitis or radiculitis.

Background

Of the subjects who received tofersen 100 mg in Studies 101 and 102, six subjects experienced SAEs of myelitis or radiculitis. Four of one hundred forty-seven participants (2.7%) who received 100 mg tofersen in Study 101C or Study 102 reported events of myelitis (preferred terms myelitis, myelitis transverse, and neurosarcoidosis), and 2 of 147 participants (1.4%) reported events of radiculitis (preferred terms radiculopathy and lumbar radiculopathy). No subject receiving placebo in Study 101C experienced an SAE of myelitis or radiculitis.

Table 76 and Table 77 summarize the case narratives of subjects who had an SAE of myelitis or radiculitis.

Table 76. Narrative Summaries of Subjects With Myelitis in Studies 101, 102, and the Expanded-Access Program

Subject	Narrative Summary
(b) (6)	42 y.o. M, 387 days of tofersen, h/o DM2, diabetic neuropathy, chronic pulmonary sarcoidosis; ALS dx (b) (6) SAE Neurosarcoid Transverse Myelitis study day 95, responded to methylprednisolone/prednisone, resolved day 198 (b) (6) Subject stopped tofersen (b) (6) "after learning risk of myelitis."
(b) (6)	35 y.o. M, ALS dx (b) (6) Study day 197 (end of study 233AS101) SAE transverse myelitis based on MRI to assess elevated WBC and protein in CSF. Asymptomatic. Last tofersen dose study day 169. Subject continued into Study 233AS102 and continued tofersen.
(b) (6)	33 y.o. F, ALS dx (b) (6) SAEs cranial hypertension (day 433), Myelitis (day 504, last dose tofersen day 446). AE chronic aseptic meningitis w/ high CSF WBC (b) (6) Asymptomatic Myelitis dx by MRI (b) (6) Tofersen interrupted, restarted (b) (6)
(b) (6)	39 y.o. F, ALS dx (b) (6); SAE myelitis study day 98, last tofersen dose day 85. Paraplegia and T10 sensory loss. Lumbar to Cervical spinal cord MRI lesion. Diagnosed with inflammatory myelopathy. Responded to methylprednisolone and plasma exchange. Resolved in ~2 months. Tofersen discontinued. Subject withdrew from study.
(b) (6)	47-y.o. male with ALS since (b) (6) began unknown tofersen dose on (b) (6) SAE of myelitis on (b) (6) The patient was also taking quinine and riluzole. The patient had complained of tingling in the legs and headache after receiving the first and second dose of tofersen. Two days after the third dose, the patient experienced numbness in the left leg up to the left side of the shoulder. Leg weakness was also noted. MRI showed multiple areas of demyelination throughout the spinal cord. CSF WBC count was observed to be increasing after each dose: As of (b) (6) (EAP data cut), the event of myelitis was not resolved. Tofersen stopped.

Source: Clinical Study Reports for 233AS101 and 233AS101, 16.2 Participant Data Listings; 120-Day Safety Update, Appendix 4.6.5.1 Integrated Summary of Safety Patient Narratives
Abbreviations: AE, adverse event; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; DM2, diabetes mellitus type 2; dx, diagnosis; EAP, expanded access program; F, female; h/o, history of; M, male; MRI, magnetic resonance imaging; SAE, serious adverse event; WBC, white blood cell; y.o., years old

Table 77. Narratives of Subjects With Radiculitis or Radiculopathy in Studies 101 and 102

Subject	Narrative Summary
(b) (6)	48 y.o. M; 1100 days of tofersen; SAE radiculopathy on study day 646 (last dose on day 617). Tofersen continued. Radiculitis diagnosed. MRI cauda equina roots enhancement. Back and thigh pain along with numbness in feet and minor loss of balance. 9 months after onset "the event of radiculitis was resolved with sequelae. The sequalae included CSF pleocytosis, elevated CSF protein, bilateral sensory loss in feet, and bilateral loss of ankle jerk reflex."
(b) (6)	41 y.o. M, 169 days of tofersen. SAE Transient Lumbar Inflammatory Radiculitis on study day 3 (last dose on day 1). Severe lower back pain affecting gait. High CSF WBC and protein. MRI normal. Resolved day 4. Tofersen continued.

Source: Clinical Study Reports for 233AS101 and 233AS101, 16.2 Participant Data Listings; 120-Day Safety Update, Appendix 4.6.5.1 Integrated Summary of Safety Patient Narratives
Abbreviations: CSF, cerebrospinal fluid; M, male; MRI, magnetic resonance imaging; SAE, serious adverse event; WBC, white blood cell; y.o., years old

In the expanded-access program there was one AE of lumbar radiculopathy in a 62-year old female in the United States. The event was reported as recovered/resolved within days. Treatment with tofersen was permanently discontinued.

Note that subject (b) (6) developed transverse myelitis in the setting of neurosarcoidosis, which was the most likely cause of that subject's myelitis.

Assessment

The class of ASOs, to which tofersen belongs, is known to be proinflammatory.[37] Inflammatory changes were also seen in the nonclinical studies of tofersen. Intrathecal injection of tofersen in cynomolgus monkeys caused mononuclear inflammatory cell infiltrates in the meninges at the lumbar spinal cord injection site, possibly as a local proinflammatory effect (Study 666853-AS01, Toxicology Written Summary, p. 21). The incidence of transverse myelitis in the general population is estimated to be approximately 0.0005 to 0.018%. In contrast, 2.7% of subjects in Studies 101C and 102 who received tofersen developed myelitis. The number of doses of tofersen 100 mg that a subject received prior to event onset varied from 1 to 24. Each event was associated with a CSF pleocytosis and elevated CSF protein. Note that WBC count increased was seen in 10% of subjects who received tofersen in Study 101C compared to 0% of placebo subjects. One case of transverse myelitis was likely caused by neurosarcoidosis (subject (b) (6) , Two cases of myelitis were asymptomatic (subjects (b) (6) and (b) (6)). One case from the expanded-access program involved lower-extremity weakness and left-sided numbness with unknown outcome. The most severe case of myelitis in subject (b) (6) led to paraplegia, which resolved after 2 months following tofersen discontinuation and immunomodulatory treatment. One case of radiculitis in subject (b) (6) led to sequelae including foot sensory loss 9 months after onset.

Conclusion

There is a safety signal for transverse myelitis and radiculitis with intrathecal administration of tofersen. This reviewer recommends describing the risks of myelitis and radiculitis in the Warnings and Precautions section of the Prescribing Information. Given the severity of ALS relative to the observed risks of myelitis in the tofersen studies and the potential benefit of tofersen, a risk evaluation and mitigation strategy is not required. Myelitis can be managed by tofersen discontinuation, in severe cases, along with standard immunomodulatory treatment. Enhanced pharmacovigilance will be requested for cases of myelitis and radiculitis in the postmarket setting.

7.7.2. Aseptic Meningitis/Cerebrospinal Fluid Protein and White Blood Cell Levels Increased

Issue

In the tofersen clinical development program, there was one SAE of meningitis chemical (Study 101C) and one SAE of meningitis aseptic (Study 102). In Study 101B, one subject dosed at 60 mg reported SAEs of CSF protein increased and CSF WBC count increased.

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[37] Review Toxicol Pathol. 2015 Jan;43(1):78-89. doi: 10.1177/0192623314551840. Epub 2014 Nov 9. Antisense oligonucleotide therapies: the promise and the challenges from a toxicologic pathologist's perspective. Kendall S Frazier

Background

Aseptic meningitis, potentially life-threatening meningeal inflammation with negative routine bacterial cultures, is seen at a rate of approximately 7.6 cases per 100,000 adults.[38] Causes include other infections (mycobacteria, fungi, spirochetes)[39], parameningeal infections, medications, and malignancies. Medication-induced meningitis has been associated with multiple medications, with one study from the French pharmacovigilance database reporting 329 cases of aseptic meningitis for a total of 429 suspected drugs from 1985 to 2017.[40]

Drug-induced meningitis may be caused by a delayed hypersensitivity type reaction or direct meningeal irritation. The CSF profile in aseptic meningitis typically has a neutrophilic pleocytosis. Symptoms often resolve a few days after drug discontinuation. CSF protein increased was observed in approximately 8% of the tofersen group compared to 3% of the placebo group in Study 101C. Approximately 10% of the tofersen group in Study 101C (versus 0% of the placebo group) had the adverse event CSF WBC count increased, although only two subjects had SAEs of aseptic meningitis (one subject [0.7%] in Study 102) or chemical meningitis (one subject [1.4%] in Study 101C), as shown in Table 78.

Table 78. Narrative Summaries of Subjects With Meningitis in Studies 101 and 102

Subject	Narrative Summary
(b) (6)	29 y.o. F, SAE meningitis chemical on study day 147. Tofersen discontinued. CSF high WBC and protein. Hospitalized with severe headache, neck pain, stiffness. Treated with antibiotics, methylprednisolone. Resolved ~ 2 weeks after onset.
(b) (6)	33 y.o. F, ALS dx (b) (6) SAEs cranial hypertension (day 433) remained unresolved. Headaches, blurred vision, migraines, tinnitus, vomiting, bilateral papilledema. Treated with acetazolamide. Elevated CSF pressure, WBC, and protein. Myelitis (day 504, last dose tofersen day 446). AE chronic aseptic meningitis w/ high CSF WBC (b) (6) Asymptomatic Myelitis dx by MRI (b) (6) Tofersen interrupted, restarted (b) (6)

Source: Clinical Study Reports for Studies 101 and 102, Subject Data Listings
Abbreviations: AE, adverse event; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; dx, diagnosis; F, female; MRI, magnetic resonance imaging; SAE, serious adverse event; WBC, white blood cell; y.o., year old

Assessment

Drug-induced aseptic (or chemical) meningitis is potentially life-threatening meningeal inflammation that often resolves spontaneously when the causative drug treatment is discontinued. There were two serious adverse events of either aseptic or chemical meningitis in the placebo-controlled (Study 101C) and OLE (Study 102) tofersen studies, with one of the reports leading to treatment discontinuation with complete resolution of symptoms within 2 weeks. There were additional reports of nonserious AEs of elevated CSF WBC and CSF

[38] Am Fam Physician. 2017 Sep 1;96(5):314-322. Aseptic and Bacterial Meningitis: Evaluation, Treatment, and Prevention. Hillary R Mount, Sean D Boyle

[39] UptoDate: Aseptic meningitis in adults. Author: Allan R Tunkel, MD, PhD, MACP Section Editor: Martin S Hirsch, MD Deputy Editor:Jennifer Mitty, MD, MPH

[40] Br J Clin Pharmacol. 2019 Nov;85(11):2540-2546. doi: 10.1111/bcp.14073. Epub 2019 Aug 1. Drug-induced aseptic meningitis: 329 cases from the French pharmacovigilance database analysis. Kevin Bihan, Nicolas Weiss, Hélène Théophile, Christian Funck-Brentano, Bénédicte Lebrun-Vignes

pleocytosis in Study 101C. Aseptic meningitis and chemical meningitis have been reported with other intrathecally administered treatments, including reports of aseptic meningitis with IT administration of another ASO.

Conclusion

This reviewer recommends describing the risk of drug-induced aseptic meningitis in the Warnings and Precautions section of the Prescribing Information. Given the severity of ALS relative to the observed risks of drug-induced aseptic meningitis in the tofersen studies and the potential benefit of tofersen, a risk evaluation and mitigation strategy is not required. Drug-induced aseptic meningitis can be controlled by tofersen discontinuation and supportive care. The nonserious risk of CSF pleocytosis (WBC elevation) and protein level elevation should be described in Section 6 of the Prescribing Information.

7.7.3. Papilledema/Elevated Intracranial Pressure

Issue

In the tofersen clinical development program, four subjects had SAEs that included papilledema as a feature. These SAE cases had preferred terms of intracranial pressure increased, nervous system disorder, and papilledema.

Background

Papilledema is optic disc swelling caused by elevated intracranial pressure. Common symptoms of elevated intracranial pressure include headache, nausea, vomiting, diplopia, and visual obscurations that can progress to reduced visual acuity, visual field loss, and ultimately blindness. The incidence of idiopathic elevated intracranial pressure (intracranial hypertension) in the general population is reported as 0.9 per 100,000 (0.0009%) in the United States,[41] compared to 4 of 139 (2.9%) subjects with an SAE of papilledema/intracranial pressure increased in Studies 101 and 102.

Table 79. Patients With Serious Adverse Event of Intracranial Pressure Increased, Safety Population, Study 233AS102

System Organ Class Preferred Term	233AS101 Part C Tofersen 100 mg to 233AS102 Tofersen N=63 n (%)	233AS101 Part C Placebo to 233AS102 Tofersen N=32 n (%)	233AS101 Part A/B All Doses to 233AS102 Tofersen N=44 n (%)	Total 233AS101 Part A, B, and C to 233AS102 Tofersen N=139 n (%)
Intracranial pressure increased	0	1 (3.1)	1 (2.3)	2 (1.4)

Source: adae.xpt; software: R

[41] Rigi M, Almarzouqi SJ, Morgan ML, Lee AG. Papilledema: epidemiology, etiology, and clinical management. Eye Brain. 2015 Aug 17;7:47-57. doi: 10.2147/EB.S69174. PMID: 28539794; PMCID: PMC5398730.

Table 80. SAEs of Elevated Intracranial Pressure or Papilledema in Study 101 or 102

Subject	Narrative Summary
(b) (6)	49 y.o. M. SAE nervous system disorder. Study Day 269, last tofersen on Day 259. Auditory & visual disturbance and headache. High CSF protein and WBC. Papilledema diagnosed 3 months after onset of symptoms. "The participant and research team preferred to alternate monthly dosing."
(b) (6)	33 y.o. F, ALS dx (b) (6); SAEs cranial hypertension (Day 433) remained unresolved. Headaches, blurred vision, migraines, tinnitus, vomiting, bilateral papilledema. Treated with acetazolamide. Elevated CSF pressure, WBC, and protein. Myelitis (Day 504, last dose tofersen Day 446). AE chronic aseptic meningitis w/ high CSF WBC (b) (6) Asymptomatic Myelitis dx by MRI (b) (6) Tofersen interrupted, restarted (b) (6).
(b) (6)	55 y.o. M, SAE Bilateral papilledema with hemorrhages on study Day 148, last tofersen dose on Day 143, tofersen interrupted, resolved on Day 338; meningitis aseptic, study Day 91, last dose tofersen Day 87. Resolved Day 115.
(b) (6)	70 y.o. M, SAE mild/moderate intracranial hypertension on study Day 198, latest tofersen dose on Day 169, tofersen was continued; remained unresolved at time of data cut-off

Source: Clinical Study Report 233AS102, 16.2 Participant Data Listings
Abbreviations: AE, adverse event; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; dx, diagnosis; F, female; M, male; MRI, magnetic resonance imaging; SAE, serious adverse event; WBC, white blood cell; y.o., years old

Assessment

All AEs and SAEs related to papilledema/intracranial pressure increased were reported in subjects who received tofersen 100 mg; no such events were reported in the placebo group. There were 4 of 139 (2.9%) subjects with an SAE of papilledema or intracranial pressure increased. In the pooled Studies 101 and 102, a further 3 of 139 (2.2%) subjects had nonserious AEs of papilledema or intracranial pressure increased.

Conclusion

This reviewer recommends describing the risk of papilledema and elevated intracranial pressure in the Warnings and Precautions section of the Prescribing Information. Given the severity of ALS relative to the observed risks of papilledema and elevated intracranial pressure in the tofersen studies and the potential benefit of tofersen, a risk evaluation and mitigation strategy is not required. Drug-induced papilledema and elevated intracranial pressure can be controlled by tofersen discontinuation, when appropriate, and supportive care.

7.7.4. Renal and Urinary Disorders

Issue

There was a higher rate of AEs in the renal and urinary disorders SOC in subjects who received tofersen (8%) compared to placebo (3%) in Study 101C.

Background

The class of ASOs, to which tofersen belongs, is nephrotoxic.[42]

Assessment

There is a nominal difference in Renal and Urinary Disorders AEs grouped by SOC, with a higher rate in the tofersen group of Study 101C compared to placebo, as shown in Table 81.

Table 81. Renal Adverse Events in Study 101C by System Organ Class and Preferred Term

		Part C (Pivotal) - BIIB067 100 mg (N = 72)			Part C (Pivotal) - Placebo (N = 36)		
SOC	PT	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)
Renal and urinary disorders		6	6	**8.3**	1	1	**2.8**
Renal and urinary disorders	Acute kidney injury	1	1	1.4	0	0	0
Renal and urinary disorders	Micturition urgency	2	2	2.8	0	0	0
Renal and urinary disorders	Pollakiuria	1	1	1.4	1	1	2.8
Renal and urinary disorders	Glycosuria	2	2	2.8	0	0	0

Source: FDA analysis
Abbreviations: PT, preferred term; SOC, system organ class

However, there was no clinically significant difference in mean change from baseline in kidney function parameters between the tofersen and placebo groups, as shown in Table 82.

Table 82. Mean Change From Baseline for Kidney Function Data Over Time by Treatment Arm, Safety Population, Study 233AS101 Part C

Chemistry at Week 28	Tofersen 100 mg Mean Change From Baseline (95% CI	Placebo Mean Change From Baseline (95% CI)	Difference in Mean Change From Baseline (95% CI)
Urea Nitrogen (mmol/L)	-0.2 (-0.5, 0.1)	0.4 (-0.2, 0.9)	-0.7 (-1.3, 0.0)
Creatinine (umol/L)	-6.2 (-8.5, -3.8)	-6.7 (-11.3, -2.1)	0.7 (-4.6, 5.9)
eGFR CKD-EPI (mL/min/1.73 m2	6.2 (2.8, 9.6)	6.5 (1.3, 11.6)	-0.4 (-6.7, 5.9)

Source: FDA analysis
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate

Table 83 shows that no subjects in the tofersen group of Study 101C developed elevated creatinine levels greater than 1.5-fold baseline levels or eGFR <25% of baseline.

[42] Review Toxicol Pathol. 2015 Jan;43(1):78-89. doi: 10.1177/0192623314551840. Epub 2014 Nov 9. Antisense oligonucleotide therapies: the promise and the challenges from a toxicologic pathologist's perspective. Kendall S Frazier

Table 83. Patients With One or More Kidney Function Analyte Value Exceeding Specified Levels, Safety Population, Study 233AS101 Part C

Laboratory Parameter	Tofersen 100 mg N=72 n/N_w (%)	Placebo N=36 n/N_w (%)	Risk Difference (%) (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	0/72 (0)	1/36 (2.8)	-2.8 (-8.1, 2.6)
Level 2 (≥2× baseline)	0/72 (0)	0/36 (0)	0 (0, 0)
Level 3 (≥3× baseline)	0/72 (0)	0/36 (0)	0 (0, 0)
eGFR, low (mL/min/1.73 m^2)			
Level 1 (≥25% decrease)	0/50 (0)	0/29 (0)	0 (0, 0)
Level 2 (≥50% decrease)	0/50 (0)	0/29 (0)	0 (0, 0)
Level 3 (≥75% decrease)	0/50 (0)	0/29 (0)	0 (0, 0)

Source: ad b.xpt; software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration was approximately 28 to 32 weeks.
Risk difference (with 95% confidence interval) is shown between tofersen and placebo.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

There were no SAEs in the renal and urinary disorders SOC in Study 101C. One subject (subject [redacted] (b) (6)) receiving tofersen in Study 102 had an SAE of nephrolithiasis that resolved without requiring tofersen interruption.

Conclusion

Although there were nominally more renal and urinary disorder AEs in the tofersen group of Study 101C, comparison of renal function laboratory parameters found no clinically significant difference between the tofersen and placebo groups. Although there is a potential class risk of nephrotoxicity, the observed data from the tofersen development program do not support a description in the Warnings and Precautions section of the labeling at this time.

7.7.5. Respiratory Failure

Issue

For all subjects who received tofersen at any dose level, the most frequent AEs (≥5%) of Common Terminology Criteria for Adverse Events Grade ≥3 were respiratory failure and pneumonia aspiration.

There was a higher rate of the AE respiratory failure in subjects who received tofersen (4%) compared to placebo (0%) in Study 101C.

Background

Respiratory muscles are also affected in ALS, leading to respiratory failure and the death of most patients within 3 to 5 years from the onset of symptoms. Respiratory failure occurs frequently in patients with ALS.

Assessment

There were more AEs of respiratory failure in the tofersen group compared to the placebo group (Table 84). When preferred terms are grouped, there was more respiratory depression in the tofersen group (5.6%) than the placebo group (0%).

Table 84. Subjects With Adverse Event of Respiratory Failure by Ellis Medical Query and Preferred Term, Safety Population, Study 233AS101 Part C

Ellis Medical Queries (EMQ) Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Respiratory Depression FDA B	4 (5.6)	0	5.6 (0.3, 10.8) *
Respiratory failure	3 (4.2)	0	4.2 (-0.4, 8.8)
Acute respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Hypoventilation	1 (1.4)	0	1.4 (-1.3, 4.1)
Oxygen saturation decreased	1 (1.4)	0	1.4 (-1.3, 4.1)
Apnea, Respiratory Failure, Cyanosis, Hypoxemia, Desaturation, Lung Injury (EMQ)	4 (5.6)	0	5.6 (0.3, 10.8) *
Respiratory failure	3 (4.2)	0	4.2 (-0.4, 8.8)
Acute respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Hypoventilation	1 (1.4)	0	1.4 (-1.3, 4.1)
Oxygen saturation decreased	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: FDA Analysis
*, 95% confidence interval does not include zero.

Table 85 shows that there were more SAEs of respiratory failure in the tofersen group compared to the placebo group. When preferred terms are grouped, more tofersen-treated subjects (3%) had SAEs of apnea, respiratory failure, cyanosis, hypoxemia, desaturation, or lung injury than subjects who received placebo (0%).

Table 85. Subjects With Serious Adverse Event of Respiratory Failure by Ellis Medical Query and Preferred Term, Safety Population, Study 233AS101 Part C

Ellis Medical Queries (EMQ) Preferred Term	Tofersen 100 mg N=72 n (%)	Placebo N=36 n (%)	Risk Difference (%) (95% CI)
Apnea, Respiratory Failure, Cyanosis, Hypoxemia, Desaturation, Lung Injury (EMQ)	2 (2.8)	0	2.8 (-1.0, 6.6)
Acute respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)
Respiratory failure	1 (1.4)	0	1.4 (-1.3, 4.1)

Source: FDA Analysis

Table 86 has brief narrative summaries of the subjects who received tofersen and had an SAE of respiratory failure in Study 101C.

Table 86. Tofersen-Treated Subjects With an SAE of Respiratory Failure in Study 101C

Subject	Narrative Summary
(b) (6)	Respiratory failure (SAEs of Pulmonary Embolus, Aspiration pneumonitis, aspiration with desat) got tracheostomy and resolved, unrelated to study treatment which was interrupted
(b) (6)	Acute respiratory failure (SAEs: aspiration pneumonitis, aspiration pneumonitis due to GI (feeding) tube, Acute on chronic respiratory failure, aspiration pneumonia, progressive acute on chronic respiratory failure Resolved, continued study treatment
(b) (6)	Respiratory failure: SAEs hypothermia, loss of consciousness due to hypothermia, congestive heart failure (h/o prior MI) resulting in death. Last dose of tofersen 3 days before death
(b) (6)	Respiratory failure. SAE respiratory insufficiency, respiratory failure, later resolved Continued tofersen without interruption.

Source: Participant Data Listings
Abbreviations: GI, gastrointestinal; h/o, history of; MI, myocardial infarction; SAE, serious adverse event

Review of the case narratives does not find any clear causal association between tofersen treatment and respiratory failure. The events of respiratory failure are consistent with the natural history of ALS.

Conclusion

Although there were nominally more respiratory failure AEs and SAEs in the tofersen group of Study 101C than in the placebo group, review of the SAE narratives found no clear causal association between tofersen treatment and respiratory failure. The events of respiratory failure are consistent with the natural history of ALS.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

Clinical studies of tofersen in subjects with hepatic impairment were not conducted. Following intrathecal injection, tofersen is distributed from the CSF to the target central nervous system (CNS) tissues. In addition, tofersen is not metabolized by CYP450s in vitro and the tofersen ASO class with 2'-MOE-modifications are expected to be metabolized by nucleases, which is not dependent on hepatic function. Therefore, hepatic impairment is not expected to influence the PK of tofersen.

Renal Impairment

Clinical studies of tofersen in participants with renal impairment were not conducted. There is no clinical data to confirm the percentage of dose excreted in urine as the parent drug, thus the risk

of tofersen dosing in subjects with renal impairment cannot be evaluated. A postmarketing commitment (PMC) study will be requested to assess the risk (See Section 24).

Other Intrinsic Factors

Based on population PK analyses, tofersen PK in plasma is unlikely to be affected by age, body weight, and race. Effects of sex and race on tofersen exposure in plasma were not considered clinically significant. The effects of these factors on tofersen exposure in the CSF are unknown. (Refer to Section 14.5.4.1 for details).

8.2. Extrinsic Factors

Drug Interactions

Due to its lack of interactions with common transporters and CYP-mediated metabolism in vitro, the potential of tofersen for drug interactions is low; therefore, no dosing adjustments are proposed for use of tofersen with concomitant medications.

Clinical drug-drug interaction studies were not conducted given the lack of any significant in vitro findings on tofersen as an inhibitor or inducer of CYP450s, or an inhibitor of major transporters. In vitro studies also indicated that tofersen is not a substrate of major transporters. Oligonucleotide therapeutics are not typically metabolized by cytochrome P450 (CYP) enzymes; they are instead primarily metabolized by endonucleases and exonucleases. It is reasonable to expect that the disposition of tofersen, as an ASO therapeutic, is not affected by inhibitors or inducers of CYP450s.

8.3. Plans for Pediatric Drug Development

ALS is an indication that rarely occurs in pediatrics and therefore automatically qualifies for a waiver of the requirement for pediatric studies. Tofersen has also received Orphan Drug (#16-5372) designation and is therefore exempt from pediatric study requirements.

No data are available for pediatric subjects (<18 years of age). SOD1-ALS is very rare in people younger than 18 years of age. The mean age of disease onset is 49.7±12.3 years.[43] Rare cases of juvenile-onset muscular weakness and/or atrophy in SOD1 mutation carriers have been reported.[44]

[43] : Bali T, Self W, Liu J, et al. Defining SOD1 ALS natural history to guide therapeutic clinical study design. J Neurol Neurosurg Psychiatry. 2017;88(2):99-105. Epub 2016/06/03.

[44] De La Torre A, Shah S, Rao V. A Case of Rapidly Progressive Juvenile-Onset Amyotrophic Lateral Sclerosis with a rare SOD1 genetic variant (P5.6-067). Neurology. 2019;92(15 Supplement):P5.6-067.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

No formal studies of tofersen in pregnant or lactating women were performed. Pregnant or lactating women were excluded from participation in the tofersen clinical studies, and women of childbearing potential were required to use acceptable methods of birth control throughout the studies.

No pregnancies were reported during the tofersen clinical studies at the time of the data cutoff. One subject treated in Study 233AS101 Part C had a positive pregnancy test prior to enrollment in Study 233AS102 and was a screening failure.

9. Product Quality

Approval With a PMC

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 215887 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess. As such, OPQ recommends approval of this NDA from a quality perspective. The chemistry, manufacturing, and controls PMCs between OPQ and the Applicant listed below should be included in the action letter (See Section 24).

- Conduct an extractables study for the rubber stopper. The aqueous extractions should use as extracting solvents pH-adjusted waters that bracket the pH of tofersen drug product. The extraction should be conducted by heating under reflux conditions to ensure they represent worst-case scenarios for extractable impurities.
- Conduct a leachables study using at least three batches of tofersen drug product. The leachables should be tested at multiple time points on stability storage - from release through the proposed shelf-life.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Review of the financial disclosures did not raise concern about the validity or reliability of the data.

Drs. Babu, Bucelli, and Genge as well as the Applicant, 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 Applicant appear acceptable in support of the respective indication.

See Section 22 for the Clinical Inspection Report.

11. Advisory Committee Summary

The Peripheral and Central Nervous System Drugs Advisory Committee Meeting was held on March 22, 2023.

The Advisory Committee (AC) discussed the strengths and limitations of the available clinical data from the placebo-controlled study and long-term extension regarding the effectiveness of tofersen for SOD1-ALS. The AC also discussed the overall benefit-risk assessment for tofersen in patients with SOD1-ALS.

The AC members were asked to vote on the following questions.

1. Is the available evidence 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?
2. Do the clinical data from the placebo-controlled study and available long-term extension study, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS?

The AC was unanimously in agreement that the available evidence was sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen in the treatment of patients with SOD1-ALS. The vote on Question 1 was nine to zero *Yes*. While the AC members acknowledged that the placebo-controlled study did not meet any of its prespecified endpoints, the data unequivocally demonstrated an effect on the SOD1 protein and a reduction of plasma NfL concentration, resulting in a strong pharmacodynamic signal and suggesting decreased injury to neurons. Many AC members pointed out the context of a rare disease such as SOD1-ALS, in which another placebo-controlled study would not be feasible and were in agreement that the totality of the evidence was sufficient to support a reasonably likely predictive benefit of the reduction in plasma NfL concentrations.

For Question 2, a slight majority of the AC members voted *No* (three *Yes*, five *No*, and one *Abstain*), agreeing that the clinical data from the placebo-controlled study and available long-term extension results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), did not provide convincing evidence of effectiveness for tofersen in the treatment of patients with SOD1-ALS. Several AC members agreed that the data from the long-term extension study are suggestive of tofersen's clinical effect, though not conclusive. The AC members who voted *No* cited the failure of the placebo-controlled study to meet its prespecified endpoints as the basis for their vote, and

two noted that the evidence presented meets the standards for accelerated, but not traditional, approval.

The AC members who voted *Yes* acknowledged the difficulty of their decision and noted that there aspects of the data presented suggested strong clinical evidence of tofersen's benefit. One member also cited the unmet need and seriousness of SOD1-ALS as contributing to their decision, and another expressed concern about the financial burden for patients due to the lack of payer coverage for tofersen if it were to be granted accelerated instead of full approval.

The AC member who abstained cited the precompetitive and noncompetitive nature of his work as the reason for his abstention.

The AC members were in agreement that the overall AE profile, in the context of the seriousness of the illness, was supportive of a favorable benefit-risk assessment for the treatment of SOD1-ALS patients with tofersen.

III. Additional Analyses and Information

12. Summary of Regulatory History

Tofersen was developed under Investigational New Drug (IND) 124264 for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a confirmed mutation of the SOD1 gene. This product was initially developed under a collaboration agreement between Biogen and Isis Pharmaceuticals. Biogen was solely responsible for the clinical development program, including the sponsorship of the initial IND application.

On January 29, 2015, a Pre-IND meeting was held to seek agreement on the design of the Phase 1 first-in-human study and to seek agreement on the nonclinical toxicology package needed to support the planned clinical program. At that meeting, the Division indicated its receptiveness to arguments that efficacy findings in a subset of faster-progressing patients with SOD1 mutation could be extended, based on similar reductions in SOD1, to slower-progressing patients with SOD1 mutation, if it could be established that disease pathogenesis in the subsets was similar.

The initial IND was submitted to the Agency on October 28, 2015, along with a request for Fast Track Designation. The initial IND contained the first-in-human Phase 1 protocol 233AS101 (Study 101), entitled, "A Phase 1, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of BIIB067 Administered [by intrathecal bolus injection] to Adult Subjects with Amyotrophic Lateral Sclerosis [ALS]." The protocol initially consisted of two parts. Part A was a randomized, double-blind, placebo controlled, single ascending-dose study in 36 patients with sporadic or SOD1 ALS. Part B was a randomized, double-blind, placebo controlled, multiple-ascending-dose (MAD) study of up to three dose levels given up to five times to 36 adults with SOD1-ALS. The IND was allowed to proceed and Fast Track designation was granted on December 23, 2015.

Study 233AS102 was a multicenter, open-label, uncontrolled extension study to assess the long-term safety, tolerability, pharmacokinetics, and effect on disease progression of tofersen administered to previously treated subjects with SOD1-ALS who had completed Part A and/or Part B of Study 233AS101, and was submitted to the IND in November 2016.

On June 20, 2017, a Type C meeting was held to discuss whether the Agency agreed that demonstration of a clinically meaningful treatment effect in a SOD1-ALS population with fast- and intermediate-progressing SOD1 mutations could be extended to all SOD1-ALS patients (i.e., including those with more slowly progressing SOD1 mutations) based on similar reductions in cerebral spinal fluid (CSF) SOD1 protein. The Division determined that the Applicant's approach appeared reasonable pending review of the data and supporting scientific justification during a future NDA review. The Applicant also requested the Agency's feedback on a new clinical endpoint based on muscle strength as measured by hand-held dynamometry (HHD). The Division advised the Applicant that the primary endpoint should incorporate a combined assessment of an acceptable muscle strength assessment and mortality and that given the high likelihood of mortality and missing data in ALS studies (particularly a study enriched for more rapidly progressing SOD1 patients), a joint-rank analysis was typically recommended.

On January 15, 2019, the Applicant submitted a protocol amendment to account for the addition of Part C (VALOR) to Study 233AS101. Part C was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study which enrolled 108 subjects >18 years of age who had weakness attributable to ALS and a confirmed SOD1 mutation. Following completion of Study 101 C, subjects were provided the opportunity to enroll in Study 233AS102 (Study 102), the open-label extension (OLE) study designed to evaluate the long-term benefit-risk of tofersen.

A preliminary Breakthrough Therapy Designation Request (BTDR) advice teleconference was held on January 16, 2019, to discuss tofersen as a potential candidate for BTD. To facilitate further discussion, the Division advised the Applicant to request a Type C meeting to discuss in greater detail tofersen's potential for BTD.

A Type C meeting was held on March 27, 2019, to further discuss tofersen as a candidate for BTD. (b) (4)

On May 30, 2019, a Type C Guidance meeting was held to further discuss the development program for tofersen. The Division agreed that an assessment of carcinogenicity could be conducted post approval, provided the available data supported such an approach. The Applicant agreed with the Division's recommendation to use a combined assessment of function and survival (CAFS) as the primary endpoint for Study 101C and stated that it would use change from baseline in ALSFRS score to Week 28 as the functional component of the endpoint. The proposed statistical analysis plan was discussed, and the Division stated the importance of having adequate statistical power given that the Applicant was proposing to conduct only a single study. In addition, assuming that deaths were handled by the joint rank analysis (i.e., CAFS), the Division agreed with the primary intention-to-treat estimand. Finally, the Division agreed that slow vital capacity (SVC), ventilation assistance-free survival and overall survival as time to event, and hand-held dynamometry (HHD) would be acceptable as secondary endpoints.

A request for BTD was submitted on April 2, 2020. The request included data from the Phase 1 MAD (233AS101) and the Phase 3 OLE (233AS102) studies. BTD was denied on June 1 2021, because the preliminary clinical evidence provided did not demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

On August 26, 2020, a Type C meeting was held to discuss the proposed design of the Phase 3 study (233AS303/ATLAS) of tofersen in presymptomatic carriers of confirmed SOD1 mutations. (b) (4) In addition, the Applicant requested feedback on the adequacy of the proposed neurofilament light chain assay for randomizing presymptomatic patients to study drug. The Division recommended that the Applicant incorporate current knowledge of the different SOD1 mutations and their clinical progression rates into the study enrollment criteria. (b) (4) the Division advised the Applicant that the study design and statistical analysis would still need to be rigorous with the usual standard of a two-sided alpha of 0.05. Finally, the Applicant asked if the Agency agreed with the use of NfL as a biomarker in the proposed study and the proposed (b) (4) NfL

threshold for enrolling subjects in Part B of the study. The Division advised the Applicant that it did not endorse a particular threshold, but it did not have an objection to the proposed threshold.

A Type B Pre-NDA meeting was requested on November 3, 2020. After initially granting the meeting as a Type B, the Division converted the meeting to a Type C guidance meeting as topline results for the Phase 3 study were not yet available. Feedback was provided on the statistical analysis plan for the VALOR study, adequacy of the nonclinical program to support an NDA, and adequacy of the data to support a TQTc waiver. The Division informed the Applicant that no additional nonclinical studies appeared necessary, and that the data submitted in the meeting package appeared reasonable to support a TQTc waiver; however, the adequacy of the data would be a matter of review. On November 6, 2020, Biogen requested a Type C meeting to discuss the chemistry, manufacturing, and control aspects of the tofersen/BIIB067 program in preparation for a future 505(b)(1) NDA. The meeting was cancelled by the Applicant upon receipt of the Office of Pharmaceutical Quality's January 12, 2021 preliminary comments.

Enrollment for Study 233AS303 (ATLAS) in presymptomatic SOD1 mutation carriers was initiated on June 18, 2021. In July 2021, the Applicant implemented an expanded access program for rapidly-progressive SOD1-ALS patients. Eligibility was expanded to include all SOD-1 ALS patients as of October 17, 2021.

A Type C meeting was held on September 17, 2021, to discuss the topline results of the pivotal Phase 3 VALOR Study 233AS101and the continued development of the tofersen program. Although the primary endpoint did not meet statistical significance, the Division agreed that the results suggested a treatment effect, especially in terms of target engagement for SOD1 and NfL reduction and supported plans to continue the development of tofersen.

On December 21, 2021, a Type C meeting was held to continue discussions on the tofersen development program, specifically regarding an NDA submission based on the data from the Phase 3 VALOR study and additional data available to date. The Division noted that it appeared that it would be a challenge for the Applicant to make a case for full approval based on the failed study. The Division allowed that the exploratory analyses of the clinical and biomarker data may be promising but noted that whether the data from the failed study are adequate to support approval would be a matter of review.

On December 21, 2021, the Applicant submitted a new intermediate-size expanded access protocol for Study 233AS001, entitled, "Global Early Access Program (EAP) to Provide Tofersen to Patients with Amyotrophic Lateral Sclerosis (ALS) Associated with a Superoxide Dismutase 1 (SOD1) Mutation."

On April 1, 2022, a Type B Pre-NDA meeting was held to discuss the content and format of an NDA for tofersen. During this meeting, the Division informed the Applicant that it was prepared to consider an NDA submission intended to support accelerated approval. The Division advised the Applicant that it would need to provide substantial evidence of effectiveness on the endpoint intended to support accelerated approval (i.e., change from baseline to Week 28 in plasma NfL, per the Applicant's proposal) and that it would need to establish that the effect on that endpoint is reasonably likely to predict clinical benefit. The Applicant proposed that should accelerated approval be granted, data to confirm the benefit of tofersen would come from either survival data in the OLE or the study in presymptomatic patients (Study 303/ATLAS) and stated that it would weigh the advantages and disadvantages of each confirmatory study approach.

Biogen submitted NDA 215887 for tofersen on May 25, 2022. The Applicant requested accelerated approval under 21 CFR Part 314 Subpart H. The NDA was granted Priority review and was reviewed under The Program due to its status as a new molecular entity. Because tofersen was granted orphan designation for the treatment of SOD1-ALS, the Applicant was exempted from the Pediatric Research Equity Act requirements.

On October 12, 2022, the Division issued a review extension letter which extended the PDUFA goal date to April 25, 2023, based on additional clinical and clinical pharmacology information received on October 5, 2022, and October 7, 2022, which together constituted a major amendment to the application. An Advisory Committee meeting was held on March 22, 2023.

The proprietary name Qalsody was found to be conditionally acceptable on July 15, 2022.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

Tofersen is an antisense oligonucleotide with a 2'MOE backbone, designed to target the 3'-untranslated region (3'-UTR) of human SOD1 mRNA. In vitro studies in cell cultures indicated suppression of human and monkey SOD1 mRNA. In vivo studies conducted in transgenic mice and rats that express human mutant SOD1 (i.e., $SOD1^{G93A}$), indicated reductions in SOD1 MRNA in tissue, and improved lifespan and rotorod performance in mouse. Tissue analysis in monkeys indicated dose-dependent decreases in SOD1 mRNA in brain and spinal cord tissue following IT administration of up to 35 mg tofersen every 2 weeks for a 13-week period. Sequence analyses did not indicate the potential for off-target effects.

13.1.2. Safety Pharmacology

Safety pharmacology assessments following IT administration of tofersen were incorporated into a single dose study in male and female SD rats (CNS) and a 13-week repeat (Q2W) dose toxicity study in cynomolgus monkeys (CNS, CV, and respiratory). CNS effects consisted of transient gait abnormalities, hindlimb splay, and decreases in activity in rat and transient reductions in activity in female cynomolgus monkeys, for which the NOAELs were 1 and 12 mg, respectively. There were no drug effects on HR, BP, or blood gas parameters. The IC_{50} for hERG inhibition in transfected HEK cells was greater than 34μM.

13.1.3. General Toxicology

Rat

Single IT doses of 0, 0.1, 0.3, 1.0, and 3.0 mg tofersen in male and female SD rats resulted in transient, drug-related clinical signs consisting of gait abnormalities and decreases in arousal, mobility, respiration, and sensorimotor observations in HDM and HDF. Additional findings at 3 mg consisted of perivascular inflammation in the brain and spinal cord without accompanying neuronal degeneration.

Mouse

There were no adverse drug effects in male and female CD1 mice administered 0, 25, and 150 mg/kg tofersen by SC injection every other week for 12 weeks. SC administration of 0, 6, 30, and 150 mg/kg tofersen every other week for 26 weeks in male and female CD1 mice resulted in dose-dependent reductions in platelet counts in males (up to 20%) and in HDF (13%). After an 8-week recovery period, dose-dependent platelet reductions of up to 15% were seen in males, and reductions of 3 and 6% were seen in LDF and MDF, respectively. Based on decreases in platelet counts at all doses in males, there was no NOAEL for SC injection of tofersen in CD1 mice.

Monkey

Repeat IT dosing of 0, 4, 12, and 35 mg tofersen every 2 weeks for 13 weeks in male and female cynomolgus monkeys resulted in transient decreases in activity in HDF and neuronal vacuolation at all doses; however, staining with Fluoro Jade did not indicate neuronal degeneration. Vacuolation was not observed after a 13-week recovery period. Repeat IT dosing with 0, 4, 12, and 35 mg tofersen every 2 weeks for a 9-month period resulted in uncoordinated leg movement and transient impairments of patellar and foot-grip reflexes in HDM and HDF. Based on neurological signs in the 9-month study, the NOAEL for IT administration of tofersen in cynomolgus monkey was 12 mg every 2 weeks, resulting in plasma C_{max} and $AUC_{0\text{-}24h}$ of 4840 ng/mL and 30,000 µg·h/mL, respectively.

13.1.4. Genetic Toxicology

Tofersen was negative for mutagenicity in an Ames assay, and negative for clastogenicity in an in vitro chromosomal aberration assay in Chinese hamster lung CHL cells.

13.1.5. Carcinogenicity

Due to the severity of the indication, the carcinogenic potential of tofersen is to be conducted post-approval.

13.1.6. Reproductive and Developmental Toxicity

The potential for drug effects on pre- and postnatal development was assessed in CD1 mice administered 0, 1, 10, and 30 mg/kg tofersen by SC injection every other day from GDs 6 to 21.

There were no effects on maternal or litter parameters. There were no drug effects on physical, neurological, or reproductive development of the offspring. The NOAEL for pre- and postnatal effects in CD1 mice administered tofersen by SC injection was 30 mg/kg. TK parameters were not assessed in the pre- and postnatal development study; however, based on TK data from the 26-week general toxicity study, exposure at the high dose of 30 mg/kg would be expected to result in an approximately four-fold margin relative to AUC in humans at the MRHD.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Introduction

Studies submitted only to the NDA consisted of an in vivo mouse bone marrow micronucleus assay, a fertility and early embryonic development study in CD1 mouse, an embryofetal development study in New Zealand white (NZW) rabbit, and a 13-week toxicity study of impurity-enriched tofersen in monkey.

13.2.2. Genetic Toxicity

BIIB067: In Vivo Mammalian Erythrocyte Micronucleus Assay in Mice

Table 87. BIIB067: In Vivo Mammalian Erythrocyte Micronucleus Assay in Mice

Study Features	Method
Study no:	P067-19-02
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	BIIB067, Lot TA666853-008, 90%
Doses in definitive study:	0, 500, 100, 2000 mg/kg/day
Frequency of dosing:	Single dose
Route of administration:	SC injection
Dose volume:	16 mL/kg BID
Formulation/Vehicle:	PBS
Species/Strain:	CD1 mice
Number/Sex/Group:	6 males/group
Satellite groups:	None
Basis of dose selection:	Limit dose
Negative control:	PBS
Positive control:	Cyclophosphamide (50 mg/kg PO)
Comment on study validity:	Study was consistent with OECD and ICH criteria

Source: Pharmacology Toxicology Reviewer's Analysis
Abbreviations: BID, twice a day; EDR, electronic document room; GLP, good laboratory practice; ICH, International Council for Harmonisation; MD, Maryland; OECD, Organisation for Economic Co-operation and Development; PBS, phosphate buffered saline; PO, by mouth; SC, subcutaneous

Results

Bone marrow micronuclei were assessed 24 or 48 h post dose for micronuclei; tofersen was negative for clastogenicity.

13.2.3. Fertility and Early Embryonic Development

Non-GLP, Dose Range-Finding Study (Mouse)

A non-GLP DRF study was conducted in female CD1 mice (eight per group) to inform dosing for the pivotal FEED study. Doses of 0, 3, 10, and 30 mg/kg tofersen were administered by SC injection every other day from GDs 6 to 14. There were no drug-related effects on maternal or fetal parameters.

Table 88. BIIB037: A Fertility and Embryo-Fetal Development Study by Subcutaneous Injection in Mice

Study Features	Methods
Study no.:	P067-17-02
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 19, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BIIB067, TA666853-001, 94%
Doses:	0, 3, 10, 30 mg/kg
Frequency of dosing:	Every 2 days
Dose volume:	2 mL/kg
Route of administration:	SC injection
Formulation/Vehicle:	PBS
Species/Strain:	CD1 mouse
Number/Sex/Group:	22
Satellite groups:	None
Study design:	Males were administered drug every other day beginning 28 days prior to cohabitation and throughout the 14-day cohabitation. Females were administered drug every other day from 15 days prior to cohabitation until GD 14. Scheduled necropsy was after the cohabitation period for males, and on GD 18 for females.
Deviation from study protocol:	No significant deviations

Source: Pharmacology Toxicology Reviewer's Analysis
Abbreviations: EDR, electronic document room; GD, gestation day; GLP, good laboratory practice; PA, Pennsylvania; PBS, phosphate buffered saline; PO, by mouth; SC, subcutaneous; QA, quality assurance

Observations and Results

Mortality and Clinical Signs

Animals were monitored twice daily for mortality or signs of morbidity, and for up to 1 to 2 h postdose. All animals survived until scheduled necropsy. There were no drug-related clinical signs.

Body Weight and Food Consumption

Body weight was assessed on dosing days. Food consumption was assessed weekly until cohabitation. There were no drug effects on body weight or food consumption.

Toxicokinetics

TK parameters were not assessed in males. In females, TK parameters were assessed on GD 6 and 14.

Table 89. BIIB037 TK Parameters

Day	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)
6	3	963	1810
	10	3630	8460
	30	16,400	52,300
14	3	1390	3420
	10	5860	17,200
	30	12,800	50,500

Source: Pharmacology Toxicology Reviewer's Analysis
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration

Dosing Solution Analysis

Dosing solutions were within 10% of the nominal values.

Necropsy

Males: There were no drug-effects on sperm parameters. Histology findings consisted of vacuolated and amphophilic macrophages in the interstitial tissues of the testis and epididymis (MDM, HDM), and seminiferous tubule degeneration or dilation, spermatid retention in testis (HDM).

Females: There were no drug effects on mating, estrous cycling, mating index, fertility index, or ovarian and uterine parameters. Pregnancy rates ranged from 81.8 to 100%. The percentages of dams per group with any resorptions were 52.9% (C), 50.0% (LDF), 70.6% (MDF), and 94.4% (HDF). There were no drug-related malformations or effects on litter parameters.

13.2.4. Embryonic Fetal Development

Non-GLP, Dose Range-Finding Study (Rabbit)

A non-GLP DRF in was conducted in female NZW rabbits (five/group) to inform dosing for the pivotal EFD study. Doses of 0, 3, 10, and 30 mg/kg tofersen were administered by SC injection every other day on GDs 7 to 19. There were no drug-related effects on maternal, uterine, or fetal parameters.

Table 90. BIIB067: An Embryo-Fetal Development Study by Subcutaneous Injection in Pregnant New Zealand White Rabbits

Study Features	Methods
Study no.:	P067-17-05
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 15, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BIIB067, Lot TA666853-001, 94%
Doses:	0, 3, 10, 30 mg/kg
Frequency of dosing:	Every other day
Dose volume:	2 mL/kg
Route of administration:	SC Injection
Formulation/Vehicle:	PBS
Species/Strain:	NZW rabbit
Number/Sex/Group:	20 females/group
Satellite groups:	TK (3/group)
Study design:	BIIB067 was administered every other day on GDs 7 to 19, with necropsy on Day 29. Dosing was based on a DRF study in pregnant NZW rabbits administered 0, 3, 10, and 30 mg/kg BIIB067 every other day by SC injection on GDs 7 to 19, in which there were no adverse findings.
Deviation from study protocol:	No significant deviations.

Source: Pharmacology Toxicology Reviewer's Analysis
Abbreviations: EDR, electronic document room; GD, gestation day; GLP, good laboratory practice; PA, Pennsylvania; PBS, phosphate buffered saline; PO, by mouth; SC, subcutaneous; QA, quality assurance

Observations and Results

Mortality and Clinical Signs

Animals were assessed twice daily for mortality or signs of morbidity. There were no drug-related mortalities or clinical signs.

Body Weight and Food Consumption

Body weights and food consumption were assessed daily; there were no drug effects.

Toxicokinetics

TK parameters were assessed on GDs 7 and 19.

Table 91. BIIB067 TK Parameters

Day	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)
7	3	14,200	41,900
	10	19,900	131,000
	30	60,900	454,000

Day	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)
	3	4140	23,800
19	10	11,900	87,500
	30	41,100	283,000

Source: Pharmacology Toxicology Reviewer's Analysis
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration

Dosing Solution Analysis

Dosing solutions were with 10% of the nominal values.

Necropsy

There were no gross findings at necropsy.

Cesarean Section Data

There were no drug effect on pregnancy or number of corpora lutea, implantations, preimplantation loss, number of fetuses, or number of early, late, or total resorptions. There were no dead fetuses in any group. There were no drug effects on male/female ratio, postimplantation loss, or mean fetal weights.

Offspring

There were no drug-related external, visceral, or skeletal malformations.

13.2.5. Special Toxicology Studies

A 13-Week Impurity Qualification Toxicity Study When Administered as an Intrathecal Bolus Injection in Cynomolgus Monkey

The potential toxicity of tofersen process impurities and degradation products was assessed by Q2W IT administration over a 13-week period in male and female cynomolgus monkeys (4/sex/group). Groups were administered vehicle or 10 mg tofersen from one of three drug batches (TAM1, TAM2, or TAM3) that had been enriched with process impurities and degradation products. IT administration was conducted Q2W for 13 weeks.

Table 92. Percentage of Impurities in Test Article Mixtures

TAM1	TAM2	TAM3
(b) (4)		

Source: Applicant provided table from Toxicology Written Summary (Module 2.6.6)

(b) (4)

All animals survived until scheduled necropsy. Clinical signs in all groups, including controls, consisted of transient decreases in spinal (flexor and perineal) reflexes, postural reactions, and general attention and activity. There were no drug effects on body weight, food consumption, ophthalmology parameters, or electrocardiogram (ECG) parameters. There were no drug-related effects on hematology, clinical chemistry, urinalysis, or CSF parameters. Histopathology findings consisted of neuronal vacuolation in brain and spinal cord, with no associated degeneration (Fluoro-Jade B staining).

14. Clinical Pharmacology

14.1. In Vitro Studies

In vitro studies of tofersen yielded the following findings:

- Tofersen is not a substrate of the BCRP, MDR1, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters.
- Tofersen up to 100µM is not an inhibitor of the MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC, BCRP, BSEP, and MDR1 transporters.
- Tofersen up to 100µM is not an inhibitor of the CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzymes.
- Tofersen up to 100 µg/mL is not an inducer of CYP1A2, CYP2B6, or CYP4A4/5.

- Tofersen at up to 30 µg/mL binds to human plasma at 98%.

14.2. In Vivo Studies

Tofersen was evaluated in two completed (Studies 233AS101 [Part A, Part B, and Part C] and 233HV101) and two ongoing (Studies 233AS102 and 233AS303) clinical studies. Clinical pharmacology data for this application are drawn from Study 233AS101 Parts A, B, and C, Study 102 (two interim analyses: data cuts on July 16, 2021 and January 16, 2022), and Study 233HV101. Table 93 summarizes the clinical pharmacology studies.

Table 93. Summary of Clinical Pharmacology Studies

Study No. Module	Dev. Phase	Study Design	Population Number of participants enrolled	Tofersen Dose/Regimen	Samples Collected			Status/ Section
					CSF	Plasma/Serum	Other	
233AS101 (CSR 233AS101 Parts A and B; CSR 233AS101 Part C) Module 5.3.5.1	1/2	**Part A SAD:** safety, tolerability, PK, PD, and immunogenicity of tofersen after a single IT injection of tofersen or placebo in participants with ALS	Participants with ALS n = 20[a]	Tofersen IT • Cohort 1 (n = 3): 10 mg • Cohort 2 (n = 3): 20 mg • Cohort 3 (n = 3): 40 mg • Cohort 4 (n = 6): 60 mg • Combined placebo (n = 5) Single Dose Day 1	PK and PD Day 1 (Predose), Days 8, 29, and 57	**PK** Day 1 (Predose and at 1, 2, 4, 6, and 24 hours Postdose [Day 2]), Days 8, 29, and 57 **PD** Days 1 (predose), 29, and 57 **Immunogenicity** Days 1 (predose), 8, 29, and 57	NA	Completed Section 3.1.1

Study No. Module	Dev. Phase	Study Design	Population Number of participants enrolled	Tofersen Dose/Regimen	Samples Collected			Status/ Section
					CSF	Plasma/Serum	Other	
	1/2	**Part B MAD:** safety, tolerability, PK, PD, and immunogenicity of tofersen after multiple ascending IT injections of tofersen or placebo in participants with SOD1-ALS	Participants with SOD1-ALS n = 50	Tofersen IT • Cohort 5 20 mg (n = 10) • Cohort 6 40 mg (n = 9) • Cohort 7 60 mg (n = 9) • Cohort 8 100 mg (n = 10) • Combined placebo (n = 12) Loading dose on Days 1, 15, and 29 Maintenance dosing on Days 57 and 85	**PK and PD** Day 1 (Predose) Day 15, 29, 57, 85,106, and 169 (predose)	**PK** Day 1 (predose and at 1, 2, 4, 6, and 24 hours [Day 2], Postdose), Days 15, 29, and 57, (predose) Day 85 (Predose and at 1,2,4, and 6 hours Postdose) Days 8, 22, 36, 64, 92, 106, and 169 **PD** Day 1 (Predose), Days 15, 29,57, 85, 106 and 169 **Immunogenicity** Day 1 (predose), Day 8, 22, 36, 64, 92, 106, and 169	NA	Completed Section 3.1.2

Study No. Module	Dev. Phase	Study Design	Population Number of participants enrolled	Tofersen Dose/Regimen	Samples Collected			Status/ Section
					CSF	Plasma/Serum	Other	
	3	**Part C Pivotal:** Efficacy, safety, PK, PD, and immunogenicity of tofersen after multiple IT injections of tofersen or placebo in participants with SOD1-ALS	Participants with SOD1-ALS n = 60 (mITT) n = 48 (non-mITT)	Tofersen IT • 100 mg (n = 72) • Placebo (n = 36) Loading doses on Days 1, 15, and 29 Maintenance dosing on Days 57, 85, 113, 141, and 169	**PK and PD** Days 1, 15, 29, 57, 85, 113, 141, and 169 (predose) Day 197 (4 weeks after last dose)	**PK** Days 1 and 85 (predose and at 1, 2, 4, and 6 hours postdose) Days 15, 29, 57, 113, 141, and 169 (predose) Day 197 (4weeks after last dose) **PD** Days 1, 15, 29, 57, 85, 113, 141, and 169 (Predose) Day 197 (4weeks after last dose) **Immunogenicity** Days 1, 15, 29, 57, 85, 113, 141, and 169 (predose) Day 197 (4weeks after last dose)	NA	Completed Section 3.1.3

Study No. Module	Dev. Phase	Study Design	Population Number of participants enrolled	Tofersen Dose/Regimen	Samples Collected			Status/ Section
					CSF	Plasma/Serum	Other	
233AS102 (CSR 233AS102 Interim 1, 16 July 2021 data cut and CSR 233AS102 Interim 2, 16 January 2022 data cut) Module 5.3.5.2	3	Long-term safety, tolerability, PK, PD, immunogenicity and efficacy of open-label tofersen after multiple IT injections of tofersen in participants with SOD1-ALS who previously completed Study 101[b]	Participants with SOD1-ALS n = 95 [Part C] n = 44 [Parts A and B]	Tofersen IT 100 mg (n = 139) Loading doses on Days 1, 15, and 29 Maintenance dosing on Weeks 8, 12, and 16 and every 4 weeks thereafter, up to Week 360	**PK and PD** Days 1, 15, and 29 (predose) Weeks 8, 12, and 16 and every 4 weeks thereafter, up to Week 360 (predose) 4 Weeks after the last dose	**PK and Immunogenicity** Days 1, 15, and 29 (predose) Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, 156, 164, 172, 180, 188, 196, 204, 212, 220, 228, 236, 244, 252, 260, 268, 276, 284, 292, 300, 308, 316, 324, 332, 340, 348, and 356 (predose) 4 Weeks after the last dose **PD** Days 1, 15, 29 (predose) Weeks 8, 12, and 16 and every 4 weeks thereafter, up to Week 360 (predose) 4 Weeks after the last dose	CNS tissues (for 3 participants who died and had autopsy samples) for PK	Ongoing 2 interim data cutoff[c] Section 3.1.4

Study No. Module	Dev. Phase	Study Design	Population Number of participants enrolled	Tofersen Dose/Regimen	Samples Collected			Status/ Section
					CSF	Plasma/Serum	Other	
233HV101 CSR 233HV101 Module 5.3.5.3	1	Open-label, 4-cohort, single-dose study to determine the safety, tolerability, and distribution of a microdose of radiolabeled tofersen co-administered with unlabeled tofersen in healthy adult participants	Healthy Volunteers n = 3[c]	Tofersen IT (containing up to 100 µg radiolabeled tofersen) 100 mg (n = 3[d]) Single dose Day 1	**PK and PD** Day 1 (predose) and 15 (postdose)	**PK** Day -1 or Day 1 (predose) (Day 1 (1, 2, 4, and 24 hours [Day 2] postdose) Days 15 and 29 **Immunogenicity[e]** Day -1 or Day 1 (predose) Day 29	NA	Completed/Terminated Section 3.1.5

[a] A total of 6 participants in Study 101 Part A did not have a SOD1 mutation, since this was not required prior to Protocol Version 2.0. None of these 6 participants enrolled in Study 102; 2 only received placebo while 4 received a single dose of tofersen.
[b] Participants entered the 233AS102 extension receiving tofersen doses corresponding to their cohort assignment from Study 101 Part B MAD (ranging from 20 to 60 mg). All participants were eventually escalated to the tofersen 100 mg dose
[c] Data are included up tofor 16 July 2021 and 16 January 2022 interim data cut off, with full cleaning and interim lock of the data.
[d] In total, 8 participants without ALS were exposed to a single dose of tofersen. Of these, tofersen 40 mg was administered to 5 participants at a site that was ultimately discontinued due to GCP noncompliance; data from these participants were reported but not analyzed. At the time of termination, remaining 3 participants completed the study at another site, 2 received unlabeled tofersen 100 mg and 1 participant received only 66.7 mg of unlabeled tofersen due top preparation error. For further details refer to CSR 233HV101.
[e] Immunogenicity samples were collected but not analyzed.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 1
Abbreviations: ALS, amyotrophic lateral sclerosis; CNS, central nervous system; CSF, cerebrospinal fluid; GCP, good clinical practice; IT, intrathecal; MAD, multiple ascending dose; mITT, modified intent-to-treat; NA, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; SOD1, superoxide dismutase 1

Study 233AS101 Part A (Single Ascending Dose)

Twenty SOD1-ALS patients were enrolled and dosed in Part A as a randomized, double-blind, placebo-controlled, single-ascending-dose study. Five participants were assigned to placebo and 3, 3, 3, and 6 to tofersen 10, 20, 40, and 60 mg, respectively. A total of 19 participants (95%) completed Part A. The CSF tofersen concentration increased with dose in a less-than dose-proportional fashion. In plasma, the median C_{max}, and AUC_{0-24} were roughly dose-proportional; however, high PK variability was observed across tofersen levels (Table 94). Following a tofersen single dose, there were no meaningful changes in CSF SOD1 protein or neurofilament levels in CSF or plasma.

Table 94. Plasma PK Parameters of Tofersen on Day 1 – SAD PK Population

Parameter	Tofersen 10 mg N=3	Tofersen 20 mg N=3	Tofersen 40 mg N=3	Tofersen 60 mg N=6
AUC_{0-24h} (h·ng/mL) mean (SD)	1050 (811)	1040 (200)	2920 (600)	5730 (2850)
C_{max} (ng/mL) mean (SD)	81.7 (67.8)	85.1 (52.6)	203 (31.1)	687 (488)
T_{max} (h) median	4	6	6	2

Source: Clinical Study Report 233AS101 (Parts A & B), Table 46
Abbreviations: AUC_{0-24h},.area under the concentration-time curve from 0 to 24 h; C_{max}, maximum plasma concentration; PK, pharmacokinetics; SAD, single ascending dose; SD, standard deviation; T_{max}, time to achieve maximum concentration

Study 233AS101 Part B (MAD)

Part B was a randomized, double-blind, placebo-controlled, MAD study that evaluated four dose levels of tofersen (20, 40, 60, and 100 mg) in SOD1-ALS subjects. In total, 50 subjects were randomized in a 3:1 tofersen-to-placebo ratio. Tofersen CSF concentrations increased with dose level, generally in a less-than dose- proportional manner. Steady state was achieved immediately

after the loading period. Moderate to high inter- and intraparticipant variabilities in the CSF concentration profiles were observed. There was little to no apparent BIIB067 accumulation in plasma or CSF following monthly dosing. The plasma PK parameters are listed in Table 95.

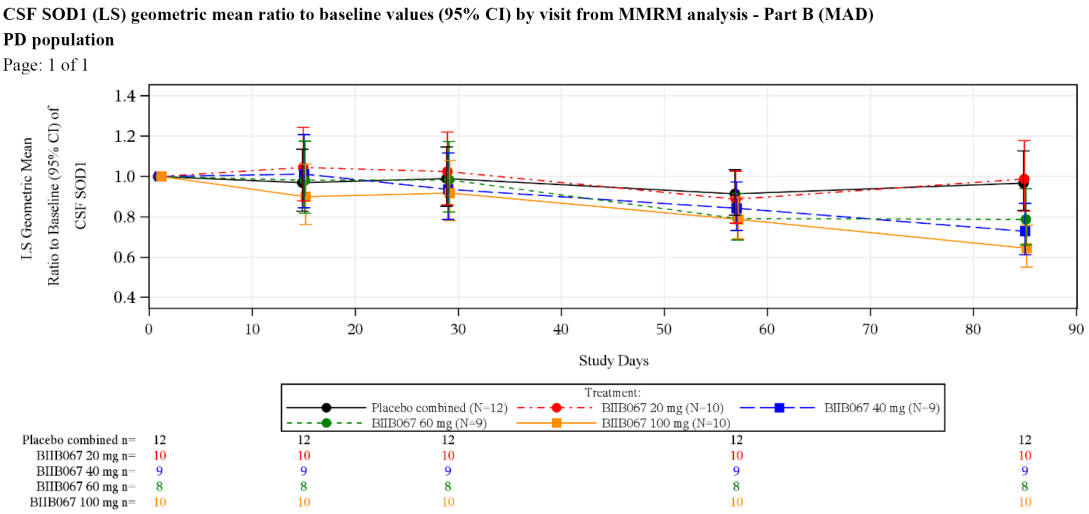
Table 95. Plasma PK Parameters of Tofersen on Day 1 – MAD PK Population

Parameter	Tofersen 20 mg N=10	Tofersen 40 mg N=10	Tofersen 60 mg N=9	Tofersen 100 mg N=10
$AUC_{0\text{-}24h}$ (h·ng/mL) mean (SD)	1192.82 (630.494)	3501.00 (2005.443)	4970.60 (2732.748)	13662.68 (7932.218)
C_{max} (ng/mL) mean (SD)	121.85 (118.837)	350.92 (315.466)	603.56 (569.433)	1414.40 (1124.249)
T_{max} (hr) median	6	6	2	3

Source: Clinical Study Report 233AS101 (Parts A & B), Table 47
Abbreviations: $AUC_{0\text{-}24h}$,.area under the concentration-time curve from 0 to 24 h; C_{max}, maximum plasma concentration; MAD, multiple ascending dose; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to achieve maximum concentration

Geometric mean ratios of SOD1 protein concentrations from baseline to Day 85 decreased by 1%, 27%, 21%, and 36% in the tofersen 20, 40, 60, and 100 mg groups, respectively, and 3% in the placebo group (Figure 33). At Day 85, the difference between the 100 mg group and the placebo group was statistically significant (p<0.0001).

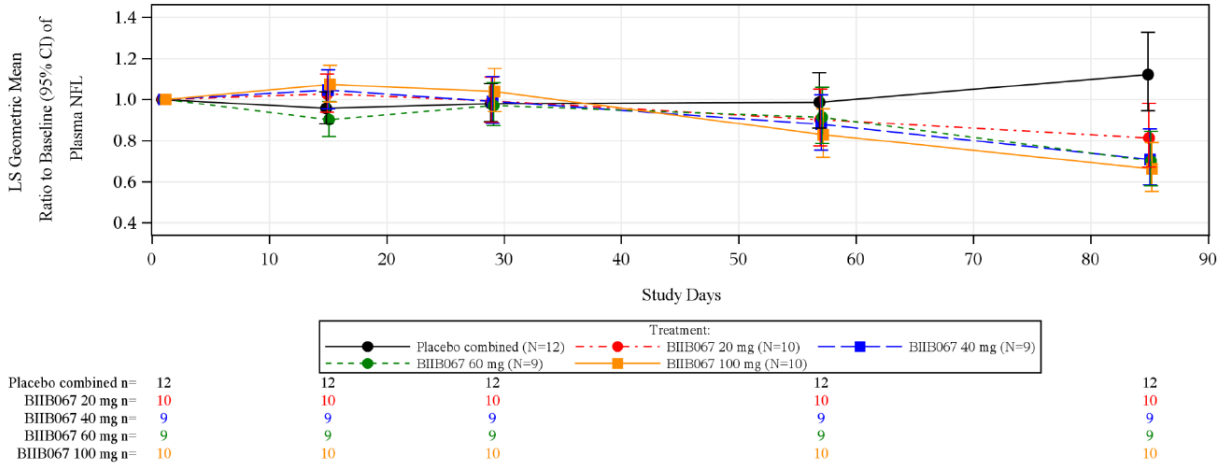
Figure 33. CSF SOD1 Geometric Mean Ratio to Baseline Values (95% CI) by Visit From MMRM Analysis – Part B (MAD) PD Population



NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Lower limit of quantitation (LLOQ) is 15.6 ng/mL.
NOTE 3: Due to some anomaly for the CSF sample at Day 15 for Participant (b) (6) the result was BLQ and looks like it is an extreme outlier. Therefore the value for this participant at Day 15 is set to missing. This value is therefore imputed.
NOTE 4: The least squares means and confidence intervals are taken from the MMRM model with natural log transformed data using an unstructured (UN) variance-covariance
matrix structure. Dose group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction terms were included in the model as explanatory variables, adjusting for disease progression type as a covariate.
NOTE 5: Data points where n = 1 are not presented.
Source: Clinical Study Report 233AS101 (Parts A & B), Figure 9
Abbreviations: BLQ, below limit of quantitation; CSF, cerebrospinal fluid; LS, least squares; MAD, multiple ascending dose; MMRM, mixed model for repeated measures; PD, pharmacodynamic; SOD1, superoxide dismutase 1

Neurofilament levels (pNfH and NfL in CSF and plasma) were evaluated as an exploratory biomarker. The mean plasma NfL level increased by 12% in the combined placebo from baseline on Day 85 as compared to a reduction of 19 to 34% in the tofersen groups based on mixed model for repeated measures (MMRM) analysis (Figure 34). The percentage plasma NfL reduction at Day 85 compared to baseline was 19%, 29%, 30%, and 34% following monthly dosing of 20 mg, 40 mg, 60 mg, and 100 mg tofersen, respectively. The mean CSF NfL levels increased by 14% from baseline in the combined placebo on Day 85 as compared to a reduction of 22% to 37% in the 20 mg, 40 mg, 60 mg, and 100 mg tofersen groups based on MMRM analysis.

Figure 34. Plasma NfL (LS) Geometric Mean Ratio to Baseline Values (95% CI) by Visit by MMRM Analysis – Part B (MAD) PD Population



NOTE 1: Baseline is defined as Day 1 value prior to the study drug. If Day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Lower limit of quantitation (LLOQ) is 0.696 pg/mL.
NOTE 3: The analysis is based on MMRM model with natural log transformed data using an unstructured (UN) variance-covariance matrix structure. Dose group, visit, treatment-by-visit interaction, baseline score, and baseline score-by-visit interaction terms were included in the model as explanatory variables, adjusting for disease progression type as a covariate.
NOTE 4: Data points where n = 1 are not presented.

Source: Clinical Study Report 233AS101 (Parts A & B), Figure 19
Abbreviations: LS, least squares; MAD, multiple ascending dose; MMRM, mixed model for repeated measures; NfL, neurofilament light chain; PD, pharmacodynamic; SOD1, superoxide dismutase 1

Overall CSF pNfH levels increased by 4% in the combined placebo group from baseline to Day 85 as compared to a mean reduction of 20% in the highest tofersen dose group (100 mg) based on MMRM analysis. Overall plasma pNfH level increased slightly by 6% in the combined placebo group from baseline to Day 85 as compared with a mean reduction of 37% in the highest tofersen dose group (100 mg) based on MMRM analysis.

Study 233AS101 Part C (Pivotal Study, Study 101C) and Study 233AS102 (Study 102)

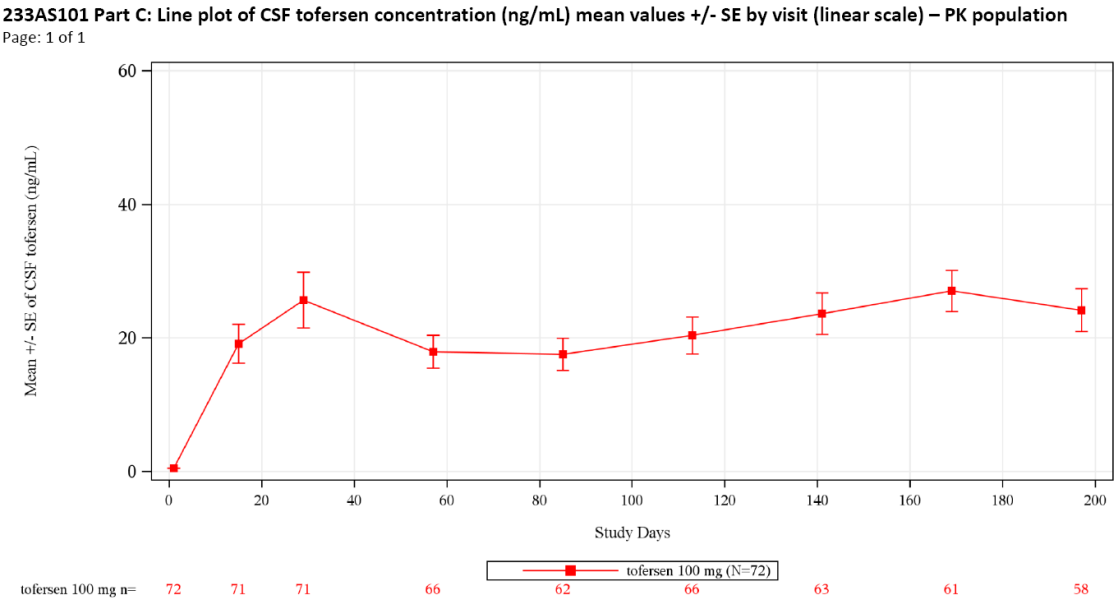
Refer to Section 6 for the discussion on study design and biomarker data of plasma NfL from Study 101C and Study 102. Refer to Section 14.7 for other biomarker data from Study 101C.

In study 101C, PK of tofersen was evaluated in CSF and plasma. PK samples in CSF were collected at pre-dose of each visit before tofersen IT administration. In CSF, steady-state concentrations of tofersen were achieved after the loading period (three doses administered every 2 weeks) with a mean CSF C_{trough} of 26 ng/mL (CV% 137%) at Day 29. The PK profile of CSF

C_{trough} showed little to no accumulation with monthly dosing after the loading phase, indicating that the effective half-life of tofersen in CSF is approximately 1 month (Figure 35). At the end of treatment (Day 197), the mean CSF C_{trough} was 24 ng/mL (CV% of 101%).

Tofersen PK in plasma was evaluated with PK sampling collected at pre-dose, 1, 2, 4, and 6 h post-dose on Days 1 and 85. Predose plasma samples were collected at each visit. A limited number of subjects had their plasma PK profiles for post-dose 1 to 6 h evaluated (N=22 on Day 1 and N=18 on Day 85) due to inadvertent omission of post-dose PK sampling in the original protocol for Study 101C. Based on the available PK data, the median T_{max} of plasma tofersen was 4 h post-dose. Minimal or no accumulation in plasma was observed. The AUC_{0-24h} and C_{max} values were generally consistent between Day 1 and Day 85 PK, with high intersubject variability.

Figure 35. CSF Tofersen Concentration (ng/mL) Mean Values ±SE by Visit (Linear Scale) – PK Population



NOTE 1: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 1 ng/mL) in calculations. The sample with concentration > 300 ng/mL is excluded from the summary.
NOTE 2: The mean values presented are arithmetic means.
Abbreviations: CSF = cerebrospinal fluid.
Source: Study report of 233AS101 Part C, Figure 28
Abbreviation: PK, pharmacokinetic

PK characterization of tofersen in CSF and plasma from pooled studies (233AS101 Part A, B, and C) was conducted via population PK modeling; see Section 14.5.4.1.

Study 233HV101

Study 233HV101 was an open-label, single-dose study designed to determine the safety, tolerability, and distribution of a microdose of ^{99m}Tc-MAG3-BIIB067 (radiolabeled tofersen) co-administered with unlabeled tofersen in healthy adult subjects. Eight subjects without ALS were exposed to a single dose of tofersen. Of them, only three subjects completed the study: two received unlabeled tofersen at 100 mg plus a microdose of ^{99m}Tc-MAG3-BIIB067 at 100 µg, and

one subject received only 66.7 mg unlabeled tofersen due to a preparation error. Radiotracer activity was quantified using SPECT/CT imaging as percentage of dose in the target brain and spinal cord parenchymal regions of interest at 1, 4, and 24 h post-dose. Radiolabeled tofersen was distributed throughout the CNS after intrathecal injection in all three subjects. Based on the SPECT/CT analysis, ^{99m}Tc-MAG3-BIIB067 distributes from the lumbar spine to the rostral cranium within 24 h. In the lumbar spine, the concentration decreases after the 1 h post-dose scan. Correspondingly, the concentration in the brain increased after the 1 h post-dose scan. Based on the modeling of radiation dosimetry data, the estimated highest equivalent dose of tofersen was found in the spine (mean 2.72 rem), followed by the brain (mean 0.61).

14.3. Bioanalytical Method Validation and Performance

14.3.1. Plasma NfL Assay Used in Studies 101C and 102

The [redacted] (b) (4) NfL assay reported in TS067-038VR is an automated two-site sandwich immunoassay using direct chemiluminometric technology. The [redacted] (b) (4) assay was used for ethylenediaminetetraacetic acid (EDTA) plasma sample analysis in Study 233AS101 Part C and Study 102. The assay uses two mouse monoclonal antibodies that bind to NfL, each recognizing a unique NfL epitope. The solid phase reagent (capture reagent) contains a biotinylated anti-NfL monoclonal antibody coupled to a paramagnetic particle conjugated to streptavidin. The light reagent (detection reagent) contains a monoclonal anti-NfL antibody conjugated to acridinium ester (AE) for chemiluminescent detection. The accumulated light signal is directly related to the sample NfL concentration. The seven-point (seven calibrators) master curve (calibration standard curve) fits to a five-parameter logistical (5-PL) model and was used to back-calculate sample concentrations. Unlike typical ligand-binding assays, the master curve was performed only once and not performed in any sample analysis runs; instead, two-point calibration was performed with a 28-day calibration interval to correct the differences between the light generated in the sample analysis runs and those in the master curve run. Three levels of quality controls were performed in each sample-analysis run. Method performance characteristics assessed in method validation experiments are listed in Table 96.

Table 96. Method Validation Summary for the [redacted] (b) (4) Plasma NfL Assay

Characteristic	Description
Calibration range	4.93 to 474 pg/mL *The concentration values were nominally derived from the recombinant NfL material used, which did not have a reliably assigned concentration in the absence of a certified reference standard. (See item C below under reviewer's assessments for further details.)
Relative accuracy	Inferred by the demonstrated parallelism for up to 310 pg/mL 92% to 93% spiking recovery assessed by spiking CSF NfL into plasma containing native NfL 104% to 107% spiking recovery assessed by spiking the recombinant NfL into plasma containing native NfL

Characteristic	Description
Precision	Inter- and intra-assay precision: 7.7% to 18.1% 20-day precision: 3.16% to 8.62%
Specificity	1000 pg/mL NfM and NfH do not impact the NfL measurement at 20 pg/mL
Selectivity	No interference from the following substances and concentrations: • Hemoglobin below 500 mg/dL • Direct bilirubin below 60 mg/dL • Indirect bilirubin below 40 mg/dL • Albumin below 6 g/dL • RF below 193 U/mL • Biotin below 3500 ng/mL • Triglycerides below 2000 mg/dL No interference from the following drugs: • Donepezil • Rivastigmine • Memantine • Galantamine • Citalopram • Mirtazapine • Sertraline • Bupropion • Duloxetine • Mipramine • Ibuprofen • Siponimod • Acetaminophen • Aspirin • Beta interferon 1a • Beta interferon 1b • Fingolimod • Dimethyl fumarate • Teriflunomide • Ocrelizumab • Mitoxantrone* • Caldribine • Alemtuzumab • Glucose • Riluzole and Edaravone • Tofersen Assay interference was observed in the presence of Mitoxantrone at concentrations greater than 0.113 mg/dL.
Stability	Five samples at concentrations of 2.53, 4.73, 5.87, 7.71, and 11 pg/mL from five donors were tested stable at the following conditions: • 6 freeze-thaw cycles • RT, 1 week • 4°C, 2 weeks • -15 to -25°C, 3 months • -60 to -90°C, 2 years Four samples at concentrations of 59.3, 106, 282, and 463 pg/mL were tested and shown to be stable for 2 year 9 months.
Parallelism	Demonstrated at concentrations up to 310 pg/mL

Source: Compiled data based on report TS067-038VR and its amendment
Abbreviations: CSF, cerebrospinal fluid; NfH: neurofilament heavy chain; NfL, neurofilament light chain; NfM, neurofilament medium chain; RF, rheumatoid factor; RT, room temperature

Summary of Reviewer's Assessments of Assay Performance Characteristics

We note that all concentration values cited in the summary below were nominally derived from the recombinant NfL material used in this NDA, which did not have a reliably assigned concentration in the absence of a certified reference standard. In other words, the numeric values of measured NfL concentrations are dependent on the specific recombinant NfL material used. Therefore, the absolute values of NfL concentrations derived from this assay/study could not serve as reference values for study enrollment or patient stratification without scientific verification, including analytical characterization of the new recombinant NfL material and demonstration of comparability between the new NfL material and that used in this study.

Precision

Precision was demonstrated to be acceptable based on testing of native NfL-containing plasma samples in two studies:

- Inter-assay precision was assessed using five concentration levels, which were prepared in NfL-depleted plasma by spiking with pooled CSF containing high concentrations of native (endogenous) NfL. The precision was 7.7% to 18.1% based on data from 16 runs performed by two analysts in 8 days at NfL levels of 4.93 to 474 pg/mL.
- Method reproducibility was assessed using donor samples at three concentration levels (6.83, 37.2, and 534 pg/mL). The samples were tested over 20 days, two runs per day. The low- and medium-concentration samples (6.83 and 37.2 pg/mL) were unaltered EDTA plasma with endogenous NfL. The high-concentration sample (544 pg/mL) was EDTA plasma spiked with NfL from a CSF sample. The 20-day test precision was 3.15 to 8.62%, indicating that the method is reproducible.

Selectivity and Specificity

Selectivity and specificity were demonstrated by several experiments that showed no interference from endogenous substances (Table 96) and concomitant drugs used to treat patients with Alzheimer disease and multiple sclerosis (Table 96).

Parallelism

The baseline plasma samples with concentrations up to 310 pg/mL were selected to dilute with the NfL-depleted pooled plasma. The serial dilutions of every sample demonstrated good parallelism, indicating that native NfL from endogenous samples behaves similarly to the calibration material (recombinant NfL), and the calibration material is suitable for measuring NfL in plasma samples from clinical studies. This also indicates that samples across the concentration range (up to ~310 pg/mL) have similar relative accuracies. Although 310 pg/mL is well below the upper limit of the validation assay range (477 pg/mL), the distribution of sample concentrations provided by the Applicant shows that the concentrations of only 0.7% (6/873) of samples were >317 pg/mL (~310 pg/mL). Thus, the parallelism data are sufficient.

Stability

Freeze-thaw, bench-top, and long-term stability were assessed using five donor EDTA plasma samples (the same matrix as the study samples) with nominal concentrations of 2.53, 4.73, 5.87, 7.71 and 11.0 pg/mL at storage time 0. The relative recovery at the time of assessment was calculated against the concentration at time point 0 and compared with the acceptance criterion of 80 to 120%. All data generated for sample concentrations of 2.53 to 11.0 pg/mL met the acceptance criteria: Supporting six freeze-thaw cycles, storage at room temperature (RT) for up to 1 week, at 4 to 8°C for up to 2 weeks, at -15 to -25°C for up to 3 months, and at -60°C to -90°C for up to 2 years. These data were included in the initial submission.

However, the samples in study 233AS101 had concentrations up to 421 pg/mL, which exceeded the range (2.53 to 11.0 pg/mL) with demonstrated stability. FDA requested additional stability data to cover the full range of NfL concentrations in the study samples. In response, the Applicant provided data from an EDTA plasma panel created in February 2020. The panel spanning the assay range was created using pooled EDTA plasmas spiked with native NfL from

CSF. The initial testing was performed between April 1 and April 10, 2020, and four samples of concentrations 59.3, 106, 282 and 463 pg/mL were retested in duplicate on January 11, 2023, after storage for 2 years and 9 months at -80°C. The percent recoveries were 89% to 98%, indicating that the higher-concentration samples are stable and met the acceptance criteria.

Taken together these two sets of data indicate that the stability is not concentration dependent. Thus, the stability data are sufficient to support the Study 233AS101 sample analysis using the (b) (4) NfL method.

Accuracy

Accuracy is a required assay characteristic to confirm the reportable concentration. To assess the Applicant's method accuracy, the review team engaged with the Applicant via multiple Information Requests (IRs). The Applicant provided multiple sets of data in their response documents. Below is a high-level summary of the review findings.

In response to IRs on September 26, 2022, and January 06, 2023, the Applicant provided parallelism data to demonstrate acceptable relative accuracy over the Study 233AS101 sample concentration range (refer to the section on parallelism above for further details).

In response to the January 6, 2023, IR to justify the uniformity of the master curve material, the Applicant provided a set of data that showed 104% to 107% spike recovery for recombinant NfL. In the experiment, plasma containing a fixed level of native NfL was spiked with recombinant NfL at the nominal concentrations of 15.01 to 249.33 pg/mL. The calculated spike recovery met the predefined criterion of 80 to 120%.

In response to the September 26, 2022, and January 6, 2023, IRs for accuracy data, the Applicant stated that accuracy was assessed with a spike recovery experiment. Eighteen samples were generated by spiking two levels of CSF NfL (i.e., native NfL) into nine native NfL-containing donor plasma samples (baseline samples) at three levels (low, medium, and high). Spike recovery was evaluated by comparing concentrations before and after spiking against the nominal spike concentration. The calculate average spike recovery over three levels was 92% to 93%, which met the predefined criterion of 80 to 120%.

- Summary of accuracy assessment: Two experiments provided supportive information for assay accuracy: (1) the parallelism data demonstrated that the assay had acceptable relative accuracy, and (2) two sets of spike recovery data demonstrated that the concentration was accurate when using the nominal concentration assigned by the Applicant using their approach (using the same yet-to-be-validated assay, see item 3 in the next section for additional comments). Based on these results, the assay is suitable for assessing NfL concentration changes over time (e.g., change from baseline) and differences between treatment groups (e.g., placebo versus tofersen). However, the reported NfL concentration values were specific to the NfL calibration material and the NfL assay used to support the clinical studies.

The method validation study had several deficiencies, which were deemed to have no significant impact on the sample analysis given the current context of use:

1. Inappropriate setup for the calibration curve

An assay should use the same material to prepare all the calibrators to produce one calibration curve (the master curve). However, this assay used NfL material from two sources to prepare one

master curve. Of the seven-point calibrators, one contained native NfL (at 7.55 pg/mL) and five contained recombinant NfL protein. The uncertainty of the uniformity of these two materials could render the reported concentrations noninterpretable and unreliable.

In addition, the seventh calibrator (S01, 0 pg/mL) comprised NfL-depleted serum but no data were provided to prove that the NfL concentration therein was 0 pg/mL. Thus, it is inappropriate to include a zero value in the standard curve for regression analysis.

However, as reported by the Applicant, one set of calibrators was used for all sample analyses, so the impact of the uniformity on samples was equal; therefore, uniformity would not influence assessment of the relative changes of NfL during tofersen treatment.

2. Inappropriate setup for assay sensitivity and range

Accuracy is a key characteristic for defining the sensitivity and range of an assay. For defining assay sensitivity, the lower limit of quantitation (LLOQ) of 4.93 pg/mL was set based on the detectable NfL level among a panel of samples, not assay accuracy and precision. The Applicant's approach to LLOQ determination did not follow the current industry standard and best practice. Further, the LLOQ value is below the concentration of the lowest calibrator of 7.55 pg/mL, excluding the seventh calibrator (concentration 0 pg/mL). Therefore, the LLOQ is outside the quantitative range of the master curve.

Assay range is a validated range of concentrations for which the assay has acceptable accuracy, precision, and linearity. The Applicant defined the assay range based on the LLOQ and linearity over a concentration range through LLOQ. The linearity range should have been assessed based on the correlation between the expected and measured concentrations. However, the expected concentrations of panel members used for this assessment were not rigorously assigned as the Applicant stated (see item 3 below). This precludes appropriate determination of assay linearity. Although the Applicant demonstrated assay precision using samples of 4.93 to 474 pg/mL, the assay range is not justifiable because (1) precision was demonstrated using the inappropriately defined LLOQ and (2) there were issues with the linearity assessment (described above).

Analysis of the distribution of concentrations in the study samples showed that only 0.5% of 899 sample concentrations were <5.1 pg/mL, and >90% of sample concentrations were >10.8 pg/mL, that is, higher than 4.93 pg/mL. Therefore, the inaccurate sensitivity may not affect this study analysis.

3. Inappropriate approach used to assign the nominal concentrations of the calibrators

The concentration of recombinant NfL stock solution should be established in the certificate of analysis using standard methods for protein concentration assessments. However, in this assay the NfL stock concentration was determined using the yet-to-be-validated (b) (4) NfL assay. This approach rendered the assigned nominal concentrations of the calibrators unreliable. Because the reported concentrations for study samples were derived from the master curve using these calibrators, the concentrations of study samples are unreliable. However, the lack of a reliable concentration for the NfL stock is likely to have limited impact on assessment of NfL concentration differences because only one recombinant NfL material was used to analyze all study samples.

Overall, the data from endogenous NfL samples demonstrated that the NfL assay has good precision, relative accuracy, selectivity, specificity, and stability. Therefore, the (b) (4)

plasma NfL assay is suitable for evaluating NfL concentration differences (e.g., placebo versus tofersen) and changes (e.g., pre- versus post-treatment) in clinical studies and the assay validation is fit for the purpose of evaluating plasma NfL to support the accelerated approval of tofersen. However, extension to other contexts of use would necessitate further scientific assessments and justifications.

14.3.2. CSF Total SOD1 Assay Used in Studies 101C and 102

The assay used the human Cu/Zn SOD (SOD1) Platinum ELISA Kit to quantitate total SOD1 in human CSF. The assay is based on the double antibody sandwich method. SOD1 is captured by the immobilized antibody and detected by the HRP-conjugated antihuman SOD1 detection antibody. Controls, calibrators, and human samples containing SOD1 are added to the coated plate. After incubation, the plates are washed free of unbound material followed by addition of an HRP-conjugated antihuman SOD1 antibody. The bound HRP conjugate is detected using the colorimetric substrate tetramethylbenzidine (TMB). Color development is stopped with acid stop solution. The intensity of the color, which is directly proportional to the amount of SOD1 in the sample, is measured using a microplate reader.

Results of the validation experiments demonstrated that the performance of the assay was acceptable in terms of calibration/standard curve range suitability, precision and accuracy including the LLOQ and ULOQ, parallelism, and prozone effect with ALS patient CSF samples (Table 97). The Applicant established stability conditions by testing one set of endogenous samples with the middle quality control concentration, which covers the upper limit of the sample concentration range: bench-top stability at ambient room temperature for 28 h, 2 to 8°C (refrigerator) stability for 27 h, stability over six freeze-thaws, and long-term stability at −60 to −80°C for 1126 days (Table 97). The established stability conditions and duration are sufficient to support in-study sample process and storage; however, the Applicant did not test endogenous samples with concentrations at the lower end of the range. The Applicant acknowledged the deficiency reflected in the IR response and committed to including lower-level endogenous quality control samples in upcoming studies. Overall, the assay is suitable for measuring the total SOD-1 concentration of samples in Studies 101C and 102.

Table 97. Summary of Method Validation for SOD1 Quantification

Characteristic	Description
Analyte	SOD1
Matrix	Human cerebrospinal fluid
Type assay	ELISA
Method number	ELISA-0675
Minimal required dilution	1:200
Assay range	0.078 to 5.000 ng/mL
Calibration curve fit model	4-PL, weighting factor of 1/y2

Characteristic	Description
QC performance Intra-assay (n=3 at each level of assay, total six assays)	**Table 98. Intra-Assay Method Validation Results** **QC (ng/mL) / Precision Range (CV%) / Accuracy/Bias Range (%)** LLQC (0.078)* / 3.2-26.7 / 0.9-16.7 LQC (0.200) / 1.6-24.9 / -3.3-10.4 MQC (1.500) / 0.2-24.3 / -6.9-5.8 HQC (3.500) / 4.1-22.9 / -4.3-19.6 ULQC (5.000) / 4.2-21.5 / -9.8-11.8 * Summary based on 5 of 6 assays.
Interassay (six assays)	**Table 99. Interassay Method Validation Results** **QC (ng/mL) / Precision (%) / Accuracy/Bias (%) / Total Error (%)** LLQC (0.078)* / 15.6 / 11.0 / 26.6 LQC (0.200) / 11.5 / 3.2 / 14.7 MQC (1.500) / 10.9 / -1.9 / 12.8 HQC (3.500) / 12.6 / 4.9 / 17.5 ULQC (5.000) / 12.0 / -0.4 / 12.4 * Summary based on 5 of 6 assays.
Parallelism	Up to 474 ng/mL and 1/800 dilution from human CSF and ALS CSF samples
Stability	Freeze/thaw (F/T): Up to 6 cycles Bench-top stability: 28 h, 25 min Refrigerator stability: 27 h, 22 min Long-term stability (−60 to −80°C): 1126 days

Source: Compiled data from report TS067-008VR and amendment
Abbreviations: ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; CV, coefficient of variation; F/T, freeze-thaw; ELISA, enzyme-linked immunoassay; HQC, high quality control; LLQC, lower limit quality control; LQC, low quality control; MQC, middle quality control; QC, quality control; SOD1, superoxide dismutase 1; ULQC, upper limit quality control

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Immunogenicity was evaluated in all completed and ongoing clinical studies. Refer to Table 113 in Section 14.8.1 for the sampling plan of each clinical study. In studies with SOD1-ALS patients, baseline samples were collected followed by predose sampling at visits including at 1 to 2 weeks to monitor the anticipated onset of early immunogenic responses. At subsequent visits, immunogenicity assessments were conducted at up to 8-week intervals to establish persistence of response. Plasma drug concentration was assessed at the same visits as immunogenicity sample collection to monitor the impact of immunogenicity on the tofersen plasma PK. The immunogenicity sampling plans are appropriate.

Anti-tofersen antidrug antibodies (ADAs) were detected using a tiered approach involving screening, confirmatory, and titer assays. Refer to Immunogenicity Consult and Assessment Review for information on the performance of ADA assay (NDA 215887, DARRTS dated January 31 2023 by Dr. Seth Thacker). Neutralizing antibodies against tofersen were not evaluated in the current submission.

In all clinical studies, subjects with at least one confirmed post-treatment positive result were considered treatment-emergent positive for anti-tofersen ADA if their baseline result was negative.

For Study 233AS101 (Parts A, B, and C), 33 of 125 (26.4%) tofersen-treated subjects had treatment-emergent anti-tofersen ADA, of which 5 (4.0%) had transient responses and 28 (22.4%) had persistent responses. In Part C, 22 of 72 (30.6%) subjects treated with tofersen (100 mg dose group) were treatment-emergent positive for anti-tofersen ADA. Of the 51 ADA-positive samples, 50 had titers of ≤200 and 1 had a titer of 400. Three and nineteen tofersen-treated subjects had transient and persistent ADA responses, respectively.

In Study 102 (at interim data cut-off date 16 January 2022), 71 of 138 (51.4%) subjects treated with tofersen (100 mg dose) were positive for treatment-emergent anti-tofersen ADA, 63 and 8 of which had persistent and transient ADA responses, respectively. Most subjects positive for anti-tofersen ADA had titers of 25 to 800; however, 11 had anti-tofersen ADA titers of 1600 to 102,400.

In pooled Studies 233AS101 Part C and 102 tofersen treatment period (at the interim data cut-off date 16 January 2022), of the 104 subjects, 3 (2.9%) were ADA positive at baseline. Of the 61/104 (58.7%) tofersen-treated subjects who became ADA positive, 9 (8.7%) were had a transient response and 52 (50.0%) had a persistent response.

Overall, of 166 subjects with postbaseline plasma ADA samples, 97 tofersen-treated subjects (58.4%) developed treatment-emergent ADAs, of which 14 were transient and 83 were persistent (based on the 15 July 2022 data cut-off for the 120-day safety update).

Effects of ADAs on Tofersen Plasma PK

In the plasma tofersen population PK model, the presence of antibodies was found to decrease the plasma CL by 32%. Refer to Section 14.5.4.1 for details on the population PK modeling for plasma tofersen.

Effects of ADAs on Tofersen CSF PK

The effects of ADA on CSF tofersen clearance cannot be reliably estimated due to the lack of serial time points of CSF tofersen and the large variability of the descriptive CSF trough concentration data. In Studies 101C and 102, sampling of CSF was performed at trough concentrations, immediately before drug administration, and the population PK model for CSF tofersen PK did not evaluate the effects of covariates.

Effects of ADAs on Biomarkers (Plasma NfL and CSF Total SOD1)

No discernable differences in total CSF SOD1 and plasma NfL reductions in ADA-positive compared to ADA-negative subjects across study visits in Studies 101C and 102. This conclusion is based on the descriptive data summary of total CSF SOD1 protein and plasma NfL change from baseline at each study visit by ADA status (negative, positive). ADA status was also tested as a covariate in two PK/PD models of tofersen: CSF tofersen-CSF total SOD1 and CSF tofersen-plasma NfL. ADA status was not a significant covariate for the CSF SOD1 protein or plasma NfL PK/PD models. Refer to Sections 14.5.4.2 and 14.5.4.3 for details.

Effects of ADAs on Clinical Efficacy

The effects of ADAs on clinical efficacy are unclear. It is challenging to draw conclusions on the comparison of ALSFRS-R in persistent ADA-positive subjects and other subjects given the small number of subjects in each group and the heterogeneity of the disease.

Effects of ADAs on Clinical Safety

ADAs do not appear to affect safety. The proportion of subjects with AEs selected by SMQ (hypersensitivity, anaphylactic reaction, and angioedema) was higher in ADA-negative subjects in the tofersen group (14/72 [19.4%]) and placebo group (11/36 [30.6%]) compared to ADA-positive subjects (5/72 [6.9%] in the tofersen group and 1/36 [2.8%] in the placebo group).

14.5. Pharmacometrics Assessment

14.5.1. Evidence From Literature: Demonstration of the Prognostic Value of Plasma NfL Levels in ALS

Introduction

ALS is a fatal neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons. Neurofilaments in plasma and CSF, a marker of axonal injury and neurodegeneration, are significantly elevated in patients with ALS. Both NfL and heavy (pNfH) chain neurofilaments are present in CSF and plasma. The objective of this study is to determine the relevance of neurofilament changes in ALS.

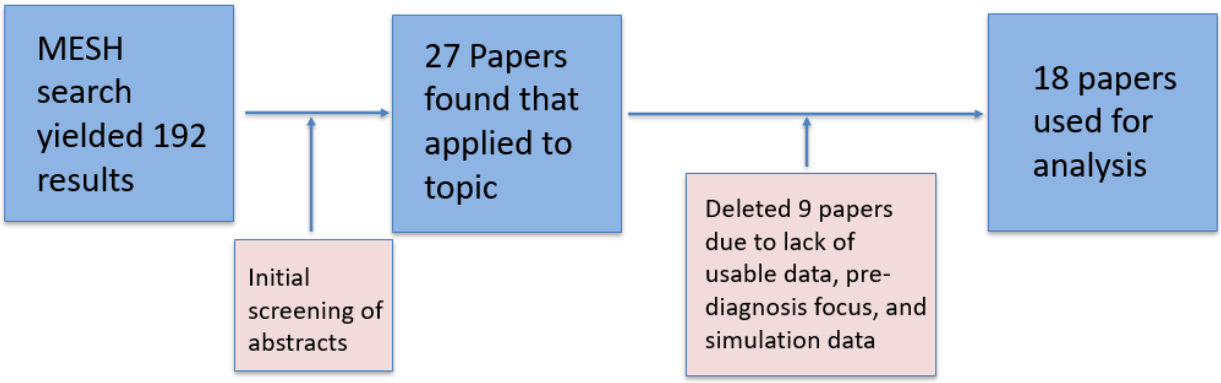
Methods

Data collection: A PubMed MESH term search was performed to identify studies evaluating the neurofilament levels in ALS patients using the following terms: (((((("Amyotrophic Lateral Sclerosis") OR ("ALS")) OR ("Charcot Disease")) OR ("Lou Gehrig Disease")) OR ("Lou Gehrig's Disease")) OR ("Motor Neuron Disease") AND ((("Blood") OR ("Plasma")) OR ("Serum"))) AND ((((("Neurofilaments") OR ("Neurofilament")) OR ("NfL")) OR ("Phosphorylated NfH")). The date range was set from 1982 to 2022. The MESH search yielded 192 results. An initial screening of the abstracts was performed to evaluate relevance to the research topic, yielding 27 relevant to neurofilaments in ALS. After evaluating data availability, 18 papers were included in the meta-analysis (Figure 36). The published meta-analysis of Zhou et al.[45] was also used to identify articles that may have been missed by the PubMed search.

The following data were extracted from the articles: author name, year of publication, region, number of subjects, demography, neurofilament measurement methods and relationship between neurofilaments (NfL and pNfH in CSF and plasma/serum) and clinical endpoints that included ALSFRS-R score, disease progression (DP) slope, and mortality.

[45] Zhou YN, Chen YH, Dong SQ, et al. Role of Blood Neurofilaments in the Prognosis of Amyotrophic Lateral Sclerosis: A Meta-Analysis. Front Neurol. 2021;12:712245. Published 2021 Oct 6. doi:10.3389/fneur.2021.712245

Figure 36. Flowchart of Document Retrieval for the Meta-Analysis



Source: Reviewer's analysis
Abbreviations: MESH, medical subheadings

Statistical analysis: Analysis was conducted using the 'metafor' package v. 3.4.0 in R v. 4.1.3. Hazard ratios with 95% confidence intervals were calculated to evaluate the association between plasma neurofilament levels and mortality risk in ALS patients. Correlation coefficients (R) were calculated to assess the relationships among plasma neurofilament levels, ALSFRS-R, and the rate of DP in ALS patients. Heterogeneity in correlation coefficients across studies was assessed by Cochran's Q test and the I^2 statistic. A random-effects model was used based on the substantial heterogeneity (I^2 >50%) in the data.

Results

Eighteen studies were included in the meta-analysis (Table 100)—15 prospective and 3 retrospective studies. These studies were conducted in various countries from 2007 to 2021.

Table 100. Summary of Publications Included in the Meta-Analysis

Study	Study Type	Region	Data Collection Period	Nf Measurement Method
Brodovitch 2021[4]	Prospective	France	NA	ECL
De-Schaepdryver 2020[22]	Retrospective	Italy	2009 - 2018	ECL
Gille 2019[3]	Prospective	Belgium	2016 - 2017	ECL
Lu 2015[13]	Prospective	UK	NA	ECL
Steinacker 2017[25]	Prospective	Germany	2012 - 2015	ECL
Thompson 2022[15]	Prospective	UK	2017 - 2020	ECL
Abu-rumeileh 2020[46]	Prospective	Italy	2009 - 2019	ELISA
Boylan 2012[47]	Prospective	USA	NA	ELISA
Gaiani 2017[48]	Retrospective	Italy	2010 - 2016	ELISA

[46] Abu-Rumeileh S, Vacchiano V, Zenesini C, et al. Diagnostic-prognostic value and electrophysiological correlates of CSF biomarkers of neurodegeneration and neuroinflammation in amyotrophic lateral sclerosis. J Neurol. 2020;267(6):1699-1708. doi:10.1007/s00415-020-09761-z

[47] Boylan KB, Glass JD, Crook JE, et al. Phosphorylated neurofilament heavy subunit (pNF-H) in peripheral blood and CSF as a potential prognostic biomarker in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013;84(4):467-472. doi:10.1136/jnnp-2012-303768

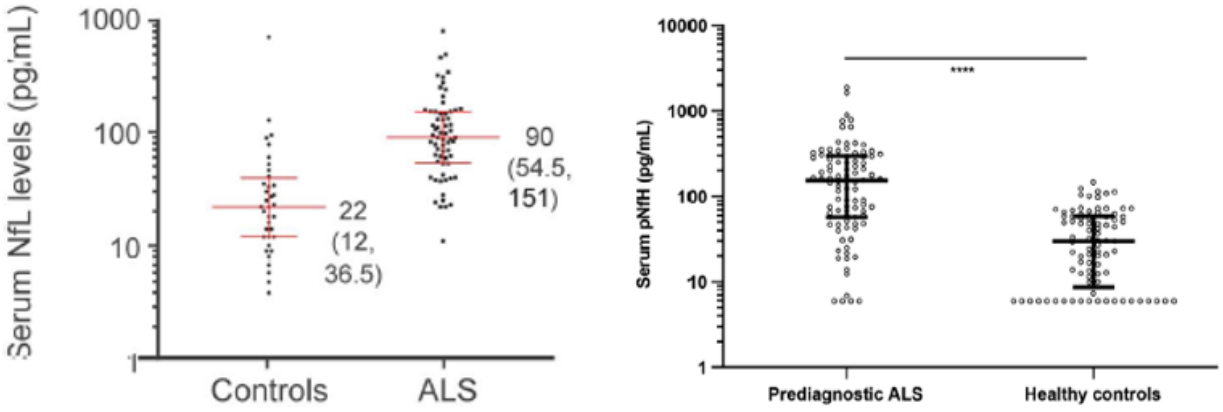
[48] Gaiani A, Martinelli I, Bello L, et al. Diagnostic and Prognostic Biomarkers in Amyotrophic Lateral Sclerosis: Neurofilament Light Chain Levels in Definite Subtypes of Disease. JAMA Neurol. 2017;74(5):525-532. doi:10.1001/jamaneurol.2016.5398

Study	Study Type	Region	Data Collection Period	Nf Measurement Method
Illan-gala 2018[49]	Prospective	Spain	NA	ELISA
Shi 2022[23]	Prospective	China	NA	ELISA
Menke 2015[24]	Prospective	UK	2009 - 2013	ELISA
De-Schaeodryver 2019[50]	Retrospective	Belgium	2007 - 2018	ELISA
Steinacker 2015[51]	Prospective	Germany	2010 - 2014	ELISA
Benatar 2020[29]	Prospective	USA	2015 - 2017	SIMOA
Thouvenot 2020[26]	Prospective	France	NA	SIMOA
Vacchiano 2021[27]	Prospective	Italy	2014 - 2021	SIMOA
Verde 2019[28]	Prospective	Germany	2010 - 2016	SIMOA

Source: Reviewer's analysis
Abbreviations: ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; Nf, neurofilament; SiMoA, single molecule array; NA, not applicable; UK, United Kingdom of Great Britain and Northern Ireland; USA, United States of America

Neurofilament levels in healthy subjects and ALS subjects: When axonal damage occurs, light and heavy chain neurofilaments are released into plasma, extracellular fluid, and CSF. Neurofilament levels were higher in ALS subjects than healthy subjects (Figure 37).

Figure 37. Comparison of Serum Neurofilament (NfL) Levels Between Healthy Subjects and ALS Subjects (Left) Comparison of Serum pNfH Levels Between Prediagnostic ALS and Healthy Controls (Right)



Source: Lu et al., 2015[13]; De Schaepdryver et al., 2019[50]
Prediagnostic ALS: Serum samples drawn prior to diagnosis of ALS
Abbreviations: ALS, amyotrophic lateral sclerosis; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain

Correlation between CSF and serum neurofilaments: The serum NfL level strongly correlates with that in CSF according to Lu et al.,[13], Gille et al.,[3] Thompson et al.,[15] and Shi et al.[23] The plasma and CSF pNfH levels are correlated according to Shi et al.,[23] and Boylan et al.[47] This suggests that serum NfL and pNfH levels are reasonable surrogates for the CSF levels of NfL

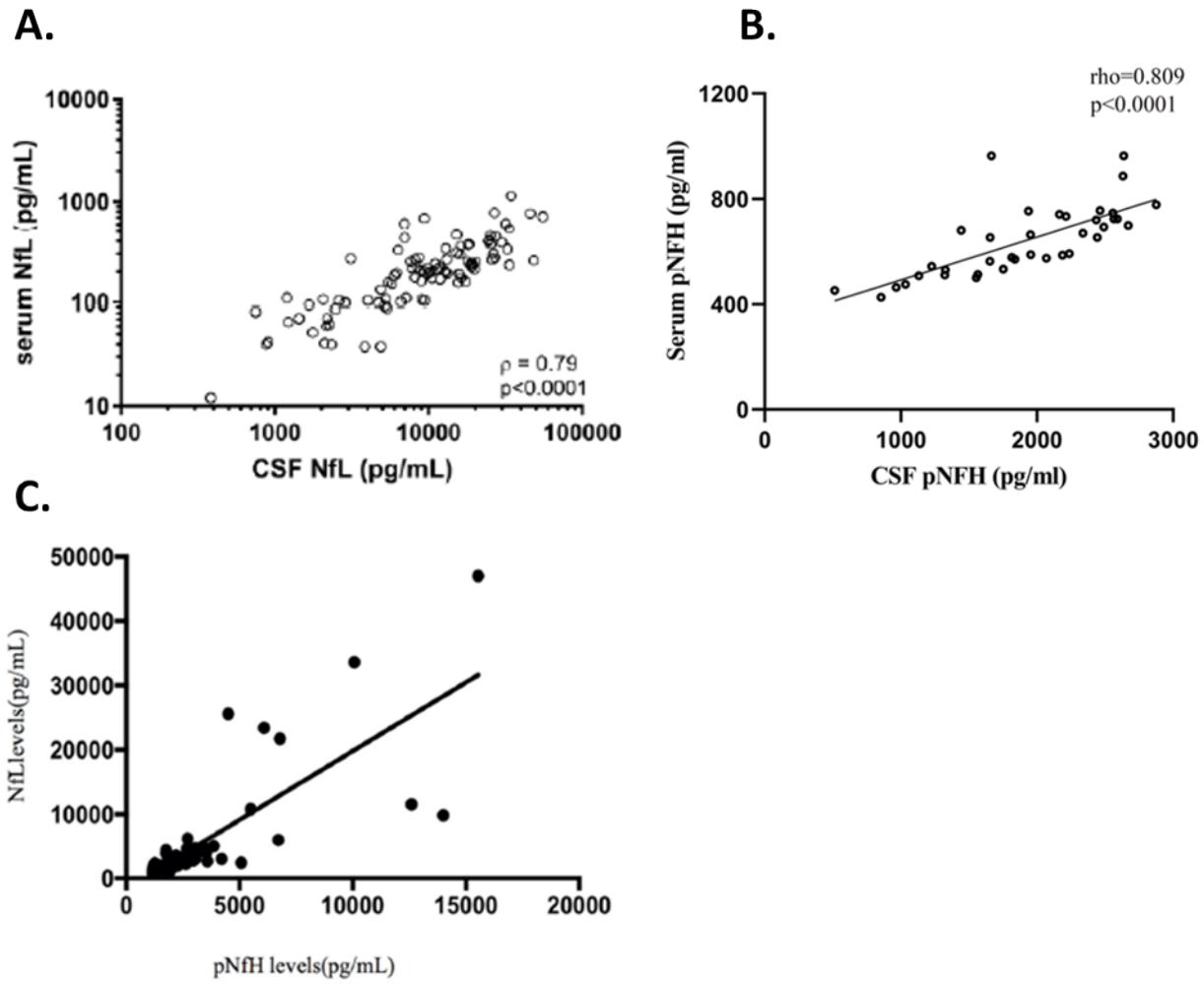
[49] Illán-Gala I, Alcolea D, Montal V, et al. CSF sAPPβ, YKL-40, and NfL along the ALS-FTD spectrum. Neurology. 2018;91(17):e1619-e1628.

[50] De Schaepdryver M, Goossens J, De Meyer S, et al. Serum neurofilament heavy chains as early marker of motor neuron degeneration. Ann Clin Transl Neurol. 2019;6(10):1971-1979. doi:10.1002/acn3.50890

[51] Steinacker P, Feneberg E, Weishaupt J, et al. Neurofilaments in the diagnosis of motoneuron diseases: a prospective study on 455 patients. J Neurol Neurosurg Psychiatry. 2016;87(1):12-20. doi:10.1136/jnnp-2015-311387

and pNfH, respectively. Also, serum NfL and pNfH levels are positively correlated, with considerable between-subject variability (Figure 38).[52]

Figure 38. (A) Correlation Between Serum and CSF NfL, (B) Correlation Between Serum and CSF pNfH, and (C) Correlation Between Serum NfL and pNfH Levels



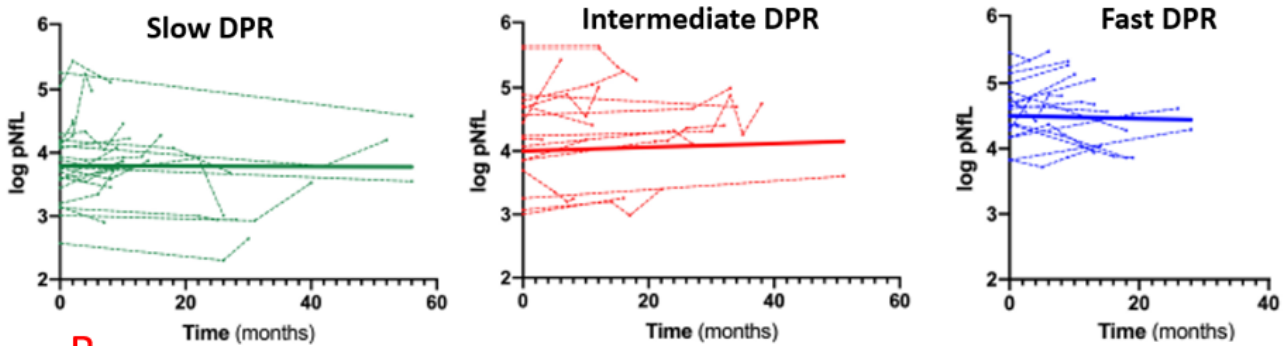
Sources: Gille et al., 2019[3]; Shi et al., 2022[23]; Li et al., 2018[52]
Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain

Longitudinal analysis of neurofilaments in ALS subjects: Neurofilament levels, once elevated during initial disease progression, are generally stable over time in ALS patients. Longitudinal changes in NfL and pNfH plasma levels have been reported. Vacchiano et al. found no significant rise or decline in the slope of plasma NfL level during follow-up in three ALS groups (differing in disease progression rate) over 40 to 60 months, once elevated during initial disease progression(Figure 39).[27] Lu et al. found little to no change in plasma and CSF NfL levels in ALS subjects. Additionally, plasma levels were stable over a 15-month follow-up period.[13]

[52] Li DW, Ren H, Jeromin A, et al. Diagnostic Performance of Neurofilaments in Chinese Patients With Amyotrophic Lateral Sclerosis: A Prospective Study. Front Neurol. 2018;9:726. Published 2018 Aug 28. doi:10.3389/fneur.2018.00726

Similar findings were reported by Poesen et al. for CSF pNfH based on serial measurements of 17 subjects; however, CSF NfL levels increased over time in 4 of 17 subjects with fast and intermediate disease progression.[53]

Figure 39. Longitudinal Changes in Plasma NfL in Slow, Intermediate, and Fast Disease Progressors

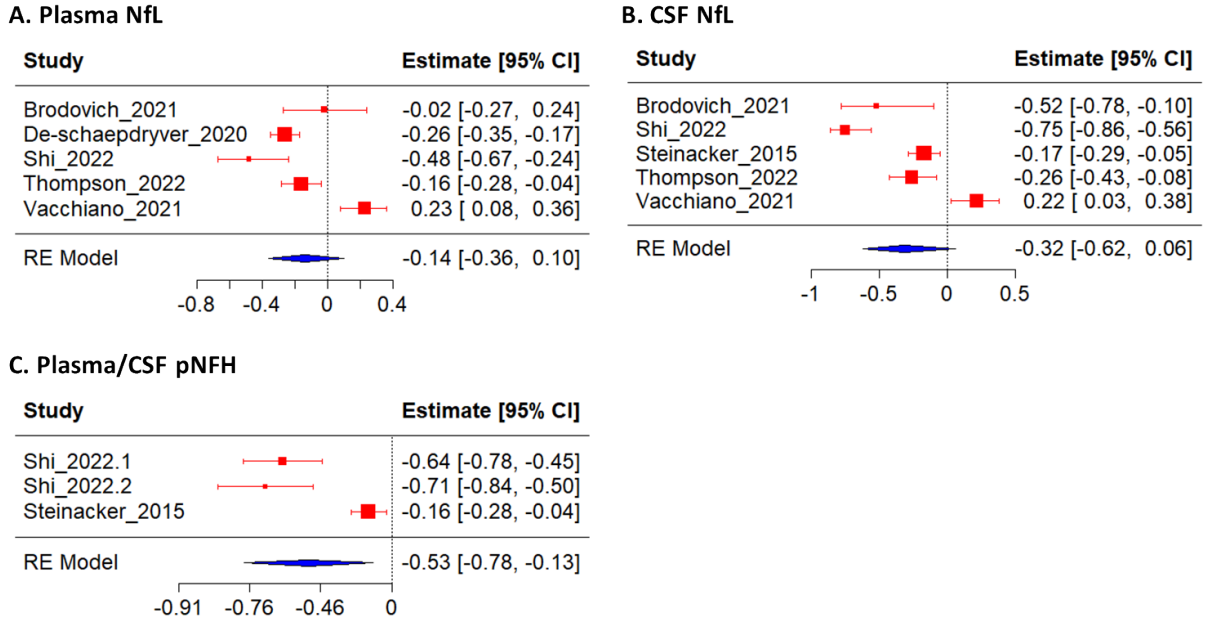


Source: Vacchiano et al., 2021[27]
Abbreviations: DPR, disease progression rate/slope; NfL, neurofilament light chain

Relationship between ALSFRS-R total score and neurofilament levels: The correlation coefficients between ALSFRS-R total score and neurofilaments (plasma NfL, CSF NfL and plasma or CSF pNfH) across studies are summarized in Figure 40. The overall correlation coefficient across studies between plasma NfL and ALSFRS-R was -0.14 (95% CI: -0.36, 0.10); and between CSF NfL and ALSFRS-R was -0.32 (95% CI: -0.62, 0.06). Similarly, there was a negative correlation between plasma/CSF pNfH and ALSFRS-R (-0.53; 95% CI: -0.78, -0.13). The negative relationship between neurofilaments and the ALSFRS-R total score suggests that higher neurofilament levels may be linked to low ASLFRS-R total scores, or a decline in physical function.

[53] Poesen K, De Schaepdryver M, Stubendorff B, et al. Neurofilament markers for ALS correlate with extent of upper and lower motor neuron disease. Neurology. 2017;88(24):2302-2309.

Figure 40. Forest Plots Showing the Correlation Coefficients Across Studies for Relationship Between ALSFRS-R Total Score and Neurofilaments (Plasma NfL, CSF NfL, and Plasma/CSF pNfH)



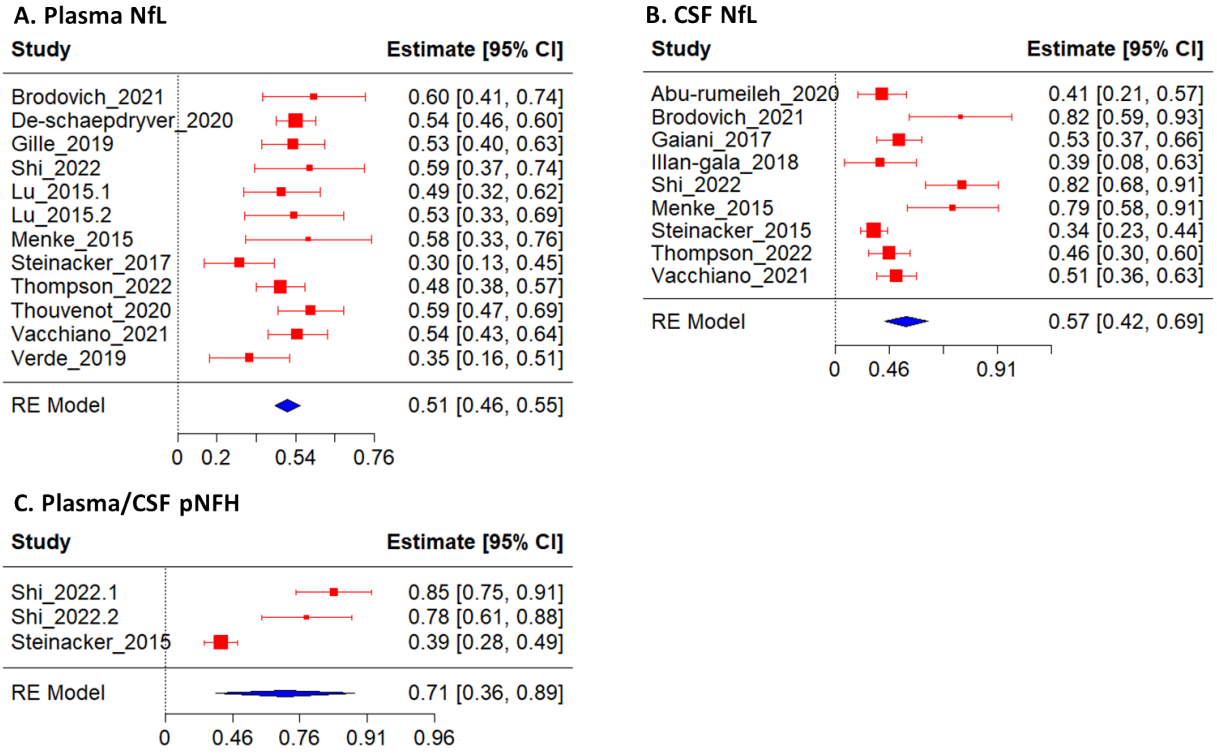
Source: Reviewer's analysis
Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain; RE, random effect

Relationship between disease progression slope and neurofilaments: DP slope was calculated as follows:

$$Disease\ progression\ slope = \frac{48 - ALSFRS\ total\ score}{\text{months from symptom onset at first sampling}}$$

There was a positive correlation between neurofilaments and DP slope (Figure 41). The overall correlation coefficient across studies between DP slope and plasma NfL was 0.51 (95% CI: 0.46, 0.55), and that between DP slope and CSF NfL was 0.57 (95% CI: 0.42, 0.69). Similarly, there was a positive correlation between plasma/CSF pNfH levels and DP slope (0.71; 95% CI, 0.36, 0.89). The positive relationship between neurofilament and DP slope suggests that disease progression worsens with increasing blood NfL levels in ALS patients.

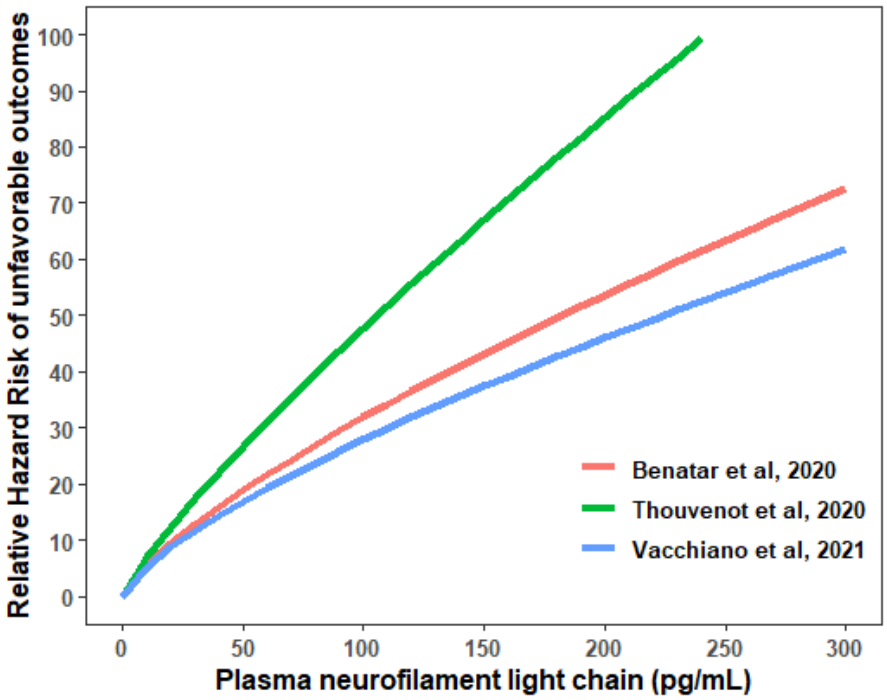
Figure 41. Forest Plots Showing the Correlation Coefficients for the Relationship Between Disease Progression Slope and Neurofilaments (Plasma NfL, CSF NfL, and Plasma/CSF pNfH)



Source: Reviewer's analysis
Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; RE, random effect; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain

Relationship between clinical outcomes and neurofilament levels: The relationship between neurofilament (plasma/CSF NfL and NfH) levels and unfavorable clinical outcomes (death, tracheostomy and/or permanent assisted ventilation) was quantified using multivariate cox-regression in prior studies. [23,26,27,29,33, 47,48,50] Patients with higher plasma NfL levels have higher risks of unfavorable clinical outcomes(Figure 42).[29,27,26] Other studies including Thompson et al.,[15] and Shi et al.,[23] have reported shortened survival for subjects with higher plasma NfL levels. Higher CSF NfL and plasma/NfH levels are consistently associated with unfavorable clinical outcomes. [23,26,27,29,33, 47,48,50] Overall, higher levels of neurofilament are associated with higher risks of unfavorable clinical outcomes.

Figure 42. Relationship Between Plasma NfL Levels and Relative Hazard Risks of Unfavorable Clinical Outcomes



Source: Reviewer's analysis
Unfavorable clinical outcomes include death, tracheostomy and/or permanent assisted ventilation.
Abbreviations: NfL, neurofilament light chain

Relationship Between NfL Levels and Clinical Outcomes Versus DP Slope and Clinical Outcomes: Literature suggested that DP slope and NfL level are important predictors of clinical outcomes in ALS patients. Various publications that reported hazard ratios for DP slope and neurofilament were included in the analysis. Abu-rumeileh et al. reported that DP slope is a significant predictor of survival in a univariate analysis, and that NfL was a significant predictor of survival in a multivariate analysis.[46] De-Schaepdryver et al. showed that only plasma NfL was a significant predictor of survival in a multivariate analysis.[22] Gille et al. found that both NfL and disease progression slope were significant predictors of survival in univariate analyses, but only NfL remained a significant predictor in a multivariate analysis.[3] Thompson et al. reported that both NfL and DP slope were significant predictors of survival in univariate analyses. However, plasma NfL was a significant predictor in a multivariate analysis.[15] Lu et al. examined multiple datasets and concluded that high NfL levels were significant predictors of survival in all datasets.

Few studies were available to assess the relationship between neurofilament levels and clinical endpoints (ALSFRS-R total score, DP slope, and survival). Although no formal sensitivity analysis or publication bias assessment (funnel plot and Egger's test) was performed in this meta-analysis, the results were at risk of publication bias due to limited data. The correlation coefficients differed among the studies, especially between ALSFRS-R total score and neurofilaments, likely because of differences in research design, sample size and statistical methods. However, the overall correlation coefficients suggest a general relationship between plasma/CSF neurofilament levels and clinical endpoints.

Conclusions

The findings suggest that plasma NfL and pNfH are correlated. Elevated plasma NfL levels were reported to be stable over 40 to 60 months after ALS diagnosis. A negative correlation was observed between ALSFRS-R total score and neurofilament (NfL and pNfH) in plasma and CSF. Both NfL and pNfH in plasma and CSF were positively correlated with DP slope. Overall, higher neurofilament levels are associated with faster DP. Also, higher neurofilament levels were associated with a higher risk of unfavorable clinical outcomes, including survival, in ALS patients.

14.5.2. Evidence From the Tofersen Clinical Program: Model-Based Approach to Identify Prognostic Factors That Affect ALSFRS-R Total Scores

Data from the placebo groups in the tofersen clinical program were used to identify factors that affect ALSFRS-R total score changes from baseline at Week 28 in ALS subjects.

Data: Table 101 summarizes the baseline demographics, biomarkers, and disease characteristics of subjects in the analysis dataset. These variables were selected based on their availability in the datasets as well as their potential clinical relevance.

Table 101. Baseline Demographics, Biomarker, and Diseases Characteristics of Subjects Used in the Analysis

Prognostic Variables	Mean (SD)	Median [Min, Max]
Age (years)	51.7 (11.3)	52.0 [34.0, 73.0]
Weight (kg)	81.1 (22.7)	78.9 [42.5, 136]
BMI (kg/m^2)	27.8 (6.42)	25.8 [16.4, 44.5]
Height (cm)	170 (10.9)	171 [146, 192]
Sex		
Female	16 (48.5%)	
Male	17 (51.5%)	
ALSFRS-R total score	37.5 (5.35)	38.0 [24.0, 47.0]
Plasma NfL (pg/mL)	77.3 (63.1)	62.7 [8.80, 260]
Plasma pNfH (pg/mL)	1640 (1960)	1130 [23.0, 9540]
Total CSF SOD1 protein	123 (66.3)	101 [55.2, 322]
ALSFRS-R slope	-1.04 (0.983)	-0.838 [-4.23, -0.0189]
SVC (% predicted)	84.9 (16.7)	83.0 [54.8, 120]
Time from symptom onset (months)	25.2 (25.6)	14.6 [2.37, 103]
Site of onset		
Brain	3 (9.1%)	
Limb	30 (90.9%)	
Other drugs		
Edaravone or Riluzole	21 (63.6%)	
Neither	12 (36.4%)	
HHD megascore	0.0724 (0.583)	-0.0523 [-0.853, 1.88]

Source: Reviewer's analysis
For categorical variables, numbers of subjects (%) are shown.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; BMI, body mass index; CSF, cerebrospinal fluid; HHD, handheld dynamometry; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain; SD, standard deviation; SOD1, superoxide dismutase 1; SVC, slow vital capacity

Methods: Linear and lasso regression methods were used. No imputation method was used for missing data due to limited missing variables. For both methods, the dependent variable was the ALSFRS-R total score change from baseline at Week 28. Independent variables included all baseline study variables in Table 101, total SOD1 protein (Study 2), and plasma NfL and NfH levels. Various transformations of neurofilament data included log neurofilament level, change from baseline, percentage change from baseline, ratio to baseline, neurofilament-time slope, log daily area under the neurofilament-time curve (daily_NfL_AUC or daily_NfH_AUC), and log linear-model-estimated area under the neurofilament-time curve (NfL_AUC_est or NfH_AUC_est). All baseline continuous variables were scaled so that all predictors were in the same range.

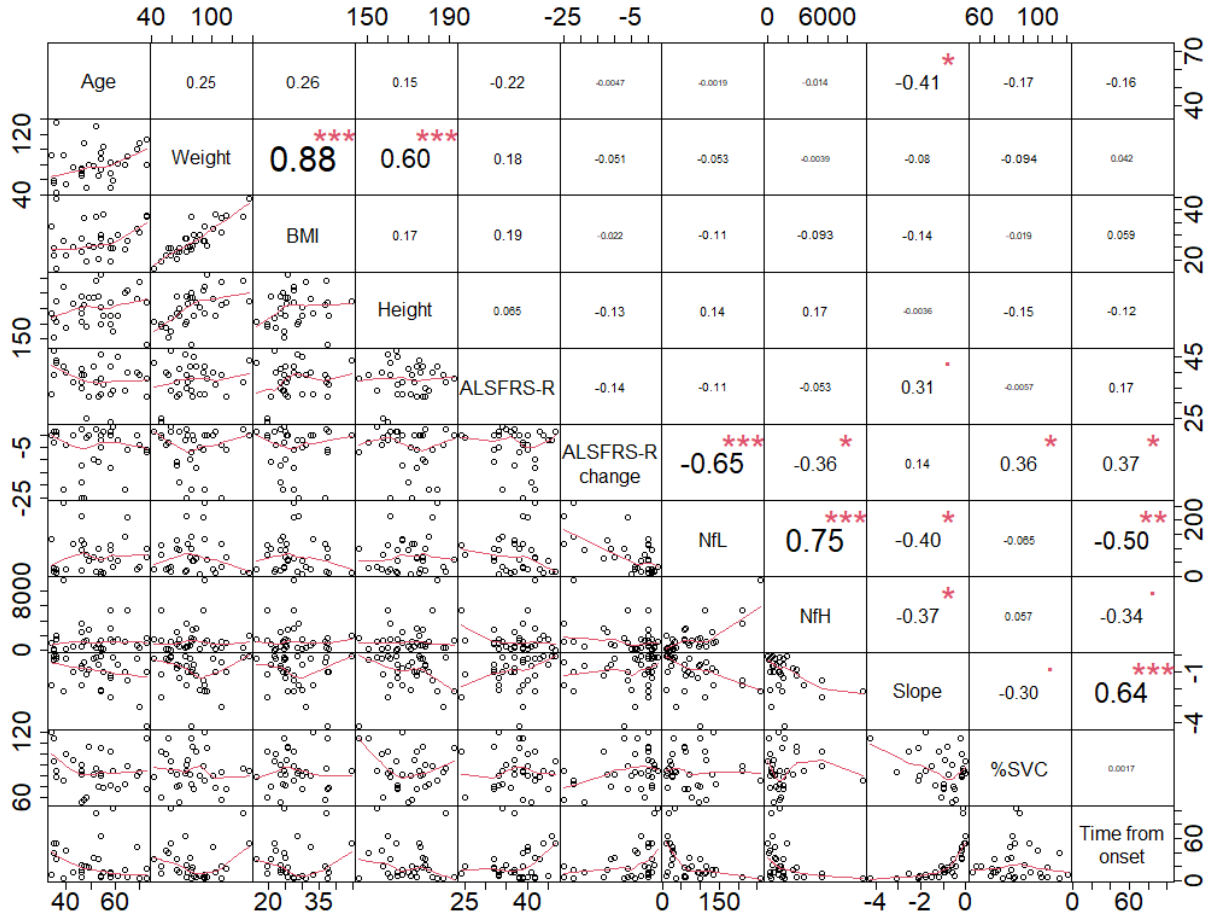
For linear regression analysis, the neurofilament data transformations were tested separately to prevent multicollinearity. For each biomarker data transformation, final linear model was identified by the Akaike information criterion in a stepwise algorithm using the covariates listed in Table 101. Because lasso regression analysis can handle multicollinearity, all study variables including the neurofilament metrics were used simultaneously. Analyses were conducted using the function cv.glmnet in the glmnet package for R.

To evaluate the prediction accuracy of the methods, leave-one-out-cross-validation (LOOCV) was used. Briefly in this method, a model was developed from a data after removing one observation in each run. For each developed model, prediction was made for the removed observation. Evaluation metrics was then calculated using all observations and predictions. The predictors identified from each run were also summarized to identify commonly selected predictors among all runs.

Results

Correlations among the study variables were first evaluated (Figure 43). The ALSFRS-R total score change from baseline at Week 28 was associated with plasma NfL ($r=-0.65$, $p<0.001$), NfH ($r=-0.36$, $p<0.05$), %SVC ($r=0.36$, $p<0.05$), and time from onset ($r=0.39$, $p<0.05$). DP, as represented by the ALSFRS-R slope, was correlated ($r> \pm 0.25$) with baseline ALSFRS-R total score, plasma NfL, plasma pNfH, and age. Several neurofilament metrics were explored in addition to baseline neurofilament levels (Table 102). The results suggested baseline plasma NfL to be the preferred neurofilament metric for evaluating the association with ALSFRS-R change from baseline at Week 28.

Figure 43. Sample Correlation Plot of Baseline Characteristics



Source: Reviewer's analysis
Slope: ALSFRS-R prerandomization slope
Triple asterisk (***), p<0.0001, double asterisk (**), p<0.01; single asterisk (*), p<0.05, dot(.), p<0.1
Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; BMI, body mass index; NfH, neurofilament heavy chain; NfL, neurofilament light chain; %SVC, percent slow vital capacity

Table 102. Correlations of Neurofilament Levels With ΔALSFRS-R Total Score at Week 28

Baseline Characteristic	Pearson Correlation Coefficients
Baseline NfL (pg/mL)	-0.65
NfL change (pg/mL)	-0.30
NfL change (%)	-0.10
NfL ratio to baseline	-0.10
NfL-time slope	-0.22
Log NfL (pg/mL)	-0.57
Log daily area under NfL-time curve (pg/mL)	-0.60
Log linear-model-estimated area under NfL-time curve until Week 28 (pg.day/mL)	-0.60
Baseline NfH (pg/mL)	-0.36
NfH change (pg/mL)	-0.18
NfH change (%)	0.03
NfH ratio to baseline	0.03
NfH-time slope	-0.17

Baseline Characteristic	Pearson Correlation Coefficients
Log NfH (pg/mL)	-0.36
Log daily area under NfH-time curve (pg/mL)	-0.42
Log linear-model-estimated area under NfH-time curve until Week 28 (pg.day/mL)	-0.40

Source: Reviewer's analysis
Abbreviations: ΔALSFRS-R, change in revised amyotrophic lateral sclerosis functional rating scale; NfH, neurofilament heavy chain; NfL, neurofilament light chain

Linear regression: The summary of linear regression findings including adjusted R-squared and residual standard error, and significant study variables ($p<0.01$) are shown in Table 103. The result suggested that baseline NfL was significant predictor for ALSFRS-R change at Week 28 in all the model tested. Other study variables such as SVC, sex, ALSFRS-R and NfH change or slope were also appeared significant in some of the test models. The LOOCV analysis (total of 33 runs) identified the same predictors ($p<0.01$); i.e., NfL (33 runs), SVC (6 runs), and sex (2 runs) and height (1 runs).

Table 103. Summary of Linear Regression Analysis Using Various Neurofilaments Metrices

Neurofilament Metrics	R^2	RSE	Significant Study Variables (p<0.01)
Logarithm (NfX)	0.63	5.094	SVC, baseline NfL
Change from baseline	0.72	4.412	Baseline NfL, NfH change
% Change from baseline	0.61	5.241	Baseline NfL
Ratio to baseline	0.61	5.241	Baseline NfL
Slope	0.75	4.178	ALSFRS-R, sex, NfH slope, baseline NfL
Log NfX_AUC_day	0.71	4.673	Sex, baseline NfL
Log NfX_AUC_est	0.61	5.231	Baseline NfL

Source: Reviewer's analysis
Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; NfH, neurofilament heavy chain; NfL, neurofilament light chain; NfX: neurofilament light chain or heavy chain; NfX_AUC_day, daily area under neurofilament-time curve; NfX_AUC_est, linear-model-estimated area under neurofilament-time curve; R^2, adjusted R-squared; RSE, residual standard error; SVC, slow vital capacity

Lasso regression: The final model identified baseline plasma NfL as only important predictors (using lambda within one standard error for model selection), consistent with linear regression results. The LOOCV analysis (total of 33 runs) identified baseline Nfl (33 runs), SVC (9 runs), Nfl_AUC_est (2 runs), and ALSFRS-R (1 run) as predictors. Evaluation metrics for both regression techniques using the LOOCV method are summarized in Table 104, and indicate similar model performance by linear and lasso regression analyses.

Table 104. Evaluation Metrics for Linear and Lasso Regression Using LOOCV Analysis

Parameter	Linear Regression N=33	Lasso Regression N=33
Relative squared error	0.909	0.836
Root mean squared error	7.89	7.57
Mean absolute error	6.36	6.04
Relative absolute error	0.957	0.909
Mean squared error	62.2	57.3

Source: Reviewer's analysis
Lower error values suggest better model performance
Abbreviations: LOOCV, leave-one-out cross-validation

Conclusions

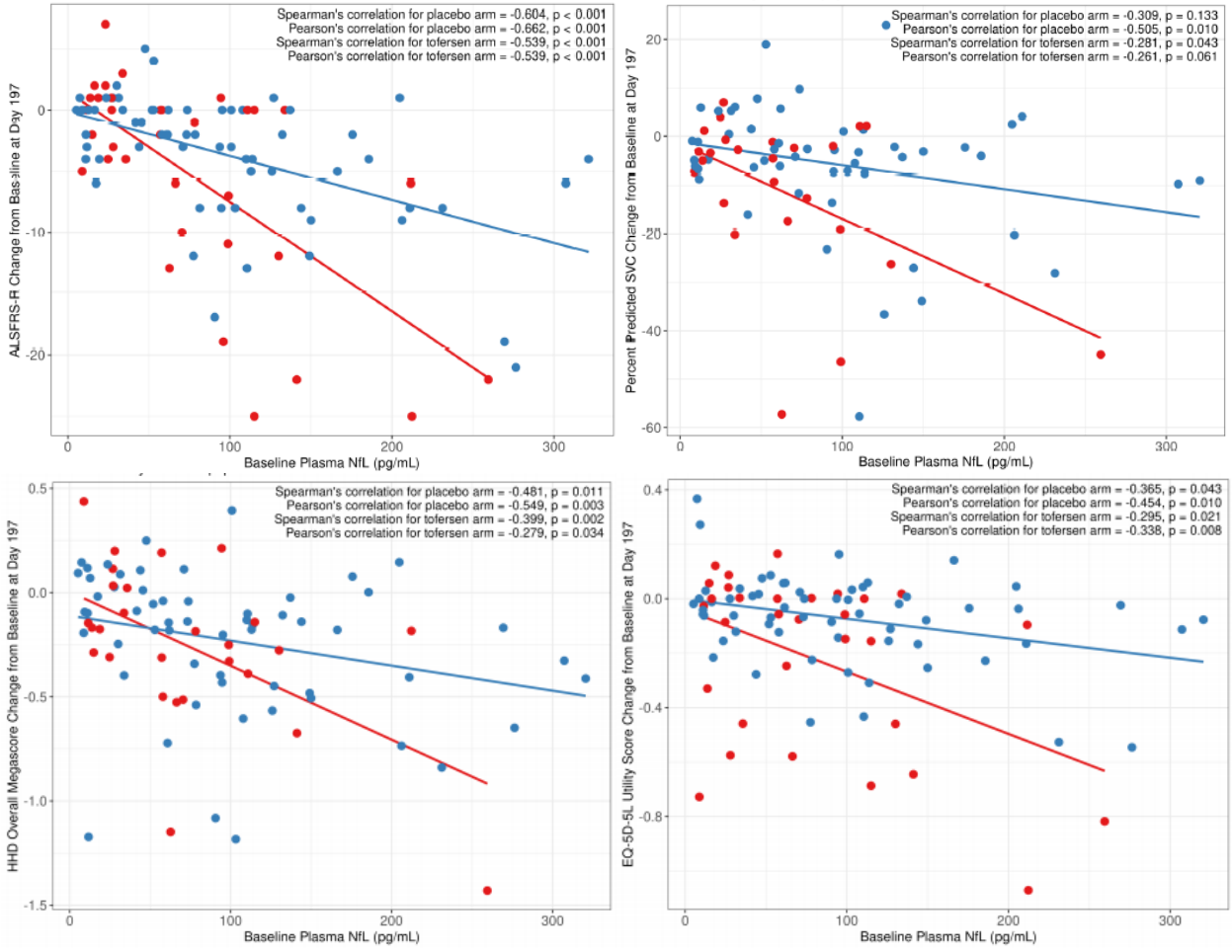
The findings from both analyses suggest baseline plasma NfL to be a significant predictor of ALSFRS-R CFB at Week 28 even after adjusting for multiple potential baseline prognostic factors and various transformations of NfL metrics.

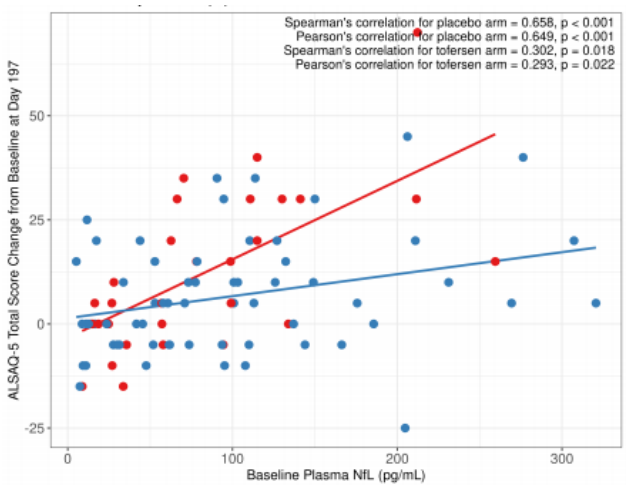
14.5.3. Analysis with Causal Inference Modeling

This is a review of the Applicant's causal inference analysis to support the relationship between the tofersen-driven reductions in plasma NfL and clinical endpoints.

The correlations between baseline NfL levels and changes from baseline (Δ) in clinical endpoints (ALSFRS-R total score, percent predicted SVC, overall HHD megascore, EQ-5D-5L utility score, and ALSAQ-5 total score) at Week 28 suggest that higher baseline NfL is associated with worsening of clinical endpoints (Figure 44). Also, subjects with higher baseline NfL values showed a greater treatment benefit compared to placebo.

Figure 44. Correlations Between Baseline Plasma NfL and Clinical Endpoints Change From Baseline at Day 197 (Week 28) in ITT Population





Source: Integrated Summary of Effectiveness-Appendix 3.3.3, pp. 18-22
Red and blue color represents placebo and tofersen group respectively.
Abbreviations: ALSAQ-5, 5-item Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; HHD, hand-held dynamometry; ITT, intent-to-treat; NfL, neurofilament light chain; SVC, slow vital capacity

Applicant's Analysis

Objective: To evaluate the relationship between the tofersen-driven reduction in plasma NfL at Day 113 (Week 16) and changes in clinical outcome measures (ALSFRS-R total score, percent predicted SVC, HHD megascore, ALSDAQ-5 total score, and EQ-5D-5L utility score) at Day 197 (Week 28).

Data: ITT population (N=108) from Study 233AS101 Part C.

Methods: The causal inference model partitioned the effect of tofersen on the change from baseline in clinical endpoint at Week 28 into three components:

1. Natural disease progression
2. Drug effect via an NfL pathway
3. Drug effect via a non-NfL pathway

Figure 45 summarizes the key equations used in the causal inference models. Briefly, equation 2.1 modeled the log-transformed NfL at Day 113 as a linear function of log-transformed baseline NfL and age in the placebo arm. Equation 2.2 modeled the change from baseline in clinical endpoint in the placebo arm as a linear function of a baseline NfL, change in NfL, and other baseline covariates for clinical function. Equation 2.3 modeled the change from baseline in clinical endpoints in the active arm as a linear function of natural disease progression and tofersen effect via non-NfL and nonbiomarker pathways. These regression equations were solved using the maximum-likelihood approach.

Figure 45. Equations Used in the Causal Inference Modeling

$$\log(z_{0it_1}) = \alpha_{0,z} + \beta_{0,z}\log(z_{0it_0}) + \sum_{j=1}^{i} \beta_{0,z}^{(j)} v_{0ij} + \epsilon_{0it_1,z} \quad (2.1)$$

$$\Delta y_{0it_2} | \Delta z_{0it_1} = \alpha_{0,y} + \beta_{0,y} z_{0it_0} + \gamma_{0,y} \Delta z_{0it_1} + \sum_{j=1}^{m_2} \beta_{0,y}^{(j)} w_{0ij} + \epsilon_{0it_2,y} \quad (2.2)$$

$$\begin{aligned} \Delta y_{1it_2} | \Delta z_{1it_1} = {} & \alpha_{0,y} + \beta_{0,y} z_{1it_0} + \gamma_{0,y} \left[e^{\alpha_{0,z} + \beta_{0,z}\log(z_{1it_0}) + \sum_{j=1}^{m_1} \beta_{0,z}^{(j)} v_{1ij}} - z_{1it_0} \right] + \sum_{j=1}^{m_2} \beta_{0,y}^{(j)} w_{1ij} + \\ & \lambda_0 + \sum_{j=1}^{m_3} \lambda_j u_{1ij} + \\ & (\gamma_1 + \gamma_2 z_{1it_0,\text{std}}) \left\{ \Delta z_{1it_1} - \left[e^{\alpha_{0,z} + \beta_{0,z}\log(z_{1it_0}) + \sum_{j=1}^{m_1} \beta_{0,z}^{(j)} v_{1ij}} - z_{1it_0} \right] \right\} + \\ & \epsilon_{1it_2,y} \end{aligned} \quad (2.3)$$

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies Appendix 1, p. 5
z_{0it0}: Baseline NfL for subject *i* in the placebo arm.
z_{1it0}: Baseline NfL level for subject *i* in the active arm.
z_{0it1}: NfL level for subject *i* in the placebo arm at Week 16.
z_{1it1}: NfL level for subject *i* in the active arm at Week 16.
Δz_{0it1}: Change from baseline in NfL at Week 16 for subject *i* in the placebo arm.
Δz_{1it1}: Change from baseline in NfL at Week 16 for subject *i* in the active arm.
$z_{1it0,std}$: Standardized baseline NfL level for subject *i* in the active arm.
y_{0it2}: Functional endpoint at Week 28 for subject *i* in the placebo arm.
y_{1it2}: Functional endpoint at Week 28 for subject *i* in the active arm.
Δy_{0it2}: Change from baseline in functional endpoint at Week 28 for subject *i* in the placebo arm.
Δy_{1it2}: Change from baseline in functional endpoint at Week 28 for subject *i* in the active arm.
v_{0i}: vector of fixed standardized covariates for NfL for subject *i* in the placebo arm.
v_{1i}: vector of fixed standardized covariates for NfL for subject *i* in the active arm.
w_{0i}: vector of fixed standardized covariates for clinical function for subject *i* in the placebo arm.
w_{1i}: vector of fixed standardized covariates for clinical function for subject *i* in the active arm.
u_{1i}: vector of fixed standardized covariates explaining the drug effect on the nonbiomarker pathway for subject *i* in the active arm.
Abbreviations: NfL, neurofilament light chain

For each endpoint of interest, the covariates were chosen from the relevant clinical impact and model fitting perspective. For ALSFRS-R total score, the covariates were baseline ALSFRS-R total score, baseline percent predicted SVC, and baseline ALSFRS-R decline slope. For percent predicted SVC, the covariate was baseline percent predicted SVC. For HHD megascore and ALSAQ-5 total score, the covariates were baseline percent predicted SVC, and their baseline score (baseline HHD megascore and baseline ALSAQ-5 total score, respectively).

Results: The parameter estimates for the tofersen effect on clinical endpoints via the NfL pathway are summarized in Table 105; they can also be interpreted as a reduction in clinical worsening with tofersen per unit NfL reduction at the sample mean baseline NfL (96.78 pg/mL). Statistical significance ($p<0.05$) was achieved for ALSFRS-R total score ($p=0.0038$) and ALSAQ-5 total score ($p=0.0056$).

Table 105. Reduction in Worsening With Tofersen Per Unit of NfL Reduction at the Sample Mean Baseline NfL of 96.78 pg/mL Across All Clinical Outcome Measures

Clinical outcome measure	Reduction in worsening with tofersen (vs. untreated) per 1 unit of NfL lowering at sample mean baseline NfL (96.78 pg/mL)
ALSFRS-R total score	0.0772 (p=0.0038)
SVC (percent-predicted)	0.1451 (p=0.0706)
HHD overall megascore	0.0029 (p=0.1303)
ALSAQ-5 total score	0.2194 (p=0.0056)
EQ-5D-5L utility score	0.0017 (p=0.0894)

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies, p. 65, Table 9
Abbreviations: ALSAQ-5, 5-item amyotrophic lateral sclerosis assessment questionnaire; ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; EQ-5D-5L, European quality of life 5-dimension 5-level; HHD, hand-held dynamometry; NfL, neurofilament light chain; SVC, slow vital capacity

The model-predicted change from baseline in clinical endpoint at Week 28 without treatment in tofersen-treated subjects in the ITT population and fast-progressors (greater than or equal to the median NfL) is demonstrated in Table 106. Per the Applicant, if the tofersen-treated subjects in Study 101 Part C (n=72) had been randomized to placebo, they would have experienced faster disease progression with an average of a 3.83-point greater decline on the ALSFRS-R, a 10.60% greater decline in percent-predicted SVC, a 0.12-point greater decline on the HHD megascore, a -7.74 point greater decline in ALSAQ-5 total score, and a 0.17-point greater decline in EQ-5D-5L utility score over 28 weeks. Across all endpoints, tofersen-treated subjects in Study 101 Part C experienced lesser decline in clinical function than the model-based prediction for a hypothetical placebo treatment.

Table 106. Observed Mean Change From Baseline in Tofersen-Treated Subjects Versus Model-Predicted Mean Change From Baseline to Week 28 Without Treatment (Assumed Sample Mean Baseline NfL=96.78 pg/mL)

Clinical outcome measure	Population	Tofersen-treated participants		Difference favoring tofersen treatment
		Observed (mean) change from baseline to Week 28	Predicted (mean) change from baseline to Week 28 without treatment	
ALSFRS-R	ITT	-3.60	-7.43	3.83
	Fast progressors (≥ median NfL)	-6.27	-11.96	5.69
SVC percent predicted	ITT	-5.75	-16.35	10.60
	Fast progressors (≥ median NfL)	-10.33	-26.00	15.66
HHD megascore	ITT	-0.23	-0.35	0.12
	Fast progressors (≥ median NfL)	-0.35	-0.60	0.25
ALSAQ-5 total score	ITT	6.56	14.29	-7.74
	Fast progressors (≥ median NfL)	10.78	24.13	-13.35
EQ-5D-5L utility score	ITT	-0.07	-0.24	0.17
	Fast progressors (≥ median NfL)	-0.13	-0.39	0.26

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies, p. 66, Table 10
Abbreviations: ALSAQ-5, 5-item amyotrophic lateral sclerosis assessment questionnaire; ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; EQ-5D-5L, European quality of life 5-dimension 5-level; HHD, hand-held dynamometry; ITT, intent-to-treat; NfL, neurofilament light chain; SVC, slow vital capacity

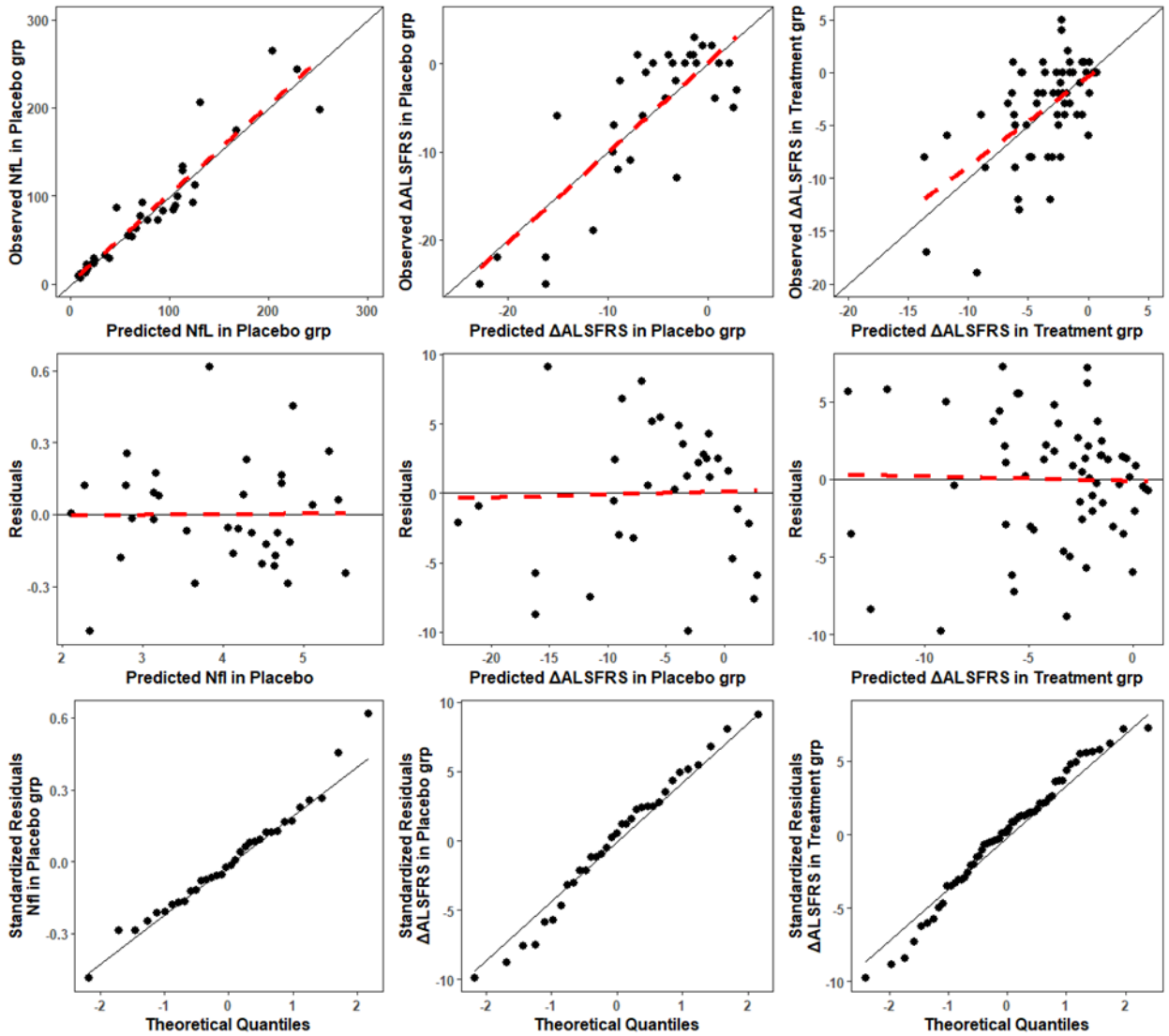
Reviewer's Analysis

The causal inference model, developed by the Applicant, was reviewed in terms of its adequacy to describe the impact of NfL reduction on clinical endpoint CFB at Week 28. The reviewer was able to reproduce the Applicant's analysis for all clinical endpoints. Overall, the model was able to reasonably describe the plasma NfL at Week 16 in the placebo group and ALSFRS-R total score CFB at Week 28 in both the placebo and treatment groups. The key aspects of the model are discussed below.

1. Assumption of a Linear Relationship

This analysis assumes a linear relationship between clinical endpoint CFB and model components (a set of baseline prognostic variables and NfL reduction). Thus, the model was evaluated for linearity, independence of explanatory variables, normal distribution of residuals, and homoscedasticity using residual plots, QQ plots, and correlation plots (Figure 46). Overall, the linear assumption was reasonable in this analysis. Considering the limited data and complex model structure, the use of a nonlinear model could have hampered model convergence and parameter estimation and might have led to high parameter uncertainty.

Figure 46. Model Diagnostics for the Final Causal Inference Model for ALSFRS-R Total Score at Week 28



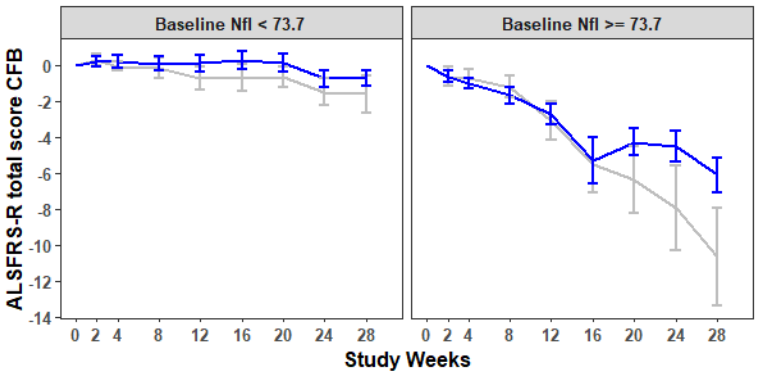
Source: Reviewer's analysis
Red dashed line is the linear regression line
Abbreviations: ΔALSFRS-R, change in revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

2. Adequacy of the Covariate Selection

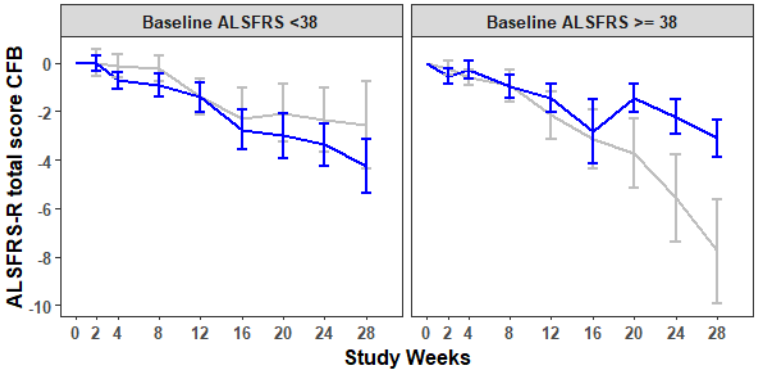
Covariate selection is a critical step in modeling. Impact of covariate selection on ALSFRS-R total score CFB at Week 28 due to plasma NfL was thus assessed. In the first step, exploratory graphical analysis was conducted to identify study baseline variables that could affect longitudinal changes in ALSFRS-R total score (Figure 47). This analysis screened 10 baseline variables: ALSFRS-R total score, ALSFRS-R decline slope, percent predicted SVC, NfL level, time since ALS diagnosis, mutation effect, edaravone or riluzole use, age, sex, and weight.

Figure 47. ALSFRS-R Total Score Mean (±SE) Changes From Baseline Across Weeks Stratified by Various Baseline Factors

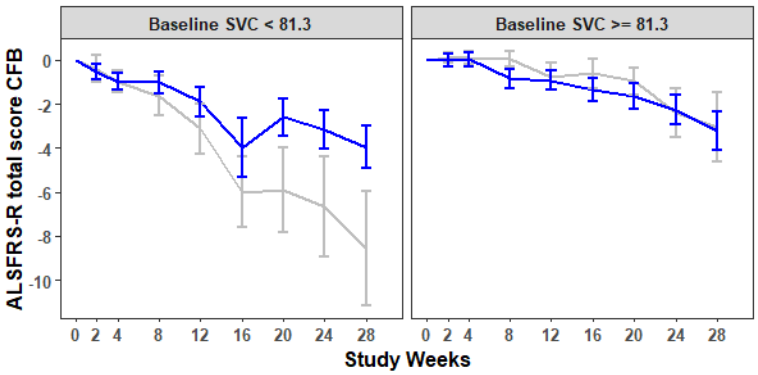
1. *Baseline Plasma NfL Level*



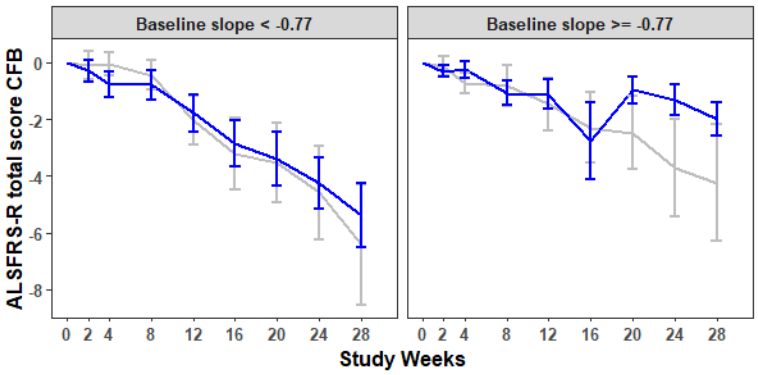
2. *Baseline ALSFRS-R Total Score*



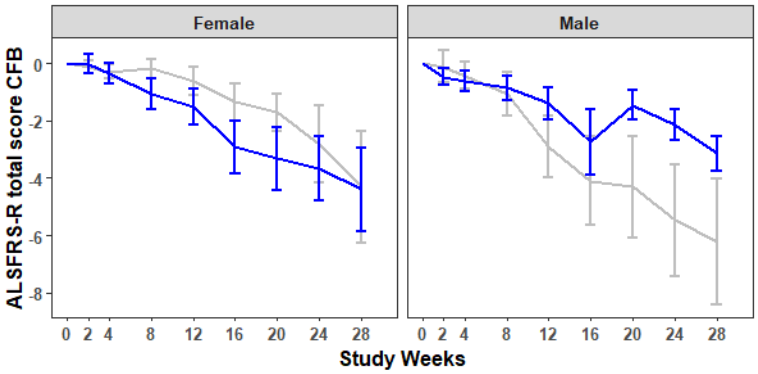
3. Baseline SVC (Percent Predicted)



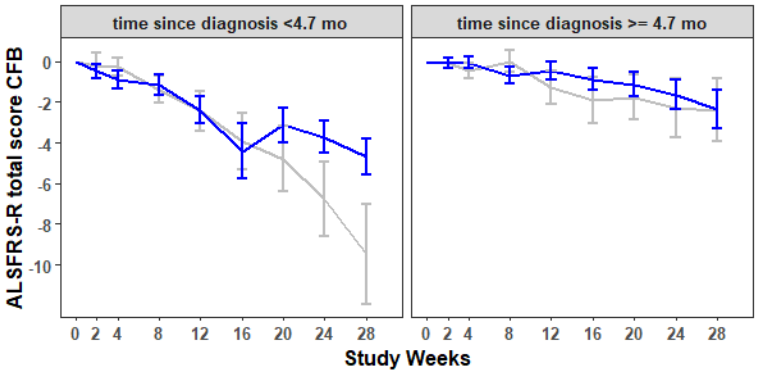
4. Baseline Prerandomization Slope



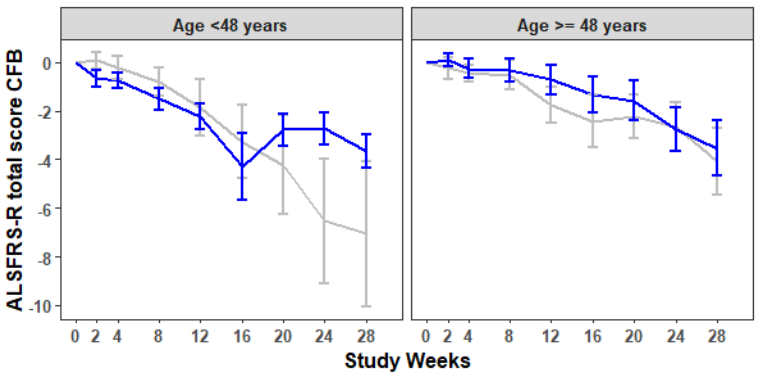
5. Sex



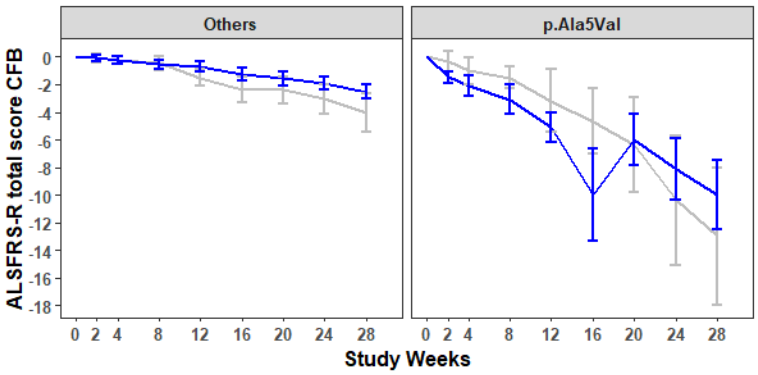
6. Time Since Diagnosis



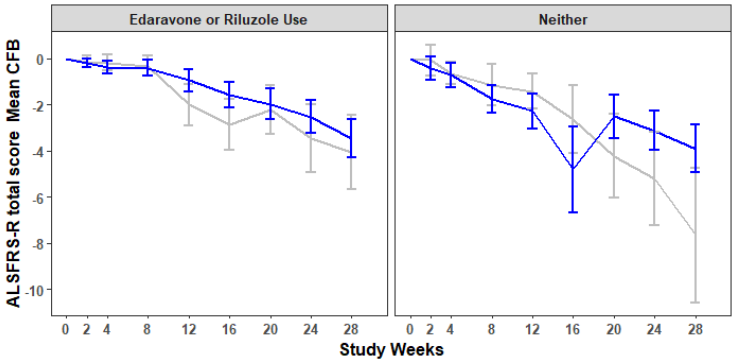
7. Age at Baseline



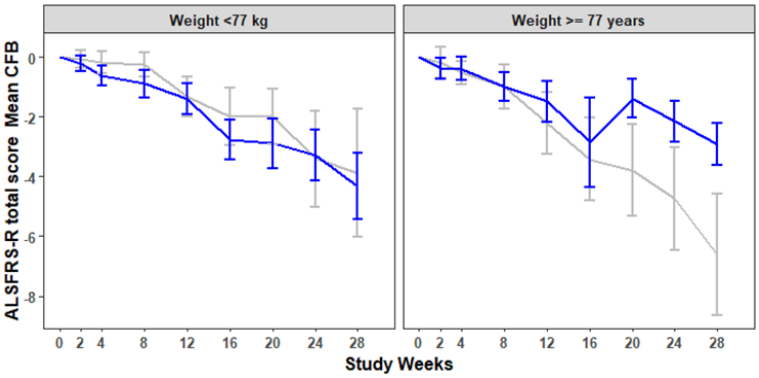
8. Mutation Type



9. Edaravone or Riluzole Use



10. Baseline Weight



Source: Reviewer's analysis
Continuous covariates were stratified by median values at baseline. Gray and blue lines, placebo and tofersen groups, respectively.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, Change from baseline; NfL, neurofilament light chain; SVC, slow vital capacity

The Applicant's model for ALSFRS-R total score included only four covariates, i.e., baseline NfL level, baseline ALSFRS-R total score, baseline percent predicted SVC, and baseline ALSFRSR decline slope. An IR was sent to the Applicant on September 28, 2022, to provide justification for inclusion of these covariates, but not other variables, such as age and mutation. The Applicant responded on October 04, 2022, stating that given the significant heterogeneity, the utility of these variables in SOD1-ALS is unclear.

However, the reviewer explored the importance of the 10 baseline variables in the causal inference model. Specifically, the 10 baseline variables (plasma NfL, SVC percent predicted,

ALSFRS-R total score, ALSFRS-R slope, time since ALS diagnosis, mutation effect, edaravone or riluzole use, age, sex, and weight) were added as covariates for ALSFRS-R total score (Table 107, full model). The full model, with six additional covariates, reduced the objective function value only by 6 units. The covariates for the reduced model were selected using the step function in R. Briefly, a linear model of ALSFRS-R total score change from baseline at Week 28 regressing against study variables (10 covariates and treatment effect) was used as the initial model in the stepwise search (forward and backward selection) using the Akaike information criterion to simplify the model without affecting its performance. Four covariates were identified in the stepwise-selected model: Baseline NfL, SVC percent predicted, p.Ala5Val mutation and edaravone or riluzole use. These covariates were added as covariates for ALSFRS-R total score in the causal inference model (Table 107, reduced model). However, inclusion of additional prognostic variables did not improve model performance, and the covariates selected in the Applicant's model were reasonable. Table 107 shows the reduction in worsening with tofersen per unit NfL reduction at a mean baseline tofersen concentration of 96.78 pg/mL for all three models. NfL reduction at Week 16 contributed to the reduction in clinical decline in terms of the ALSFRS-R total score in all explored models.

Table 107. Causal Inference Models for ALSFRS-R Total Score

Model	Baseline Covariates Selected	Objective Function Value	Reduction in Worsening With Tofersen (vs. Untreated) Per Unit of NfL Lowering at Mean Baseline (96.78 pg/mL)
Applicant model	NfL, ALSFRS-R, SVC %predicted, ALSFRS-R decline slope	265	-0.0772 (0.0038)
Reviewer model			
Full model	NfL, ALSFRS-R, SVC %predicted, ALSFRS-R decline slope, Time since ALS diagnosis, mutation, edaravone or riluzole use, age, sex, weight	259	-0.0505 (0.1028)
Reduced model	NfL, SVC %predicted, mutation, Edaravone or riluzole use	266	-0.0497 (0.0951)

Source: Reviewer's analysis
Abbreviations: ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; NfL, plasma neurofilament light chain; SVC, slow vital capacity

3. Selection of Plasma NfL Reduction at Week 16

Because the model assesses the predictive nature of plasma NfL, Week 16 was selected as the earliest time at which plasma NfL was reduced and stabilized (Figure 10). Sensitivity analyses were also performed at the Week 12, 16, 20, 24, and 28 visits to evaluate its impact on the estimation of drug effect via the NfL pathway (Table 108). The results suggested that the impact of the reduction in plasma NfL on the reduction in clinical decline of ALSFRS-R CFB at Week 28 was consistent across Weeks 16, 20, 24, and 28. Also, the impact of NfL reduction at Week 12 on ALSFRS-R CFB was smaller because the maximum NfL reduction was not achieved until Week 16, and thus Week 12 was not appropriate to evaluate for surrogacy.

Table 108. Relationship Between Plasma NfL Reduction and Reduction in Clinical Decline of ALSFRS-R Total Score in Study 233AS101 Part C

Timepoint Used for Plasma NfL Value	Reduction in Worsening With Tofersen (vs. Untreated) Per 10 Unit of NfL Lowering at Sample Mean Baseline NfL (96.78 pg/mL)
Week 12	0.361 (p=0.1149)
Week 16	0.772 (p=0.0038)
Week 20	1.075 (p<0.0001)
Week 24	0.789 (p<0.0001)
Week 28	0.733 (p=0.0003)

Source: Response to FDA Information Request (17 January 2023); Table 1
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

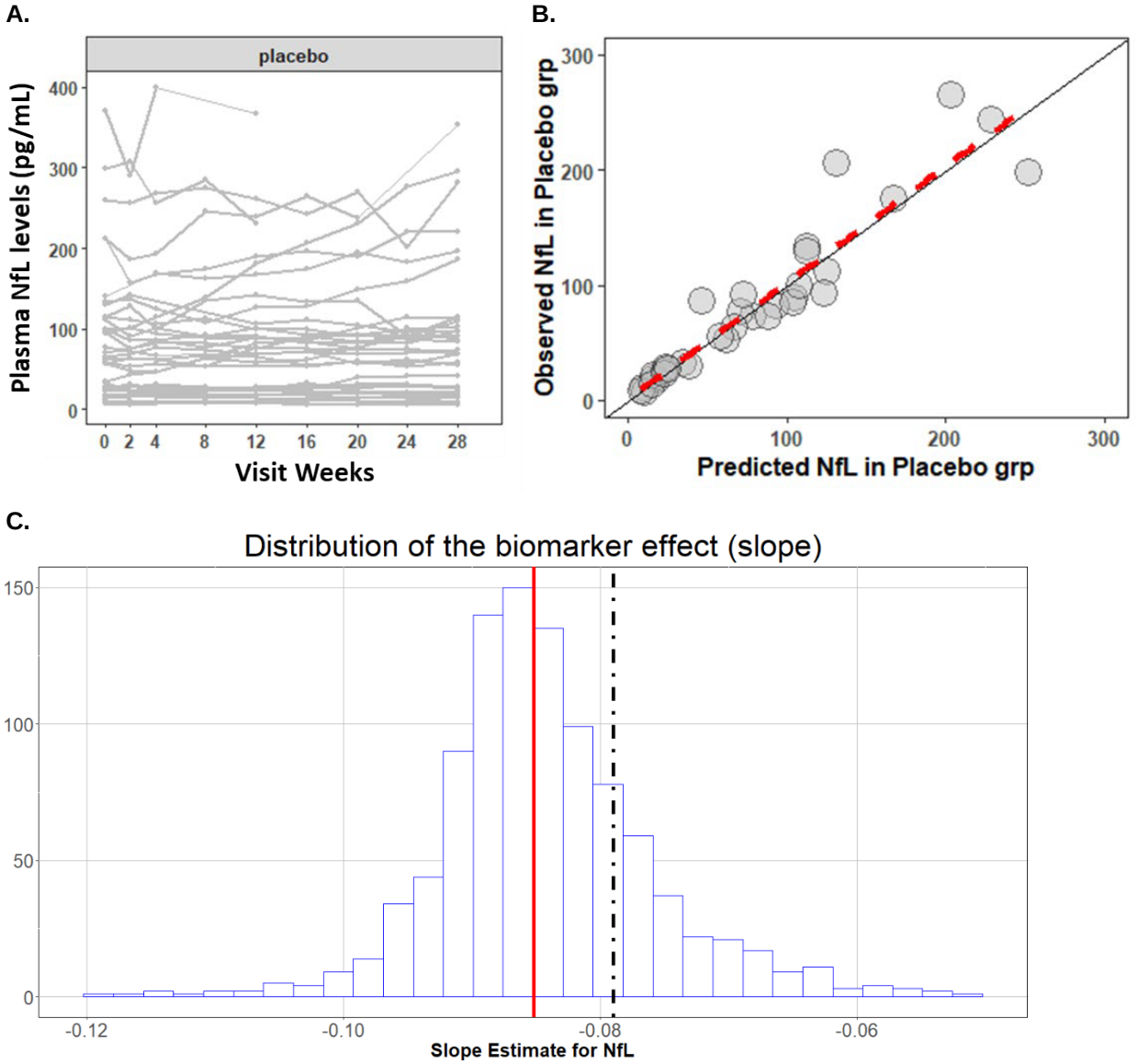
4. Effect of Baseline NfL Level

The effect of baseline NfL level on the relationship of plasma NfL reduction and ALSFRS-R CFB at Week 28 was evaluated using a causal inference model (Figure 13). The model was used to predict the tofersen effect at Week 28 in three typical subjects with baseline NfL levels of 50, 100, and 150 pg/mL with varying degrees of plasma NfL reduction. Overall, reductions in plasma NfL with tofersen administration were associated with less decline in clinical endpoints. Also, the treatment effect was greater in subjects with higher baseline Nfl levels.

5. *Effect of No Residual Error Model for NfL Natural Progression in the Treatment Group*

The NfL natural progression in the treatment arm was predicted based on the placebo data and does not add a residual error term in the model. Observed data suggest that, for most individuals, plasma NfL levels at Week 16 is almost the same as their baseline NfL (Figure 48A). The predicted NfL, following the exponential transformation back to original scale, in the placebo arm without residual error well describe the observed NfL levels at Week 16 in the placebo group (Figure 48B). Therefore, the effect of no residual error term on the NfL natural progression model in the treatment group is expected to be small, and unlikely to affect the estimate of the effect of NfL reduction on clinical decline. To confirm this, we introduced the residual error component of NfL progression in the model; the median estimate (-0.085, n=1000 simulations) of the NfL effect was approximately 8% steeper (better) than the parameter estimate from the model with no residual error component of NfL progression (Figure 48C).

Figure 48. (A) Longitudinal Changes in Plasma NfL Levels Up to Week 28; (B) Model Diagnostic for Plasma NfL in the Placebo Group; and (C) Distribution of the NfL Reduction Effect (or, Slope) on ALSFRS-R CFB at Week 28



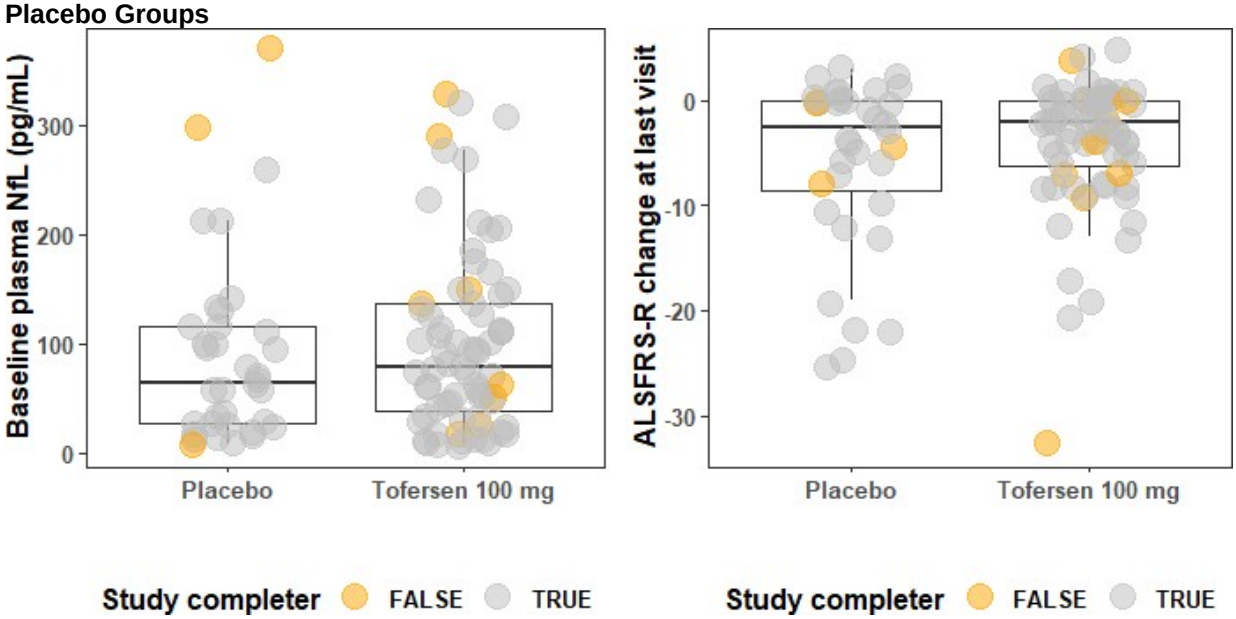
Source: Clinical Pharmacology Reviewer's analysis
Figure C: Red line is median slope estimated from 1000 simulations with residual error component for NfL added in the model; while the black dashed line is a parameter with no residual error component for NfL added in the model.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; grp, group; NfL, neurofilament light chain

6. Discussion on Analysis Based on Study Completers

The analysis was based on study completers, accounting for approximately 90% of the enrolled patients, with the assumption of missing completely at random. The study noncompleters (12 of 108; treatment, 9 subjects; placebo, 3 subjects) included one death in the tofersen group. Out of these 12 subjects, 7 subjects were enrolled for at least Week 16. The study-completers do not appear to be apparent outliers across treatment groups as they have similar values of baseline NfL and ALSFRS-R changes at the last visit prior to their discontinuation (Figure 49). The exclusion of two placebo-treated study noncompleters with high baseline NfL (>260 pg/mL) in

the analysis is unlikely to affect the treatment effect estimation because the tofersen group has its own matched control. Overall, the impact of these missing data on the relationship between NfL reduction and ALSFRS-R decline is expected to be low.

Figure 49. Baseline NfL Levels and ALSFRS-R Total Scores at Last Visit in the Treatment and Placebo Groups

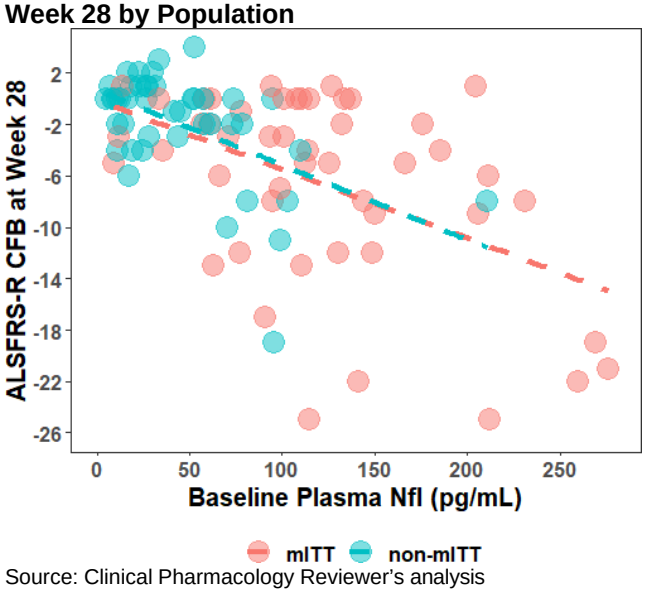


Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

7. Selection of the ITT Population for the Analysis

The analysis was performed on the ITT population to maximize the information from the study (n=108); this population was not narrowed by any selection criteria such as mITT or baseline NfL. Subgroup analysis using the mITT and non-mITT populations was not performed because it would have notably shortened the range of key study variables (including DP slope, baseline NfL, and ALSFRS-R change), such that identifying a relationship in a smaller number of patients with a narrower range of key variables would be more challenging. For instance, the subjects from the non-mITT population (n=48) had lower baseline NfL, whereas the mITT population (n=60) had subjects with higher baseline NfL (Figure 50). These differences in baseline NfL would affect both DP and the treatment effect, and thus would yield a biased estimate for the plasma NfL reduction effect. Therefore, the ITT population was more appropriate for estimation of the plasma NfL reduction effect on the clinical endpoints.

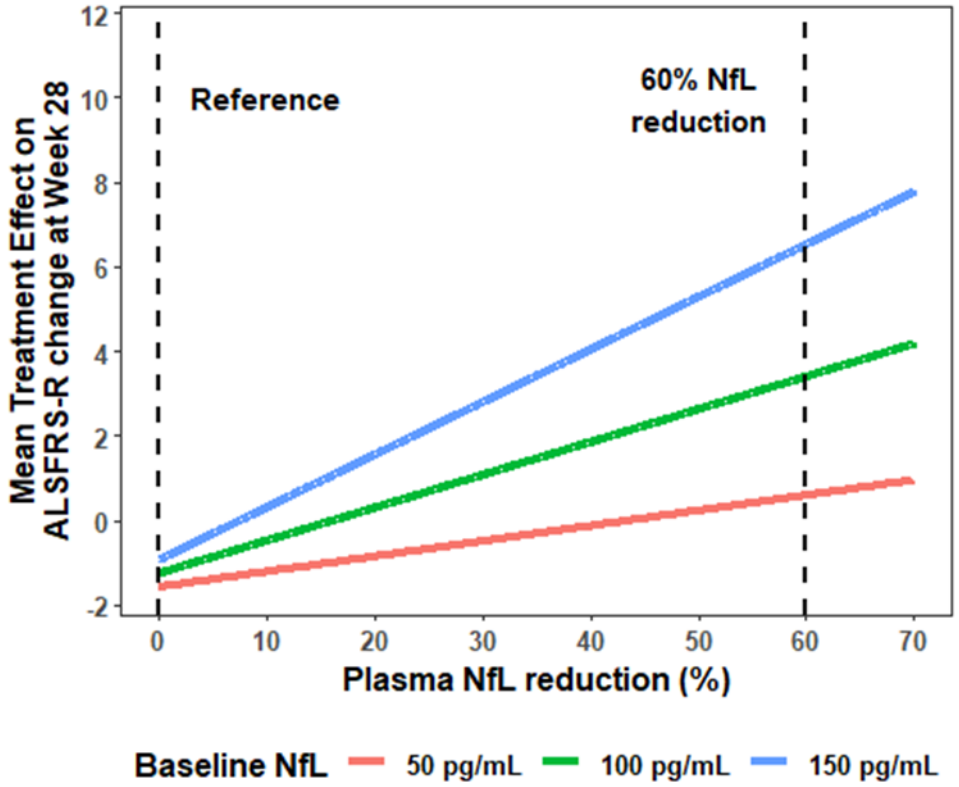
Figure 50. Correlation Between Baseline Plasma NfL and ALSFRS-R Change From Baseline at Week 28 by Population



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; CFB, change from baseline; mITT, modified intent-to-treat; NfL, neurofilament light chain

Overall, the findings of the causal inference model support a relationship between NfL reduction and the reduction in clinical function decline.

Figure 51. Relationship Between Plasma NfL Reduction at Week 16 and Reduction in Clinical Worsening of ALSFRS-R Total Score According to Baseline NfL Level



Source: Reviewer's analysis
Black dashed line represents 60% reduction in NfL.
Numbers represents changes in ALSFRS-R total score at 60% NfL reduction.
Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; NfL, neurofilament light chain

14.5.4. Population Pharmacokinetic and Pharmacodynamic Analyses of Tofersen

This is a review of the Applicant's pharmacometric study report (CPP-21-004), which characterizes the PK and pharmacodynamics (PD) of tofersen in SOD1-ALS subjects.

14.5.4.1. Pharmacokinetic Analysis of Tofersen

Applicant's Analysis

Objectives: To characterize the plasma and CSF PK of tofersen in SOD1-ALS subjects, and to identify the covariates affecting PK variability.

Data: The PK data of 166 subjects from Study 101 and Study 102 were used for the analysis. The covariate characteristics of the data are provided in Table 109.

Table 109. Summary Statistics of the Subjects in the Final Modeling Dataset

STUDY	101				102			
# Subjects	176				140			
Sex	M		F		M		F	
	98 (49%)		78 (51%)		82(48%)		58(52%)	
Race	white	Asian	other	Unknown	white	Asian	other	Unknown
	111	10	4	51	83	9	4	44
Age, mean (min,max)	49 (21, 78)				49 (23, 75)			
Baseline body weight (WT), mean (min,max)	78.7 (42.5, 146.5)				80.3 (42.5, 146.5)			
Baseline BSA, mean (min,max)	1.92 (1.37, 2.71)				1.95 (1.38, 2.71)			
Baseline BMI, mean (min,max)	26.8 (15.8, 46.5)				27.1 (16.4, 45.2)			
Baseline CRCL, mean (min,max)	144.7 (50.2, 393.3)				147.7 (50.2, 307.9)			
Subject level ADA status	Total study 101 subjects have positive record		Positive subjects match with PKPD time point		Total study 102 subjects have positive record		Positive subjects match with PKPD time point	
	33		22		24		8	

Source: CPP-21-004, p. 31, Table 5
* For continuous variables, mean (minimum, maximum) values are provided.
Abbreviations: ADA, antidrug antibodies; BMI, body mass index; BSA, body surface area; CRCL, creatinine clearance; F, female; M, male; PKPD, pharmacokinetics pharmacodynamics

Method: Nonlinear mixed effect PK modeling in serum and CSF was conducted using NONMEM, v. 7.4.3. Two PK models were developed to characterize the PK exposures in plasma and CSF. For the plasma PK model, covariate modeling was first performed using a full model approach and subsequently by stepwise backward elimination ($p<0.01$) to identify the parsimonious PK model. The CSF PK model was based on only trough concentrations; therefore, covariate analysis was not conducted. The final PK models were evaluated using goodness-of-fit plots and visual predictive checks.

Results: The plasma PK of tofersen was described by a two-compartment model with linear elimination and a depot compartment. Subject-level ADA status and baseline body surface area were added on clearance, and sex was added on central volume of distribution. For the PK in CSF, a one-compartment linear model was used. The results of the CSF PK model were derived to provide an approximation of exposure for the population PKPD models of NfL and SOD1 protein. The population PK parameter estimates from the final PK models are listed in Table 110. The PK models were able to reasonably characterize the observed data (Figure 52).

Table 110. Population Parameter Estimates of the Final Population PK Model for Tofersen

A. Plasma

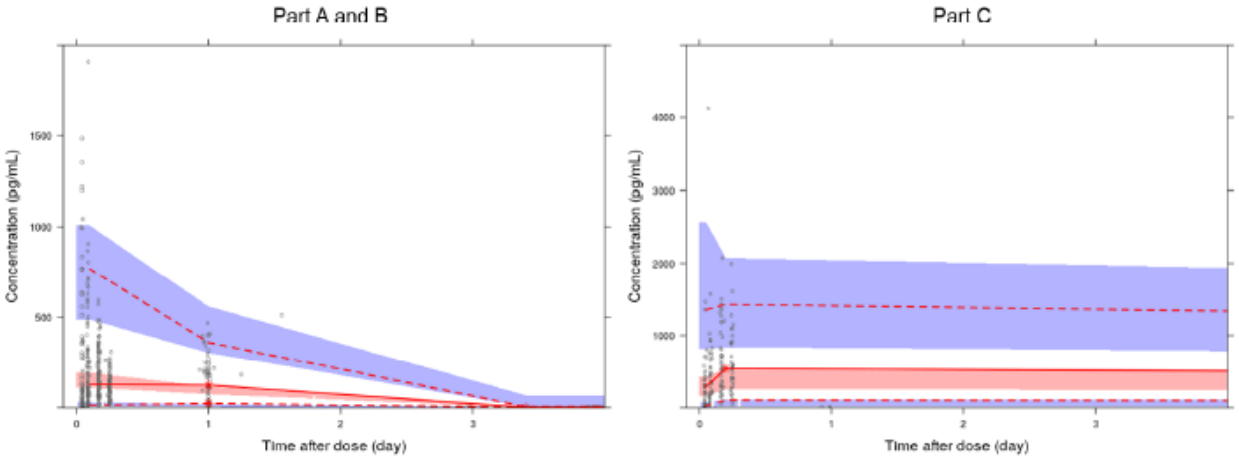
Parameter	Plasma PK Final Covariate Model, run 23001930	
	Estimate (RSE)	**CI[1]**
CL (L/hr)	9.04 (0.0704)	(7.79 – 10.3)
Ka (/hr)	0.142 (0.0887)	(0.117 – 0.167)
V2 (L)	58.2 (0.234)	(31.5 – 85.0)
V3 (L)	5807 (0.233)	(3154 – 8460)
Q (L/hr)	2.80 (0.151)	(1.97 – 3.63)
Random Effects (IIV)		
CV on CLp	0.696 (0.112)	(0.520 – 0.835)
CV on Ka	0.498 (0.164)	(0.298 – 0.639)
CV on V2	1.29 (0.122)	(0.934 – 1.57)
CV on	1.31 (0.0694)	(1.11 – 1.47)
CV on Qp	0.668 (0.123)	(0.481 – 0.813)
Covariate Effects		
ADA status on CL	-0.429 (0.231)	(-0.623 – -0.235)
BSA baseline on CL	1.26 (0.265)	(0.604 – 1.91)
Sex on V2	-0.579 (0.221)	(-0.830 – -0.329)
Residual Variability		
Additive error	0.395 (0.0504)	(0.356 – 0.434)
Proportional error	0.465 (0.0389)	(0.429 – 0.50)

B. CSF

Parameter	CSF PK model, Run2320510	
	Estimate (RSE)	**95% CI**
Model Parameters		
Central volume distribution V (L)	8730 (0.118)	(6705 – 1.075e+04)
Rate of elimination K (/h)	0.000876 (0.109)	(0.000688 – 0.00106)
Random Effects (IIV)		
CV on V	1.05 (0.0694)	(0.893 – 1.18)
CV on K	0.841 (0.0622)	(0.732 – 0.938)
Residual Variability		
Proportional error	0.790 (0.0151)	(0.767 – 0.814)

Source: Summary of Clinical Pharmacology, p. 105, Table 20; CPP-21-004, p. 49, Table 9
Abbreviations: ADA, antidrug antibody; BSA, body surface area; CI, confidence interval; CL, clearance; CSF, cerebrospinal fluid; CV, coefficient of variation; Ka, rate constant of absorption; PK, pharmacokinetics; RSE, residual standard error; Q, intercompartmental clearance; V2, plasma central volume of distribution; V3, plasma peripheral volume of distribution

Figure 52. Prediction-Corrected Visual Predict Check of the Final PK Model of Tofersen in Plasma



Source: CPP-21-004, p. 48, Figure 9
Abbreviations: PK, pharmacokinetic

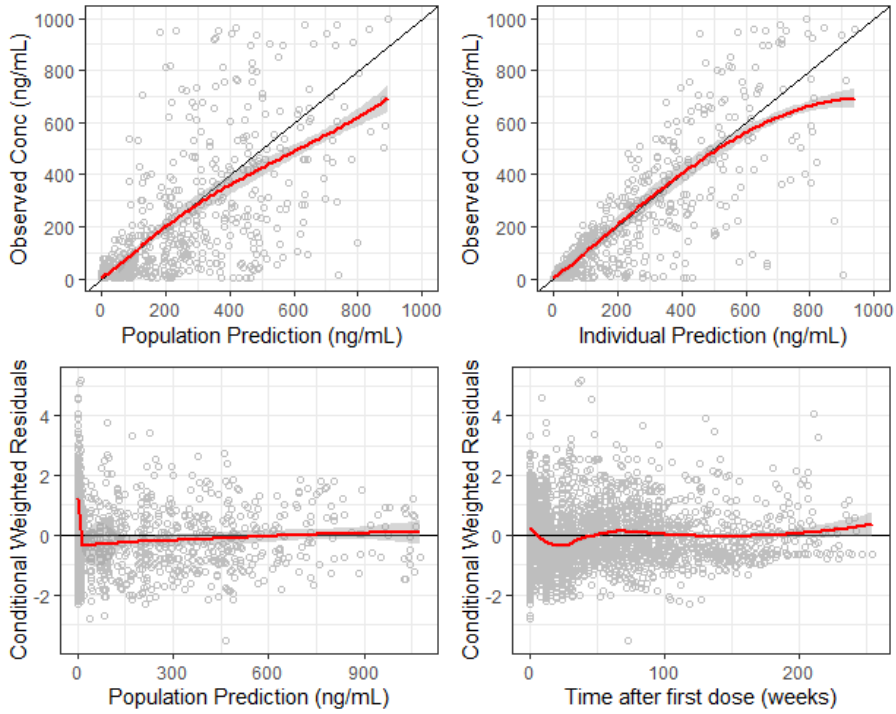
Reviewer's Comments

Reviewer was able to reproduce the PK models for tofersen in plasma and CSF, with similar model diagnostic plots (Figure 53). The plasma PK model suggested that AD- positive subjects had 42.9% lower clearance; and female subjects had 57.9% lower central volume of distribution. The PK model did not identify race, bodyweight, or age as important covariates influencing the PK of tofersen. The Applicant conducted a further analysis by adding race on both clearance and/or volume of distribution parameter of the final plasma PK model. However, race was not identified as a covariate in the analysis, possibly due to collinearity with baseline BSA. The result should be interpreted with caution as the estimated effect may be affected by the small dataset, sparse sampling, and underlying effects not captured by the current model. Also, the plasma and CSF compartments are downstream of the CNS, which is the tofersen site of action. In clinical studies, the dose of tofersen was not adjusted based on race, sex, bodyweight, or age. No conclusion can be drawn for the efficacy subgroup analysis based on sex and other covariates due to the small sample size and baseline study imbalances between the treatment groups.

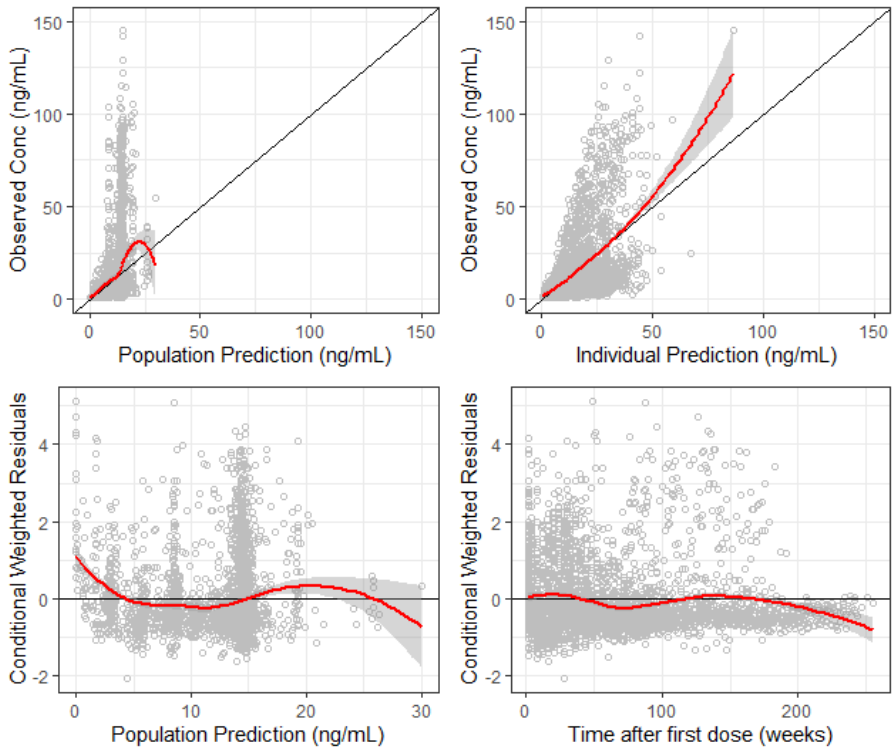
An IR was sent to the Applicant on March 30, 2023, to evaluate the impact of time-varying ADA on plasma/CSF PK exposure, total CSF SOD1 protein, and plasma NfL levels. The Applicant responded on March 03, 2023. The PK dataset was revised by adding 39 ADA-positive subjects, and the resulting PK model included time-varying ADA as a covariate on clearance. The revised PK model showed that the presence of ADA decreased plasma clearance by 32%. The impact of ADA on CSF PK exposure was not evaluated.

Figure 53. Goodness-of-Fit Plot of the Final PK Model of Tofersen

A. Plasma



B. CSF



Source: Reviewer's analysis
Red line represents Loess spline approximations of the data; black solid line represents line of unity.
Abbreviations: Conc, concentration; CSF, cerebrospinal fluid; PK, pharmacokinetics

14.5.4.2. Population PK-SOD1 Analysis of Tofersen

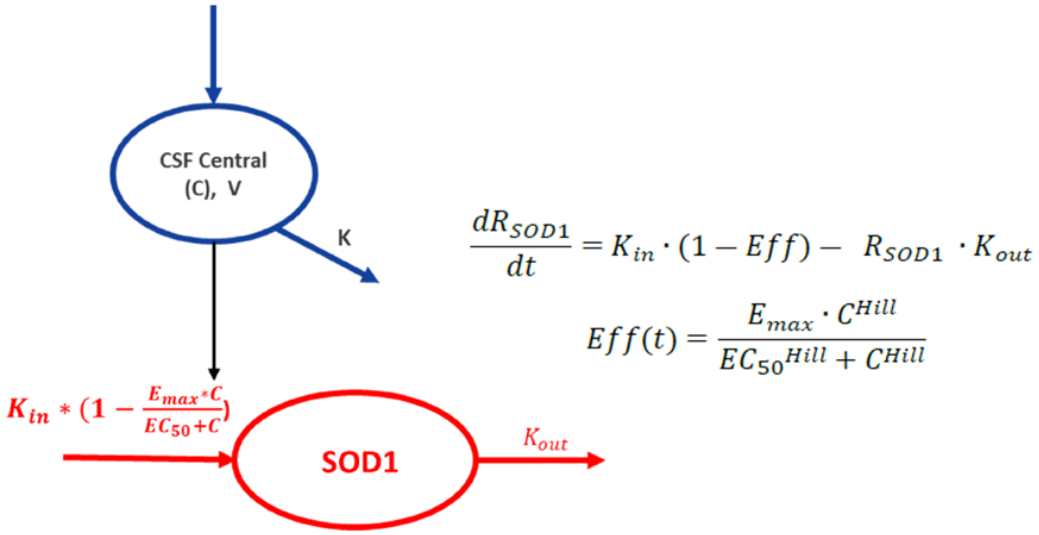
Applicant's Analysis

Objectives: To characterize and quantify the relationship between tofersen CSF PK exposures and the resulting SOD1 response.

Data: The data of 176 subjects from Study 101 and Study 102 was used for the analysis. The covariate characteristics of the data is provided in Table 109.

Method: Nonlinear mixed effect modeling in serum and CSF was conducted using NONMEM v. 7.4.3. A structural PKPD model was first developed to describe the relationship between tofersen CSF exposure and the CSF SOD1 protein reduction time course. Statistical significance of covariate-parameter relationships was assessed using the likelihood ratio test. If multiple covariates were identified for PK-SOD1 models, a formal covariate search was planned using the full model approach with stepwise backward elimination. The final PK/PD model was evaluated using goodness-of-fit plots and visual predictive checks. The PK/PD simulations (n=1000) were performed to determine whether a higher dose (150 mg and 200 mg) than the currently investigated 100 mg monthly dose could be beneficial, in terms of CSF SOD1 reduction, to SOD1-ALS subjects.

Figure 54. Schematic of the PK/PD Model of Tofersen for SOD1 Protein



K = rate of drug clearance; V= central volume of distribution. Kin = rate of synthesis, Kout = rate constant of degradation, Emax: maximum drug effect on SOD1 elimination, EC50 = drug concentration to produce 50% of the maximum effect. C: drug concentration in central compartment

Source: CPP-21-004, p. 56, Figure 13
Abbreviations: CSF, cerebrospinal fluid; SOD1, superoxide dismutase 1; PD, pharmacodynamics; PK, pharmacokinetics

Results: The PK/PD relationship was best described by an indirect response model with post hoc CSF tofersen exposure acting on the inhibition of SOD1 production in the SOD1 PD effect compartment (Figure 54). No covariate was identified for the final PK-SOD1 model. The population parameter estimates from the final PK-SOD1 models are provided in Table 111. The models were able to reasonably characterize the observed data, as shown in Figure 55.

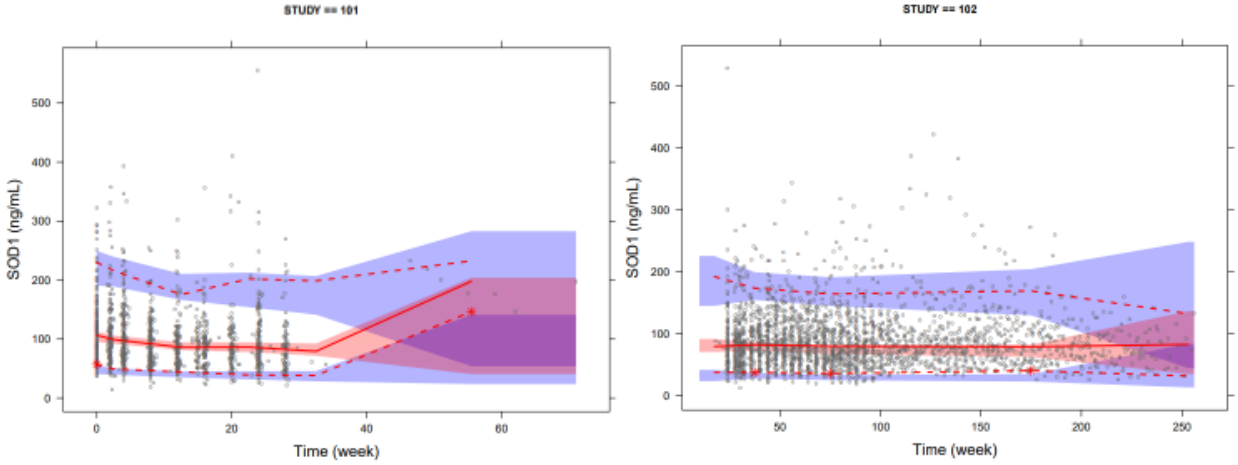
The PK-SOD1 model was used to simulate CSF SOD1 reductions at 100 mg, 150 mg and 200 mg monthly doses, including two initial biweekly loading doses (Figure 56). The median SOD1 reduction from baseline after 6 months of dosing was 29.1% at 200 mg versus 23.4% at 100 mg. Per Applicant, the increases in SOD1 reduction using higher doses (150 mg or 200 mg) would be marginal compared to the current highest dose (100 mg), considering the high interindividual variability of E_{max} in the PK-SOD1 model.

Table 111. Population Parameter Estimates of the Final Population PK-SOD1 Model for Tofersen

Parameter	CSF- SOD1 Final Base Model, run 202037 (combined Study 101+102)	
	Estimate (RSE)	**CI**
Model Parameters		
K_{out}	0.000974 (0.106)	(0.000772 – 0.00118)
EC_{50}	8.91 (0.479)	(0.539 – 17.3)
Logit Emax	-0.436 (0.616)	(-0.962 – 0.0905)
Emax	0.393 (0.616)	NA
Base	106 (0.0310)	(99.9 – 113)
Random Effects (IIV)		
CV on Emax*	1.38 (0.139)	(0.929 – 1.71)
CV on Baseline	0.415 (0.0545)	(0.368 – 0.457)
CV on K_{out}	0.258*0.415=0.107	NA
CV on EC_{50}	NA	NA
Corr (Base, Emax)	0.314 (0.167)	(0.182 – 0.379)
Corr (K_{out}, Baseline)	-1 fixed	NA
Corr factor	-0.258 (0.570)	(-0.545 – 0.0302)
Residual Variability		
Proportional error (Study 101)	0.223 (0.0422)	(0.205 – 0.241)
Proportional error (Study 102)	0.295 (0.0314)	(0.277 – 0.313)
Condition number	35.2	

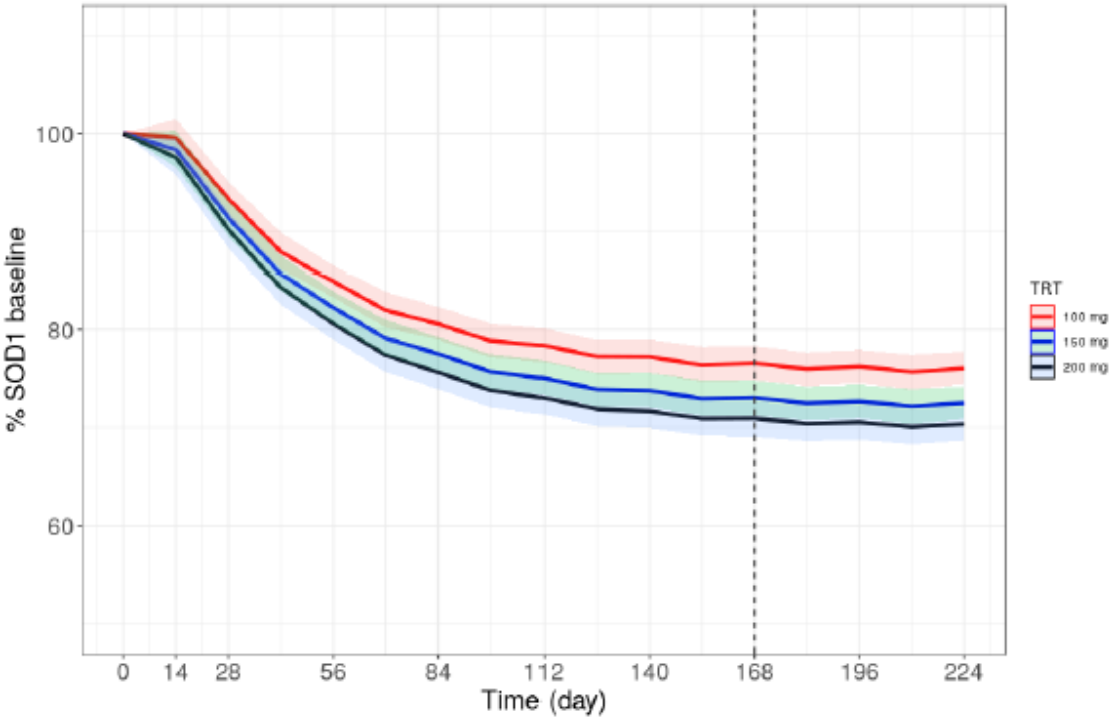
*CV on Emax is additive in logit scale
CI of parameter estimates were calculated based on SE.
Source: Summary of Clinical Pharmacology, p. 108, Table 21
Abbreviations: CSF, cerebrospinal fluid; CV, coefficient of variation; EC_{50}, drug concentration to produce 50% of the maximum effect; E_{max}, maximum drug effect on SOD1 elimination; K_{out}, rate constant of degradation; NA, not applicable; PK, pharmacokinetics; RSE, residual standard error; SOD1, superoxide dismutase 1

Figure 55. Prediction-Corrected Visual Predictive Check of the Final PK-SOD1 Model of Tofersen



Source: CPP-21-004, p. 72, Figure 19
The red solid and dashed lines represent the median, 5th, and 95th percentile of observed data; shaded areas represent the 95% prediction intervals of the simulated 50th (red), 5th, and 95th (blue) percentiles
Abbreviations: PK, pharmacokinetic; SOD1, superoxide dismutase 1

Figure 56. Population Mean Simulations of CSF SOD1 Reduction at Different Doses (Two Loading Doses With Monthly Maintenance Doses) Based on the Final CSF PK-SOD1 Model



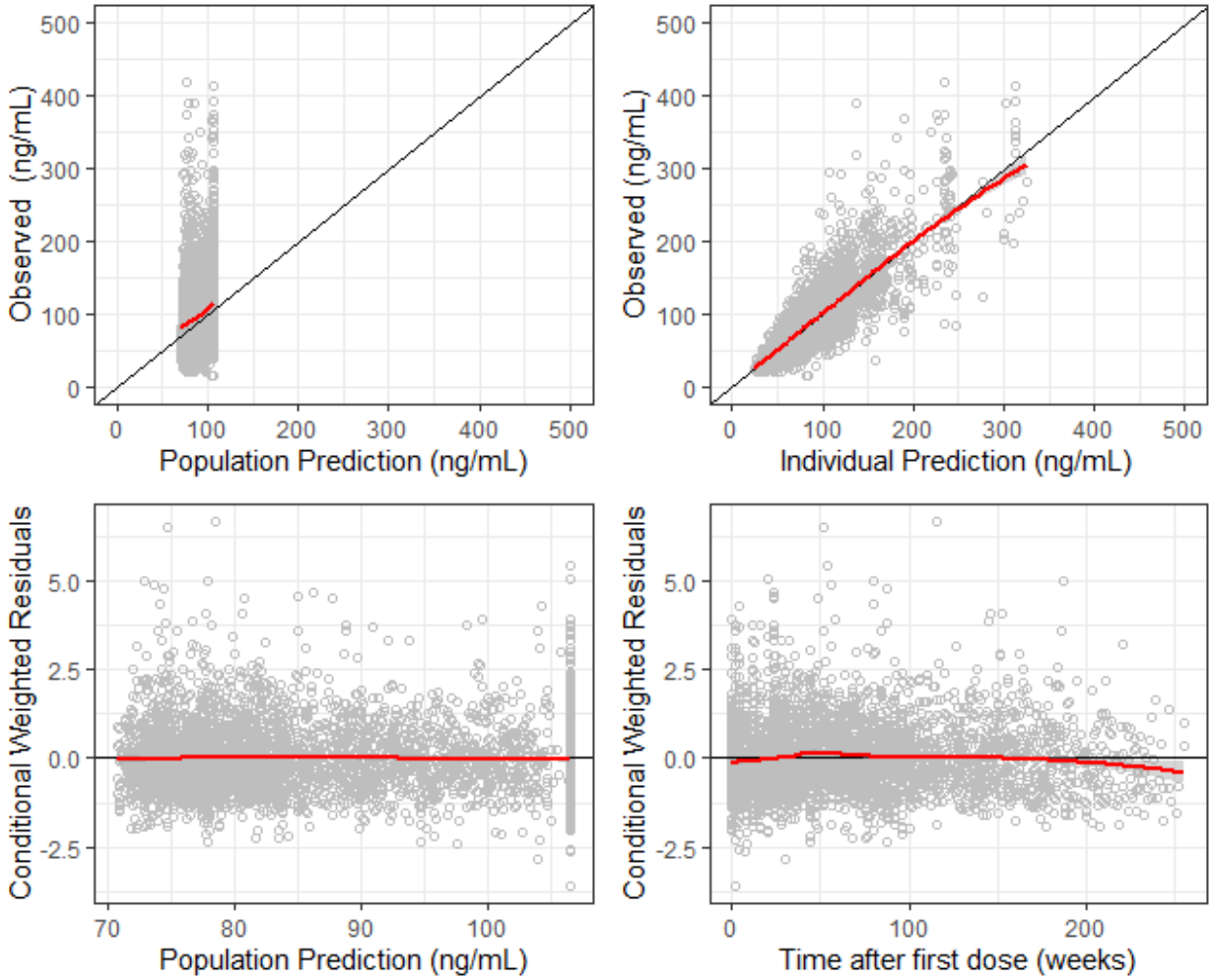
Source: CPP-21-004, p. 74, Figure 20
Dotted vertical line represents cut off at the end of 6 months. Shaded area: 95% confidence interval of uncertainty.
Abbreviations: CSF, cerebrospinal fluid; PK, pharmacokinetic; SOD1, superoxide dismutase 1; TRT, treatment group

Reviewer's Comments

The reviewer was able to reproduce the PK-SOD1 models for tofersen, with similar model diagnostic plots (Figure 57). The PK/PD model reasonably described the data, with the estimated E_{max} of ~40% of the baseline and the EC_{50} was in the range of the exposures produced by the

60 mg dose. The interindividual variability of E_{max} was high, likely due to both the natural variability of the SOD1 PD response and the sparsity of the data. The PK-SOD1 model did not identify ADA as a significant covariate in the analysis. The model extrapolated that the benefit in terms of SOD1 reduction of increasing the dose to 150 mg or 200 mg compared to the current highest dose (100 mg) is marginal. There are no data available to support the model extrapolation and so the results should be interpreted with caution.

Figure 57. Goodness-of-Fit Plot of the Final PK-SOD1 Model of Tofersen



Source: Reviewer's analysis
Red line represents Loess spline approximations of the data; black solid line represents line of unity
Abbreviations: PK, pharmacokinetics; SOD1, superoxide dismutase 1

14.5.4.3. Population PK-NfL Analysis of Tofersen

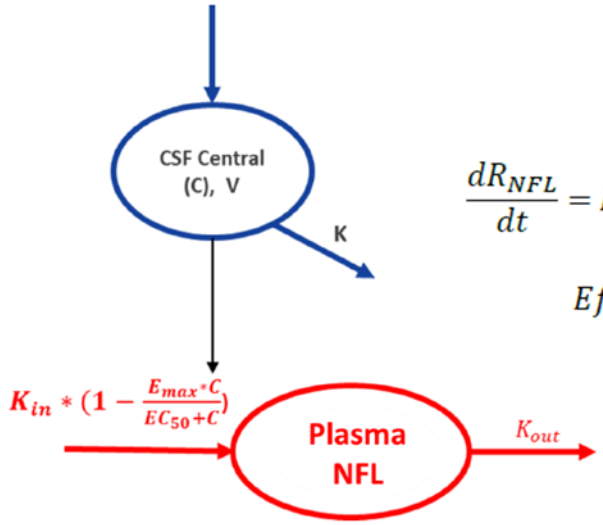
Applicant's Analysis

Objectives: To characterize and quantify the relationship between tofersen CSF PK exposures and the plasma NfL response.

Data: The data of 176 subjects from Study 101 and Study 102 were used for the analysis. The covariate characteristics of the data are provided in Table 109.

Method: Nonlinear mixed-effects modeling was conducted using NONMEM v. 7.4.3. A structural PKPD model was first developed to describe the relationship between tofersen CSF exposure and the plasma NfL reduction. The statistical significance of covariate-parameter relationships was assessed using the likelihood-ratio test. If multiple covariates were identified for PK-NfL models, a formal covariate search was planned using the full model approach with stepwise backward elimination. The final PK/PD model was evaluated using goodness-of-fit plots and visual predictive checks. PK/PD simulations (n=1000) were performed to determine whether a higher dose (150 mg and 200 mg) than the currently investigated 100 mg monthly dose could be beneficial, in terms of plasma NfL reduction, to SOD1-ALS subjects.

Figure 58. Schematics of PK/PD Model of Tofersen for SOD1 Protein



$$\frac{dR_{NFL}}{dt} = K_{in} \cdot (1 - Eff) - R_{NFL} \cdot K_{out}$$

$$Eff(t) = \frac{E_{max} \cdot C^{Hill}}{EC_{50}{}^{Hill} + C^{Hill}}$$

K = rate of drug clearance; V= central volume of distribution. Kin = rate of synthesis, Kout = rate constant of degradation, Emax: maximum drug effect on NFL elimination, EC50 = drug concentration to produce 50% of the maximum effect. C: drug concentration in central compartment

Source: CPP-21-004, p. 77, Figure 21
Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; PD, pharmacodynamics; PK, pharmacokinetics

Results: The PK/PD relationship was best described by an indirect response model with the post hoc CSF tofersen exposure acting on the inhibition of NfL production of the effect compartment (Figure 58). No covariate was included in the final PK-NfL model. The population parameter estimates from the final PK-NfL models are provided in Table 112. The models were able to reasonably characterize the observed data.

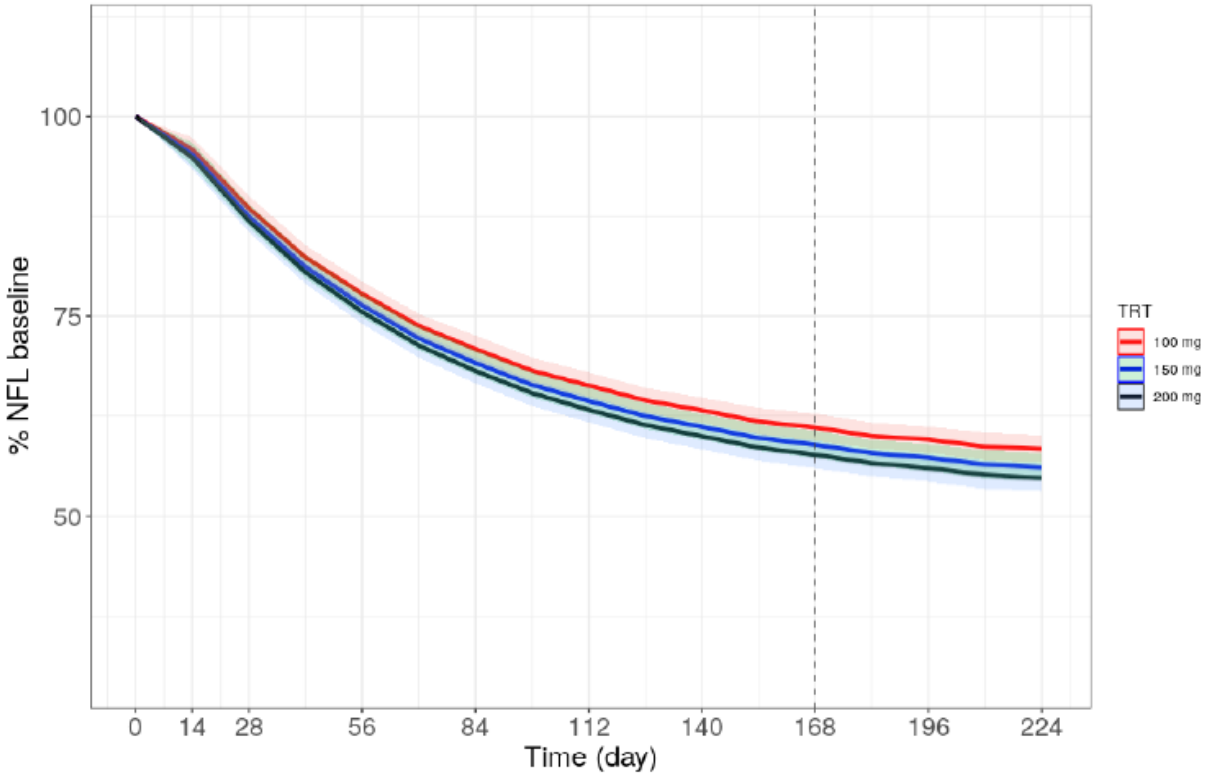
The PK-NfL model was used to simulate plasma NfL reductions at 100 mg, 150 mg and 200 mg monthly doses including two initial biweekly loading doses (Figure 59). The median NfL reduction from baseline after 6 months of dosing was 42.4% at 200 mg versus 39% at 100 mg. Per the Applicant, the gain in terms of plasma NfL reduction using higher doses (150 mg or 200 mg) would be marginal compared to the current highest dose (100 mg), considering the high interindividual variability of E_{max} in the PK-NfL model.

Table 112. Population Parameter Estimates of the Final Population PK-NfL Model for Tofersen

Parameter	CSF PK – plasma NfL final Model, run 3020340 (combined Study 101+102)	
	Estimate (RSE)	**CI**
Model Parameters		
K_{out}	0.000579 (0.0872)	(0.000481 – 0.000679)
EC_{50}	2.53 (0.329)	(0.900 – 4.16)
Logit Emax	0.394 (0.703)	(-0.148 – 0.936)
Emax	0.597	NA
Base	53.6 (0.0853)	(44.6 – 62.5)
Random Effects (IIV)		
CV on K_{out}	0.428 (0.166)	(0.252 – 0.549)
CV on EC_{50}	1.03 (0.158)	(0.631 – 1.30)
CV on Emax	1.94 (0.157)	(1.20 – 2.47)
CV on Baseline	1.11 (0.0383)	(1.02 – 1.19)
Residual Variability		
Proportional error (Study 101)	0.192 (0.0677)	(0.167 – 0.218)
Proportional error (Study 102)	0.327 (0.124)	(0.248 – 0.407)
Condition number	46.0	

Source: Summary of Clinical Pharmacology, p. 111, Table 22
Abbreviations: CSF, cerebrospinal fluid; CV, coefficient of variation; EC_{50}, drug concentration to produce 50% of the maximum effect; E_{max}, maximum drug effect on SOD1 elimination; K_{out}, rate constant of degradation; NA, not applicable; NfL, neurofilament light chain; PK, pharmacokinetics; RSE, residual standard error; SOD1, superoxide dismutase 1

Figure 59. Population Mean Simulations of Plasma NfL Reduction at Different Doses (Two Loading Dose With Monthly Maintenance Doses) Based on the Final CSF PK-SOD1 Model

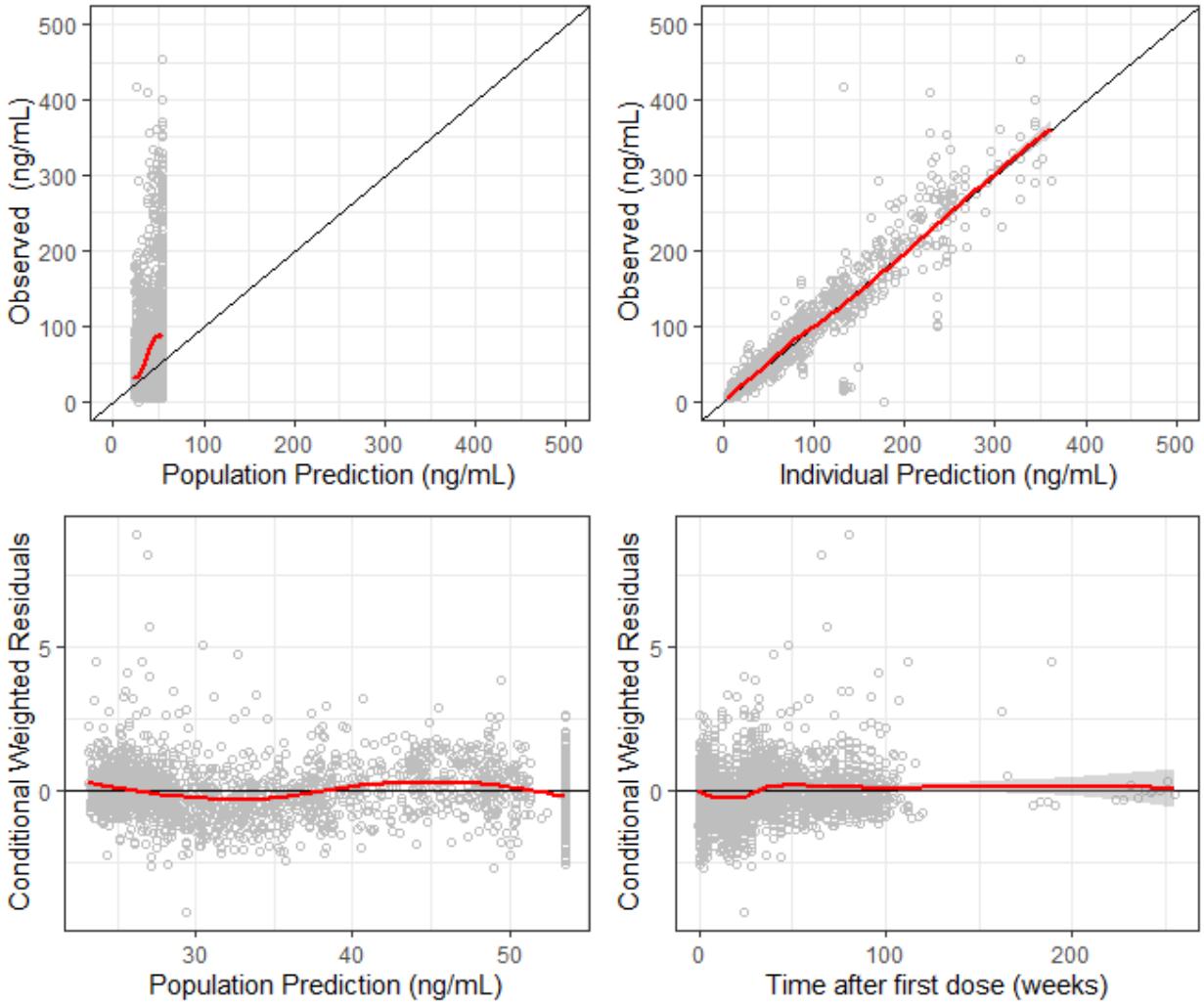


Source: CPP-21-004, p. 93, Figure 28
Dotted Vertical Line represents cut off at the end of 6 months. Shaded area: 95% confidence interval of uncertainty.
Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; PK, pharmacokinetic; SOD1, superoxide dismutase 1; TRT, treatment group.

Reviewer's Comments

The reviewer was able to reproduce the PK-NfL models for tofersen, with similar model diagnostic plots (Figure 60). The PK/PD model reasonably described the NfL data; the estimated E_{max} was ~60% of the baseline and the EC_{50} was in the range of the exposures produced by the 40 mg dose. The interindividual variability of E_{max} was high likely due to both the natural variability of the PD response and the sparsity of the data. The PK-NfL model did not identified ADA as a significant covariate in the analysis. The model extrapolated that the benefit of increasing dose to 150 mg or 200 mg compared to the current highest dose (100 mg) is marginal in terms of plasma NfL reduction. There are no data available to support the model extrapolation and so the results should be interpreted with caution.

Figure 60. Goodness-of-Fit Plot of the Final PK-NfL Model of Tofersen



Source: Reviewer's analysis
Red line represents loess spline approximations of the data; black solid line represents line of unity.
Abbreviations: NfL, neurofilament light chain; PK, pharmacokinetic

References

1. CPP-21-004-BIIB067: Population Pharmacokinetic and Pharmacodynamic Analysis of BIIB067 Tofersen data, dated April 2022
2. 2.7.2 Summary of Clinical Pharmacology Report

14.6. Pharmacogenetics

Refer to Section 14.8.2.

14.7. Supporting Information From Other Biomarkers

Analyses of the utility of plasma NfL as a reasonably likely surrogate are described in Section 6.3. The other biomarkers explored in this NDA are discussed below.

14.7.1. CSF SOD1

The human SOD1 gene, encoding copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), is ubiquitously expressed and involves the conversion of superoxide (O_2-) to oxygen (O_2). The mechanisms by which the SOD1 mutations cause motor neuron degeneration in SOD1 ALS patients are unclear, but the toxic gain-of-function of mutated/misfolded SOD1 protein is the most widely investigated candidate. According to the Applicant, no assay that can accurately and reliably measure the amount of misfolded/toxic SOD1 (form of protein generated by gain of function mechanism) in CSF is available. The validated bioanalytical assay for SOD1 protein measures total SOD1 protein, including native and mutant forms, in CSF.

Following tofersen treatment, the total SOD1 reduction in CSF provided indirect evidence of target engagement, the binding of tofersen to SOD1 mRNA. However, the biomarker data of CSF total SOD1 were not used to predict the clinical benefit of tofersen in treating SOD1-ALS because of the following limitations: 1) the total CSF SOD1 level does not distinguish mutant/misfolded from native SOD1 protein, and only the former is implicated in SOD1-ALS; 2) consistently, the total CSF SOD1 level has not been reported to correlate with disease progression rate in SOD1-ALS; 3) the level of total SOD1 reduction in CSF may not reflect the level of SOD1 reduction at target sites (i.e., CNS tissues).

The Applicant also reported reduction of a deamidated SOD1 (DSOD1) peptide, which is a fragment of SOD1 protein, in Study 101C. Based on a prior article, elevated deamidated SOD peptide (DSOD) in CSF (approximate 9-fold difference at the group level) was found in SOD1-ALS patients compared to subjects with neurogenerative disease or healthy controls.[54] Therefore, DSOD1 was believed to be more specific to SOD1-ALS than total SOD1. The tofersen-driven DSOD1 reduction provided additional evidence of target engagement. However, bioanalytical assay validation for DSOD1 was not included in the current submission, and so the DSOD1 data should be interpretated with caution.

Analyses of total SOD1 protein and DSOD1 peptide in Study 101C are described below.

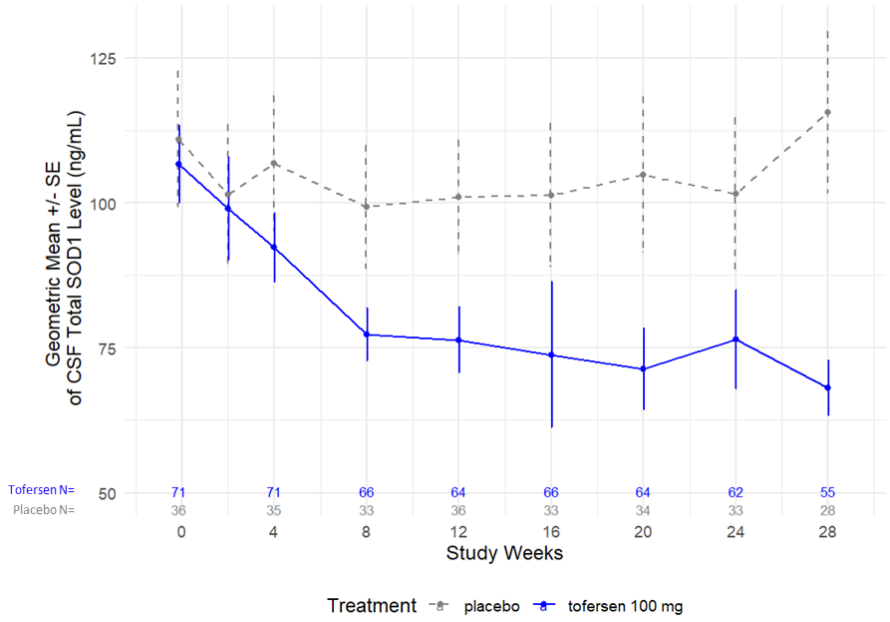
Total SOD1 Protein in CSF

Because tofersen is designed to bind and degrade mutant and wild-type SOD1 mRNA to reduce SOD1 protein synthesis and accumulation, the reduction of total SOD1 protein level is regarded as an indirect marker of target engagement of tofersen.

[54] Gertsman I, Wuu J, McAlonis-Downes M, et al. An endogenous peptide marker differentiates SOD1 stability and facilitates pharmacodynamic monitoring in SOD1 amyotrophic lateral sclerosis. JCI Insight. 2019;4(10):e122768. Published 2019 May 16. doi:10.1172/jci.insight.122768

In Study 101C, change of total SOD1 in CSF at Week 28 in the mITT population was a secondary endpoint. CSF was sampled before dosing at each visit in which treatment was administered (Days 1, 15, and 29 and every 4 weeks thereafter) and the final visit (4 weeks after the last dose). A reduction in total CSF SOD1 protein was observed at Week 28 in the tofersen compared to the placebo group (38% difference in geometric mean ratios for tofersen to placebo, nominal p<0.0001) in the mITT population. At Week 28 in the intent-to-treat (ITT) population, reductions in total CSF SOD1 protein of approximately 35% (geometric mean ratio [GMR] to baseline) in the tofersen group and approximately 2% in the placebo group were observed (difference in GMRs for tofersen to placebo approximately 34%; nominal p<0.0001, Figure 61).

Figure 61. Total CSF SOD1 Protein Level (Geometric Mean ±SE) by Visit (Observed Data) From Study 101 Part C, ITT Population



Source: Clinical Pharmacology Reviewer's analysis
Abbreviations: CSF, cerebrospinal fluid; ITT, intent-to-treat; SE, standard error; SOD1, superoxide dismutase 1

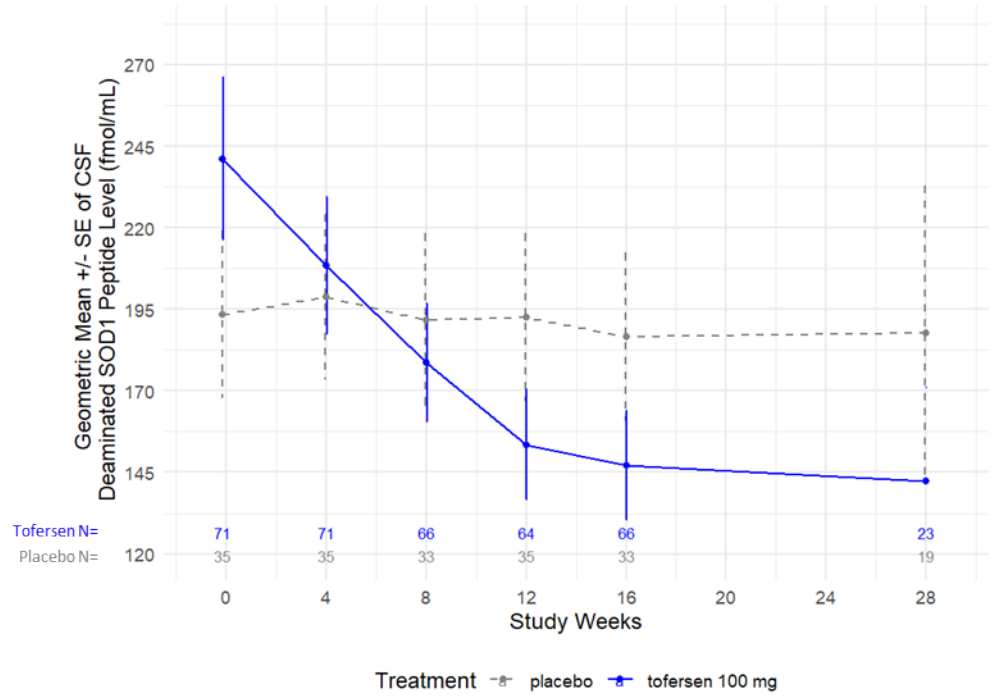
Based on literature findings, the total CSF SOD1 level is elevated in ALS patients compared to healthy subjects but did not show statistical differences between neurological disease controls (NDC) and ALS patients[55]. In addition, the total CSF SOD1 protein was not reported to be correlated with disease progression (ALSFRS decline/month) in sporadic ALS patients. Considering the current studied a different ALS population of SOD1 ALS, the review team also explored the prognostic value of CSF total SOD1 in SOD1-ALS patients. Based on the results of Study 101C, the baseline level of total SOD1 in CSF was not correlated with ALSFRS-R change from baseline (CFB) at Week 28 in the placebo group of the ITT population (Pearson correlation coefficient -0.014, p=0.94, N=33).

DSOD1 Peptide in CSF

[55] Winer L, Srinivasan D, Chun S, et al. SOD1 in cerebral spinal fluid as a pharmacodynamic marker for antisense oligonucleotide therapy. JAMA Neurol. 2013;70(2):201-207. doi:10.1001/jamaneurol.2013.593

Reduction in DSOD1 peptide in CSF was observed following tofersen treatment in Study 101C (Figure 62). By Week 16 (Day 113) in the ITT population, a reduction of 37% (geometric mean ratio to baseline) in the tofersen group and an increase of 2% in the placebo group were observed. Compared to Week 16, data from Week 28 had similar CFB% values of DSOD1 in the tofersen and placebo groups despite most of the data being missing.

Figure 62. CSF DSOD1 Peptide Level (Geometric Mean ±SE) by Visit (Observed Data) From Study 101 Part C, ITT Population



Source: Reviewer's analysis
Abbreviations: CSF, cerebrospinal fluid; DSOD1, deaminated superoxide dismutase 1; ITT, intent-to-treat; SE, standard error; SOD1, superoxide dismutase 1

Because CSF DSOD1 may be more proximal to the pathophysiology of SOD1-ALS, the review team explored the correlation of baseline CSF DSOD1 with ALSFRS-R CFB at Week 28 to examine the prognostic value of CSF DSOD1 in SOD1-ALS patients. Based on the results of the placebo group in Study 101C, the baseline level of CSF DSOD1 was not correlated with ALSFRS-R CFB at Week 28 in the placebo group of the ITT population (Pearson correlation coefficient -0.048, p=0.79, N=32).

14.7.2. CSF NfL

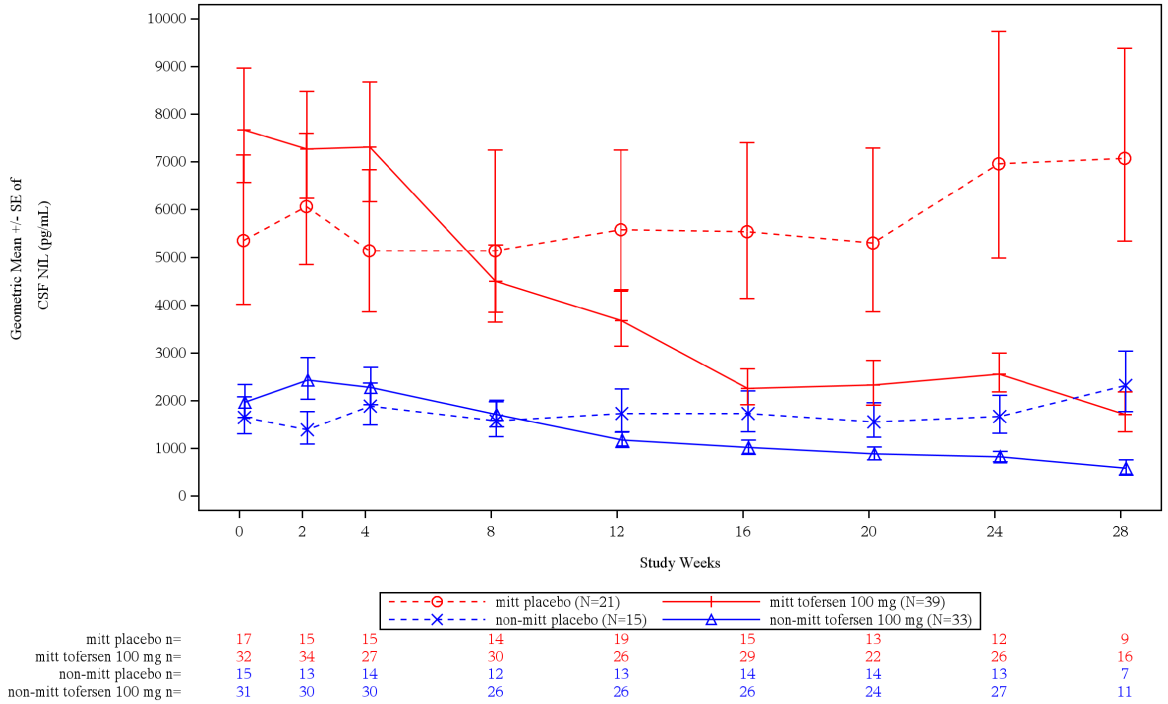
NfL levels in the CSF of SOD1-ALS patients were evaluated in Study 101C. The CSF NfL level was approximately 60-fold that in plasma at baseline for all subjects in Study 101C. Consistent with literature findings, a strong correlation between plasma NfL and CSF NfL was found in SOD1-ALS patients in Study 101C.

Using the plasma NfL and CSF NfL data from Study 101C, a strong correlation was found between baseline plasma NfL and CSF NfL levels (N=95, Pearson correlation coefficient 0.81,

p<2.2e-16). In addition, a strong correlation was found between the plasma NfL percentage change from baseline and CSF NfL percentage change from baseline at Week 16 (N=73, Pearson correlation coefficient 0.8, p<2.2e-16) and Week 24 (N=72, Pearson correlation coefficient 0.78, p<4.2e-16).

In Study 101C, a reduction in CSF NfL level was observed at Week 28 in the tofersen group compared to the placebo group (difference in geometric mean ratios for tofersen to placebo of 69% and nominal p<0.0001, ITT population). The difference in geometric mean ratios at Week 28 for tofersen to placebo in the mITT population was 72% (Figure 63). The majority of patients (64% in the tofersen group, 58% in the placebo group) had missing CSF NfL data in Week 28. Therefore, the reduction of CSF NfL was compared between the tofersen and placebo groups at Week 24 (fewer missing values); the results were similar.

Figure 63. CSF NfL (pg/mL) Geometric Mean Values ±SE by Visit (Observed Data)



Source: 233AS101 Part C, Section 14.3.5.2, Output 33
Abbreviations: CSF, cerebrospinal fluid; mITT, modified intent-to-treat; NfL; neurofilament light chain; SE, standard error

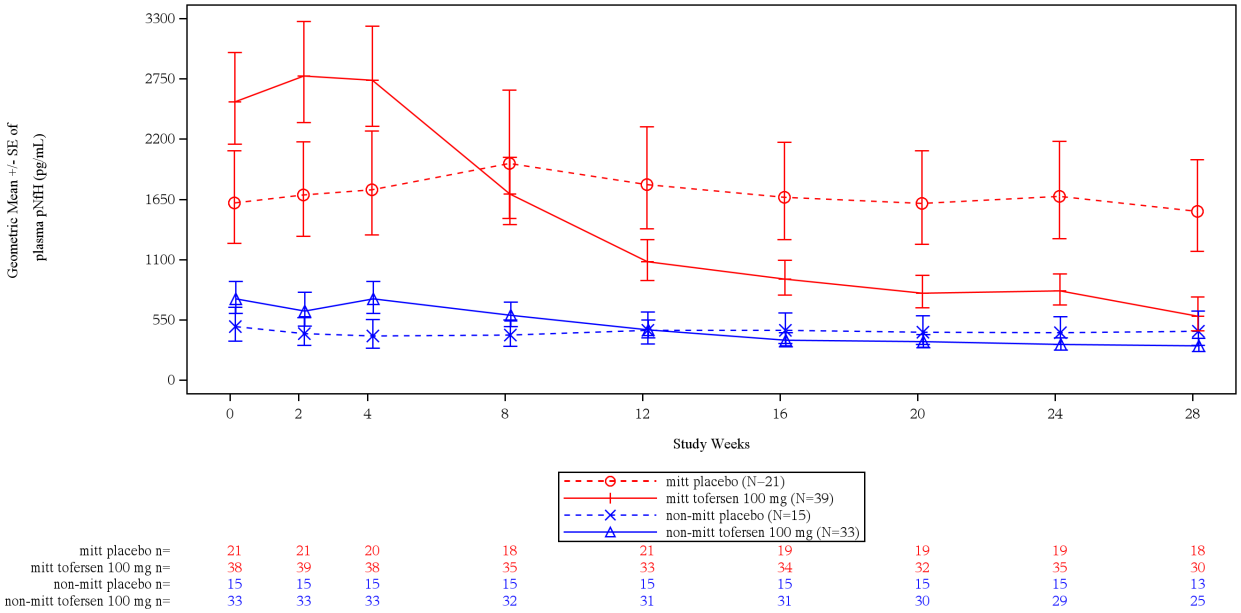
14.7.3. Phosphorylated Neurofilament Heavy Chain (pNfH)

In Study 101C, pNfH levels in plasma and CSF samples were analyzed as exploratory biomarkers. In Study 101C, reductions in plasma pNfH levels from baseline to Week 28 (Day 197) were observed in the mITT and non-mITT populations (Figure 64). There was a 77% reduction (difference in geometric mean ratios for tofersen to placebo) and nominal p<0.0001 in the mITT population and a 41% reduction and nominal p=0.0033 in the non-mITT population.

Reductions in CSF pNfH levels from baseline to Week 28 were observed in the mITT and non-mITT populations (Figure 65). There was a 73% reduction (difference in geometric mean ratios

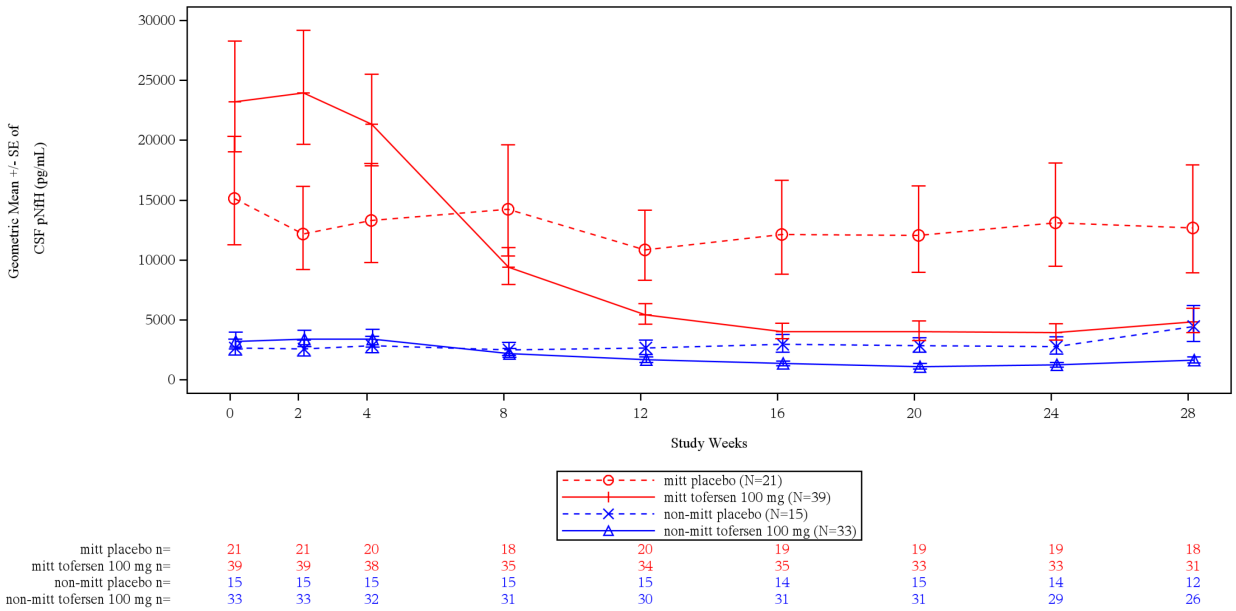
for tofersen to placebo) and nominal p<0.0001 in the mITT population and a 62% reduction and nominal p<0.0001 in the non-mITT population.

Figure 64. Study 233AS101 Part C: Plasma pNfH (pg/mL) Geometric Mean Values ±SE by Visit (Observed Data)



Source: 233AS101 Part C, Section 14.3.5.2, Output 13
Abbreviations: mITT, modified intent-to-treat; pNfH, phosphorylated neurofilament heavy chain; SE, standard error

Figure 65. Study 233AS101 Part C: CSF pNfH (pg/mL) Geometric Mean Values ±SE by Visit (Observed Data)



Source: 233AS101 Part C, Section 14.3.5.2, Output 19
Abbreviations: CSF, cerebrospinal fluid; mITT, modified intent-to-treat; pNfH, phosphorylated neurofilament heavy chain; SE, standard error

14.8. Additional Comments on the Enrichment Criteria of Study 233AS101 Part C

14.8.1. Exploratory Evaluation of Disease Progression in Placebo Based on the Enrichment Criteria Using the Prerandomization Slope

In the Study 101C mITT population, 38% (N=8) of placebo group and 44% (N=17) of tofersen group had SOD1 mutations historically associated with shorter survival and had a prerandomization slope >0.2 points/month. Other mITT patients, 62% (N=13) of the placebo group and 56% (N=22) of the tofersen group, were selected because they had a prerandomization ALSFRS-R slope >0.9 without SOD1 mutations historically associated with shorter survival.

To assess whether prerandomization ALSFRS-R slope reliably reflects the decline of ALSFRS-R for disease progression, prerandomization ALSFRS-R slope (rate of decline from the day of symptom onset to the randomization visit) is compared with the in-study slope (rate of decline from randomization to Day 197) at the group level. Data from the run-in slope were initially considered for comparison. However, due to the large intersubject variability and the shorter duration used for slope calculation (mean 37 days) for the run-in ALSFRS-R slope, the reliability of the run-in slope to characterize disease progression may be limited. Compared to the prerandomization ALSFRS-R slope, the in-study ALSFRS-R slope for the placebo groups of the mITT and ITT populations indicated slower function decline (Table 113).

Table 113. Group-Level Prerandomization ALSFRS-R Slope and in-Study ALSFRS-R Slope in the ITT and mITT Populations

	Prerandomization Slope		In-Study Slope	
Population	N	Mean±SE	N	Mean±SE
mITT Placebo	21	-1.81±0.26	21	-1.41±0.31
ITT Placebo	36	-1.16±0.20	36	-0.96±0.22

Source: Reviewer's analysis
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; SE, standard error

Based on the Applicant's statistical analysis plan, the sample size of the Study 101C mITT population was selected based on an assumption of a decline of ALSFRS-R at 3.83 points/month in the placebo group and 0.74 points/month in the tofersen 100 mg group (pooled SD of 3.166 points/month). Based on the information submitted by the Applicant, the basis of this assumed treatment effect and variability is literature findings[56] and experience from Study 101 Part B MAD with matched protocol-defined enrichment criteria. The observed mean prerandomization slope was -1.8 (SD 1.2) and -1.7 (SD 1.6) for the placebo and tofersen groups in the mITT population, respectively. Comparing the in-study slope (rate of decline from Days 1 to 197 after randomization) to the prerandomization slope in the placebo group, the mITT and ITT populations had 22% and 17%, respectively, slower rates of decline in-study. In conclusion, the

[56] Benatar M, Wuu J, Andersen PM, et al. Randomized, double-blind, placebo-controlled trial of arimoclomol in rapidly progressive SOD1 ALS. Neurology. 2018;90(7):e565-e574. doi:10.1212/WNL.0000000000004960

mITT population of the tofersen and placebo groups had a slower rate of decline in ALSFRS-R during the study compared to that predicted or expected based on the prerandomization slope.

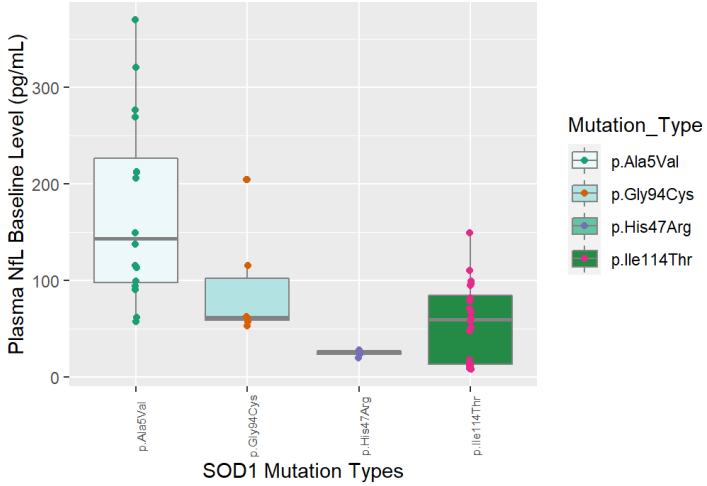
14.8.2. Evaluation of mITT Population Enrichment Based on SOD1 Genotypes

SOD1 mutation type was included in the enrichment criteria based on prior knowledge of survival. The prespecified SOD1 mutations historically associated with shorter survival were p.Ala5Val (A5V), p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly.

In Study 101C, variability of disease progression rate in the change of ALSFRS-R was noted among A5V carriers, although this is based on a small subgroup. Specifically, subjects with the A5V mutation had a wide range of baseline prerandomization slopes and plasma NfL levels. The prerandomization slopes for ALSFRS-R decline ranged from 0.4 to 4.9 points/month in the placebo group (N=6) and from 0.4 to 5.3 points/month in the tofersen group (N=11). Subjects with the A5V mutation receiving placebo (N=6) showed DP slopes of 0.3 to 4.2 points/month during the 6-month double-blind study phase. In A5V SOD1 carriers, the progression rate varies according to the phase of the disease. In A5V carriers receiving placebo (N=6), the differences between the in-study and prerandomization slopes showed a wide range (-3.8 to 0.2) at the individual level.

We also evaluated the baseline plasma NfL level in subjects in Study 101C with the SOD1 p.Ile114Thr (N=20), p.Ala5Val (A5V) (N=17), p.Gly94Cys (N=6), and p.His47Arg (N=5) mutation. In patients with the A5V mutation, the plasma NfL level was higher than in patients with the other three most common SOD1 mutations (p.Ile114Thr, p.Gly94Cys, and p.His47Arg) with large intersubject variability (Figure 66). In patients with the A5V mutation, the baseline plasma NfL levels ranged from 57.1 to 370 pg/mL in the placebo group and from 61.9 to 321 pg/mL in the tofersen group.

Figure 66. Baseline Plasma NfL Level According to SOD1 Mutation Type



Source: Reviewer's analysis
Abbreviations: NfL, neurofilament light chain; SOD1, superoxide dismutase 1

The number of patients (N<3) with each of the other SOD1 mutations historically associated with short survival in Study 101C was insufficient to conduct an exploratory analysis on the DP rate or baseline NfL.

Over 200 SOD1 gain-of-function variants are known to cause SOD-1 ALS. Based on its mechanism of action and binding to the 3'-UTR of SOD1 mRNA, tofersen is expected to bind to and degrade SOD1 mRNA irrespective of the SOD1 variant.

The Applicant enrolled 42 subjects with unique SOD1 variants. The most common SOD1 mutation types (>10% of subjects) were p.Ile114Thr (n=20/108; 18.5%), and p.Ala5Val (n=17/108; 15.7%).

Below are listed all the SOD1 variants enrolled in Study 101C:

- Ala5Ser
- Ala5Thr
- Ala5Val
- Gly13Arg
- Phe21Ile
- Gln23Leu
- Gly38Arg
- Leu39Val
- Gly42Asp
- Gly42Ser
- His44Arg
- His47Arg
- Glu50Lys
- Phe65Leu
- Leu85Phe
- Asn87Ser
- Ala90Val
- Ala90Thr
- Asp91Ala
- Gly94Ala
- Gly94Arg
- Gly94Asp
- Gly94Cys
- Gly94Ser
- Glu101Gly
- Glu101Lys
- Asp102Gly
- Ile113Thr
- Ile114Thr
- Arg116Gly
- His121Gln
- Asp125Val
- Leu127Ser
- Thr138Ile
- Ala141Gly
- Leu145Ser
- Leu145Phe
- Ala146Thr
- Gly148Ser
- Val149Gly
- Ile150Thr
- c.358-10T>G

All subjects underwent centralized genetic testing and were required to have a SOD1 variant independently classified by the central laboratory (b) (4) as pathogenic or likely pathogenic, in accordance with the ACMG guidelines (Richards 2015, PMID: 25741868). Independently of the Applicant, variants (e.g., those classified as variants of uncertain significance) could be reclassified by (b) (4) in accordance with the ACMG variant classification guidelines.

A total of five randomized subjects at screening had variants (p.Ala90Val, p.Ala141Gly, p.Thr138Ile, c.358-10T>G) initially classified as variants of unknown significance (VUS) and reclassified to likely pathogenic based on adjudication by a central independent laboratory (b) (4) and the ACMG guidelines. Twenty-three patients with ALS failed screening by testing negative for a SOD1 variant, and two subjects had variants in SOD1 that were considered VUS (c.169+152_169+58del, Gly62Arg) and so were not eligible for study entry.

14.9. PK/PD Supporting Dose Selection

The proposed dosing regimen for tofersen consists of three loading doses of tofersen 100 mg once every 2 weeks, followed by maintenance doses once every 4 weeks administered via intrathecal (IT) bolus injection. The selected dose was evaluated and supported by the findings from clinical Studies 101C and 102, using NfL reduction as a surrogate reasonably likely to predict slowing of clinical function decline (Section 6.3). Results from PK-SOD1/NfL and PBPK modeling were also proposed by the Applicant to support the dose selection, however, the uncertainties in the modeling and simulation limited the interpretation of the results.

Multiple monthly doses of 100 mg tofersen were evaluated in Study 233AS101 Part B and Part C. Because tofersen is given via the IT route and the therapeutic targets are in the CNS, tofersen exposure in the CSF is more relevant than the systemic exposure (i.e., blood exposure) for the evaluation of exposure-response. Administration of tofersen 100 mg in Study 233AS101 Part B led to the highest tofersen CSF exposures, and greatest reductions in total CSF SOD1 protein, plasma and CSF NfL, and plasma and CSF pNfH compared to lower monthly doses (20 mg, 40 mg, and 60 mg). In the Study 233AS101 Part C population, monthly dosing of 100 mg tofersen demonstrated a mean CSF C_{trough} of 24 ng/mL with large intersubject variability (CV% 101%). Tofersen 100 mg led to a mean reduction of 35% in total CSF SOD1 and a mean plasma NfL reduction of 55% compared to baseline in SOD1-ALS patients in the ITT population. More importantly, the effect of tofersen at 100 mg in reducing NfL can be used as a surrogate reasonably likely to predict the effect of tofersen on the decline of clinical function (ALSFRS-R) in SOD1-ALS patients (refer to Section 6.3).

PK/PD models were developed to characterize the relationships between CSF tofersen exposure and responses of two biomarkers (CSF total SOD1 protein and plasma NfL). The PK-SOD1 model had an E_{max} of 39% for SOD1 reduction and an EC_{50} of 8.91 ng/mL. The PK-NfL model had an E_{max} of 60% for plasma NfL reduction and an EC_{50} of 2.53 ng/mL. Higher doses (150 mg and 200 mg) were also evaluated in PK-SOD1/NfL model simulations. The results showed marginal gains in SOD1 reduction (<6%) and NfL reduction (<4%) for doses of 150 mg and 200 mg compared to the current highest dose (100 mg). However, the review team believes that the PK/PD models developed using a dose range of 20 to 100 mg may have limited ability to predict responses to higher doses due to the lack of clinical data for higher doses (150 and

200 mg). The biomarker response at doses >100 mg cannot be reliably predicted at this time. Refer to Sections 14.5.4.2. and 14.5.4.3 for details.

In addition to clinical data, the Applicant submitted the PBPK modeling of tofersen exposure and the prediction of SOD1 protein reduction in human CNS tissue based on nonclinical data from NHPs and transgenic mouse models. Because the total CSF SOD1 reduction threshold for clinical benefit has not been established and the predictability of the PBPK modeling on SOD1 protein reduction in human CNS tissue cannot be verified, there are uncertainties in using the PBPK modeling results to support dose selection of tofersen. (b) (4)

However, the prediction of SOD1 reduction in human CNS tissue was based on many assumptions and there are no observed data to verify the predictivity of SOD1 protein reduction in human CNS tissue. Specifically, the translational PBPK model used volume-based scaling from NHPs to human to predict tofersen exposure in different human CNS tissue regions, assuming the same CNS-related drug transfer rate between NHP and human. The predicted tofersen exposures in the CNS were used to interpolate the expected human SOD1 reduction from the exposure-SOD1 mRNA curve in human transgenic mice. This interpolation was based on the assumptions of identical tofersen potencies in human and mouse and that the percentage reduction in mRNA directly translates to equal percentage reductions in SOD1 protein. These assumptions cannot be verified at this time. Despite this limitation, the review team believe that the observed 67% reduction in NfL will likely result in clinical benefit based on the available understanding of the prognostic value of NfL. To support tofersen's distribution in human CNS tissue, the tissue tofersen concentrations in samples of CNS regions of autopsied subjects were submitted from three SOD1-ALS patients. The tofersen concentration was measurable in the brain tissues of two subjects, confirming the distribution of tofersen in human CNS tissue. However, the predictive power of the translational PBPK model for tofersen human exposure cannot be confirmed because of the small number of human tissue samples available and the variable interval between death and collection of autopsy samples.

15. Study/Trial Design

15.1. Additional Statistical Concerns

Issues with Sample Size Planning

In the Study 101C Clinical Study Report, the sample size justification was based on an assumed mean slope of decline of -3.83 per month for the placebo participants (i.e., 24.7-point decline over 28 weeks) and -0.74 per month for the tofersen 100 mg participants (approximately a 4.8 decline over 28 weeks), with a pooled SD of 3.166. Furthermore, the survival at Week 28 was assumed to be 82% in the placebo control and 90% in the tofersen 100 mg group. Under the above assumptions, with N = 60 participants in the mITT population and a two-sided significance level of 0.05, the Joint Rank Test gave 84% power.

The study actually had 60 patients in the mITT population (as planned) and the survival rates were better than expected. One reason the study failed may have been that decline in both the placebo and treatment groups was much less than expected. The actual observed decline over 28

weeks was approximately an 8.1 decline in the placebo arm and a 7-point decline in the tofersen arm, a mean difference of about 1 point instead of the difference of 20 that was assumed. The survival rate in both arms combined was 59/60 (one death in the tofersen arm). Assuming these observed rates of decline and a common survival rate of 59/60 and leaving the other assumptions unchanged, a future study would need 12,000 participants to achieve 80% power to detect a mean difference of 1.1 points decline in ALSFRS-R. However, there is some uncertainty about the effect and it may be larger than 1.1. Also, the effect may be larger with longer follow-up. If the effect is larger than 1.1., a smaller sample size may be adequate.

Issues with Method of Imputation of Missing Data

For the prespecified statistical methods (i.e., joint rank or ANCOVA) for the primary endpoint, multiple imputation using MCMC under the normality assumption was used to handle missing data or noncompleters. The statistical analysis plan did not specify an alternative method for handling missing data in case that the normality assumption did not hold. The Applicant did not check the normality assumption.

16. Efficacy

16.1. Quality of Life Measures in Study 102

As described in Section 6.2.2.4, the primary efficacy endpoint for Study 101C was the change from baseline to Week 28 (Day 197) in ALSFRS-R total score. This study failed to show any statistically significant difference between the tofersen and placebo groups for the primary endpoint.

The Applicant continued to accrue efficacy data from the OLE Study 102 for supplemental analyses. Data from the Phase 3 (Part C) subjects in Studies 101 and 102 were integrated to enable 52 weeks of assessment of early-start (participants who initiated tofersen 100 mg in Study 101C and continued to receive tofersen during the open-label Study 102) versus delayed-start (subjects who received placebo in Study 101C and later initiated tofersen 100 mg in Study 102, ~6 months later) tofersen. Ninety-five of one hundred eight (87%) subjects randomized in Study 101 Part C went on to receive tofersen in Study 102, as outlined in Section 6.2.2.4.

Reviewer's Comment: The results of the supplemental analyses at Week 52 of ALSFRS-R, SVC, and HHD changes compared to baseline showed nominally less worsening in the early-start compared to the delayed-start tofersen group. The statistical limitations of these analyses are described in more detail in Section 6.2.2.4.

The Applicant also continued to accrue data for changes from the Study 101C baseline for the following quality-of-life measures to Week 52.

- ALSAQ-5
- FSS
- EQ-5D-5L Utility Score
- EQ-5D VAS

The ALSAQ-5 is a patient self-reported health status questionnaire about physical mobility, activities of daily living, eating and drinking abilities, communication, and emotional functioning. The questions are followed by five responses and raw scores range from 0 = Never to 4 = Always or cannot do at all. The score for each question was calculated as (raw score ÷ 4) × 100[57], ranging from 0 to 100, with lower scores representing better health-related status.

The Fatigue Severity Scale (FSS) is a self-reported questionnaire designed to assess disabling fatigue and consists of nine questions using a 7-point Likert scale ranging from strongly disagree to strongly agree. The scores for each question are totaled, with lower scores indicating less fatigue in everyday life.

The European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L) Utility Score is a standardized generic measure of health status and consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions is measured on a 5-point scale: no problems (score 1), slight problems, moderate problems, severe problems, and extreme problems (score 5). Lower scores indicate better health-related status.

The European Quality of Life Five Dimension Questionnaire (EQ-5D) Visual Analog Scale (VAS) records the respondent's self-rated health on a vertical scale ranging from 0 to 100, where 100 indicates *best imaginable health state* and 0 indicates *worst imaginable health state*. A positive change indicates an improvement in health state.

The results of these analyses are summarized in Table 114. The analysis used a multiple imputation model based on all subjects in the ITT population and includes baseline plasma NfL, treatment, use of riluzole or edaravone, relevant baseline scores and postbaseline values. Adjusted means, treatment differences and corresponding 95% CIs and nominal p-values are obtained from the ANCOVA model for change from baseline in conjunction with multiple imputation. The ANCOVA models include treatment as a fixed effect and adjust for the following covariates: baseline plasma NfL, relevant baseline score, and use of riluzole or edaravone.

[57] Jenkinson C, Fitzpatrick R. Reduced item set for the amyotrophic lateral sclerosis assessment questionnaire: development and validation of the ALSAQ-5. J Neurol Neurosurg Psychiatry. 2001;70(1):70-3.

Table 114. Change in QoL Measures From Study 101 Part C Baseline (ITT Population)

Endpoint	ISE Based on Jul 2021 Data cut	ISE Based on Jan 2022 Data cut
	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 40**	Early-start tofersen (n=72) vs. placebo → delayed-start tofersen (n=36) Change from baseline to **Week 52**
Change from baseline on ALSAQ-5 Adjusted means: Tof;placebo Tofersen-placebo: adjusted mean (95% CI) p-value (ANCOVA+MI)	 7.4, 16.5 -9.1 (-17.0, -1.16)	 9.6, 19.9 -10.3 (-17.33, -3.20) 0.0044
Change from baseline on FSS Adjusted means: Tof;placebo Tofersen-placebo: adjusted mean (95% CI) p-value (ANCOVA+MI)	 3.9, 2.4 1.6 (-3.3, 6.4)	 1.3, 5.1 -3.8 (-9.03, 1.38) 0.1493
Change from baseline on EQ-5D-5L Utility Score Adjusted means: Tof;placebo Tofersen-placebo: adjusted mean (95% CI) p-value (ANCOVA+MI)	 -0.06, -0.30 0.23 (0.131, 0.335)	 -0.1, -0.3 0.2 (0.13, 0.32) <0.0001
Change from baseline on EQ-5D VAS Adjusted means: Tof;placebo Tofersen-placebo: adjusted mean (95% CI) p-value (ANCOVA+MI)	 -8.3, -14.5 6.2 (-0.9, 13.2)	 -7.0, -12.9 5.9 (-1.54, 13.25) 0.1209

Source: Summary of Clinical Efficacy, Table 23, p. 97
Abbreviations: ALSAQ-5, amyotrophic lateral sclerosis assessment questionnaire 5-item; ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-5L, European quality of life 5-domain 5-level questionnaire; EQ-5D VAS, European quality of life 5-domain questionnaire visual analog scale; FSS, fatigue severity scale; ISE, integrated summary of efficacy; ITT, intent-to-treat; MI, multiple imputation; QoL, quality of life; Tof, tofersen

Reviewer Comment: The results in Table 114 show that the early-start tofersen group had nominally less worsening of quality-of-life and fatigue compared to the delayed-start group as measured by ALSAQ-5 total score, EQ-5D-5L utility score, EQ-5D-VAS, and FSS.

Overall, these supplemental 52-week analyses beyond the original 28 weeks of the pivotal Study 101C are suggestive of longer-term efficacy of tofersen in treating ALS and stand in contrast to the clearly negative result of the primary endpoint of the pivotal study at Week 28. Note that some of these supplemental analyses are described as prespecified *by the Applicant, but they were planned only after the negative result of the pivotal Study 101C (see the statistical discussion of these results in Section 6.2.2.4).*

16.2. Survival of A5V Fast Progressors

The A5V variant (also known as p.Ala5Val, ala4val, or A4V) of SOD1-ALS, present in approximately 50% of all North American families with identifiable SOD1 variants, is consistently associated with a rapid average disease course and survival of only 1 year[58]. The Division sent an information request to the Applicant on 19 September 2022 for an updated

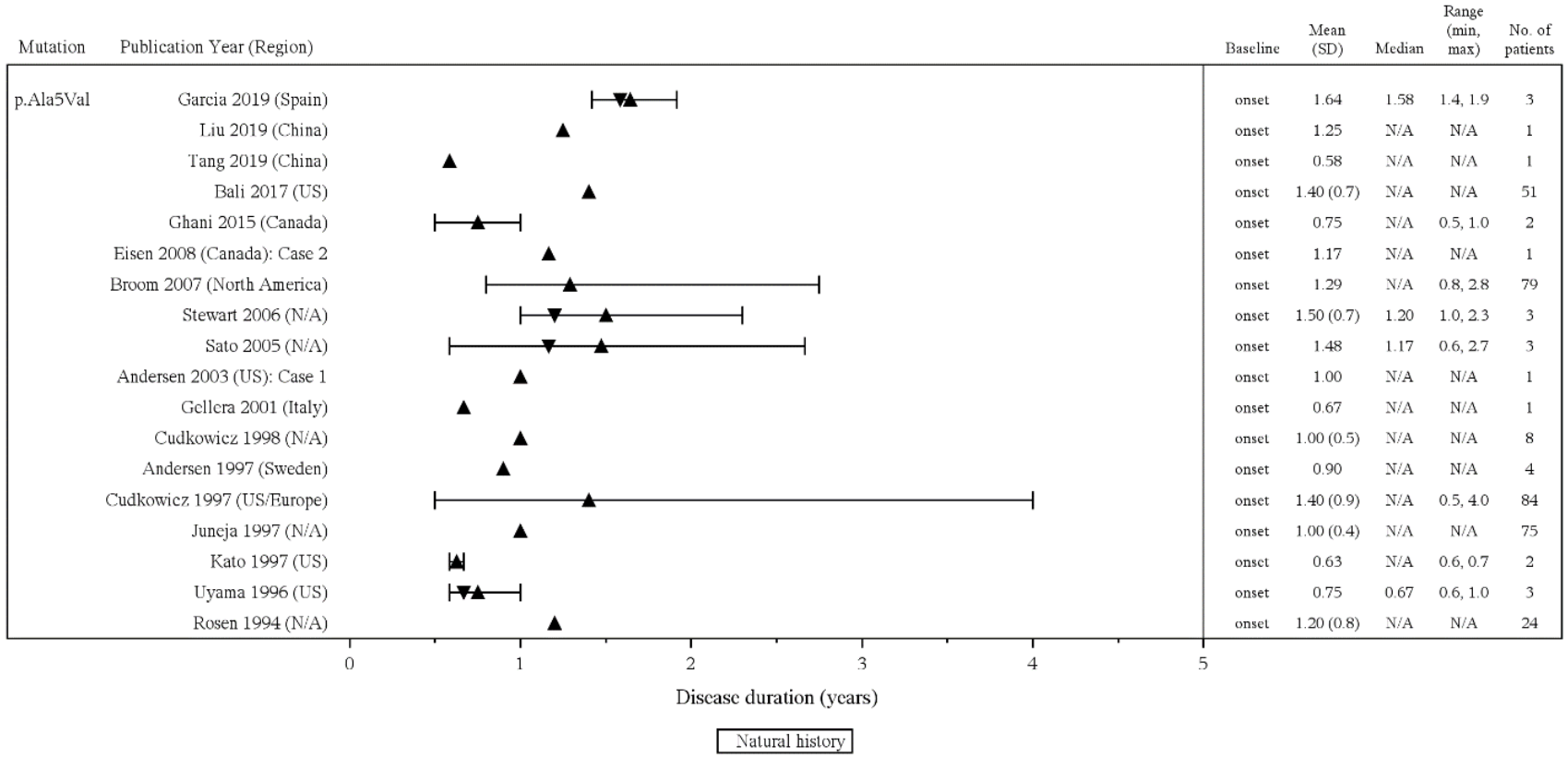
[58] Neurology. 1997 Jan;48(1):55-7. Prognosis in familial amyotrophic lateral sclerosis: progression and survival in patients with glu100gly and ala4val mutations in Cu,Zn superoxide dismutase. T Juneja 1, M A Pericak-Vance, N G Laing, S Dave, T Siddique. PMID: 9008494

summary of subject survival in Studies 233AS101 and 233AS102 (the pivotal and extension studies, respectively), for ongoing patients with the A5V variant, with reference to the available literature regarding the natural history and expected survival of patients with this mutation.

The longest reported survival after disease onset of a patient with A5V SOD1-ALS is 4 years[59]. Figure 67 shows the A5V survival durations reported in the scientific literature.

[59] Ann Neurol 1997;41:2 10-221. Epidemiology of Mutations in Superoxide. Dismutase in Amyotrophic Lateral Sclerosis. M. E. Cudkowicz, MD,*T D. McKenna-Yasek, RN,* P. E. Sapp, BS,*$ W. Chin, BS,*$ B. Geller, BS,*$ D. L. Hayden, MS,$ D. A. Schoenfeld, PhD,S B. A. Hosler, PhD,* H. R. Horvitz, PhD,$ and R. H. Brown, MD, PhD.

Figure 67. Survival Duration Comparison With Natural History From Literature for p.Ala5Val Variant



Source: Applicant's response to the Information Request of 19 September 2022
Note 1: Upward triangle symbol represents mean disease duration and downward triangle represents median disease duration.
Note 2: All values are based on descriptive statistics reported in each publication.
Abbreviations: N/A, not applicable; US, United States of America

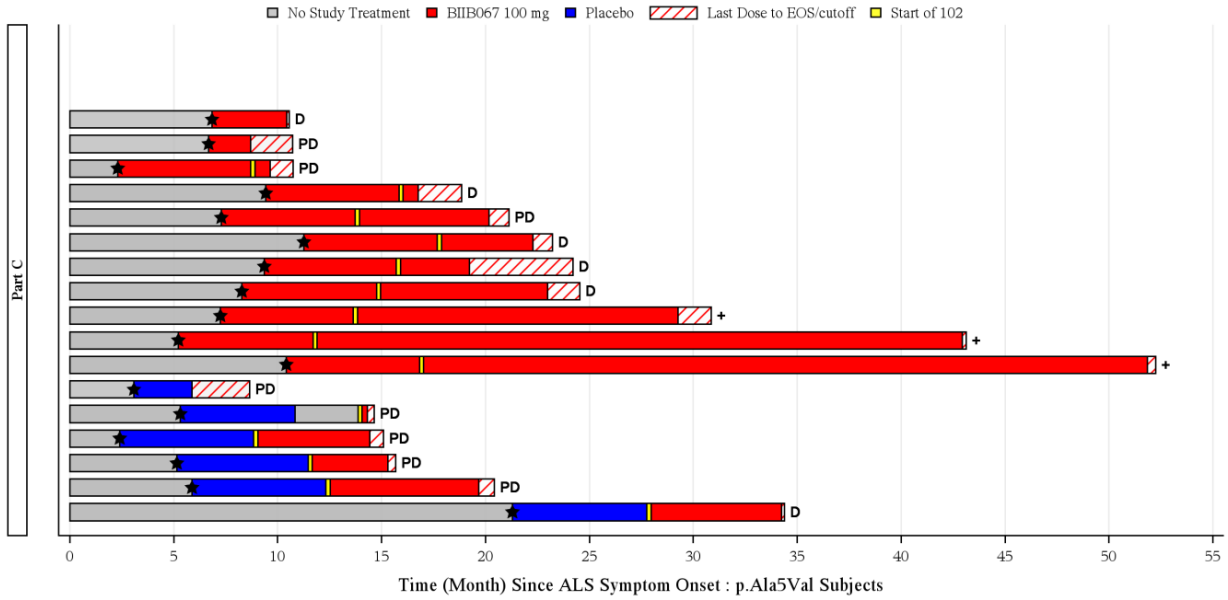
Table 115 shows the survival durations of the three A5V SOD1-ALS subjects in Studies 101C and 102.

Table 115. Disease Durations (as of Last Study Visit) of the Three A5V Carriers Who are Ongoing in the Open-Label Extension Study 102

Participant IDs (Study 101 Part C/Study 102)	Date of ALS onset	Study participation status	Last dosing/contact date	Disease duration as of last follow-up
	(b) (6)	Ongoing	(b) (6)	~2.4 years
		Ongoing		~4.3 years
		Ongoing		~3.6 years

Source: Applicant's response to the Information Request of 19 September 2022
Abbreviations: ALS, amyotrophic lateral sclerosis

Figure 68. Disease Duration Since Symptom Onset for p.Ala5Val Subjects From Studies 101C and 102



Source: Applicant's Response to FDA Information Request of 31 October 2022
Note 1: Star indicates the time of study treatment initiation; plus sign indicates that the subject is ongoing.
Note 2: Yellow solid line indicates initiation of study treatment in Study 233AS102.
Abbreviations: D, death; EOS, end of study (not enrolled in 233AS102); LTF, lost to follow up; O, other; PD, progressive disease; WBS, withdrawal by subject

As seen in Table 115 and Figure 68, one subject with A5V SOD1-ALS who was receiving tofersen has exceeded the maximum survival duration for A5V SOD1-ALS patients reported in the scientific literature. A second A5V subject was nearing the 4-year threshold with a survival duration of 3.6 years at the time of the report.

Reviewer's Comment: Although notable, these data are of limited interpretability due to the small number of subjects. However, these data suggest that tofersen has a survival benefit in this aggressive SOD1-ALS variant compared to the natural history of the disease.

17. Clinical Safety

17.1. ECGs

The Interdisciplinary Review Team for Cardiac Safety Studies was consulted for this NDA and made the following conclusions.

The incidence of abnormalities in ECG measurements in Study 101C was slightly higher in the tofersen group compared to the placebo group, with eight subjects (11.3%) having a maximum increase from baseline in QTcF >30 to 60 ms in the tofersen group compared to two subjects (5.6%) in the placebo group. No subject in the tofersen or placebo group had an increase from baseline in QTcF >60 ms, and no subject had a maximum postbaseline QTcF >480 ms.

One subject receiving tofersen had a fatal cardiac failure congestive AE. There were no significant ventricular arrhythmias in this study.

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

Seven hundred nineteen digital ECGs and one hundred ninety-seven paper ECGs were submitted. Overall, ECG acquisition and interpretation in this study appear to be acceptable.

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

Ten subjects in the tofersen 100 mg group experienced a heart rate of >100 beats/min. The percentage of subjects with a heart rate of >100 beats/min was balanced between the placebo and tofersen groups.

None of the subjects in the tofersen 100 mg group experienced a PR >220 ms and a 25% increase over baseline.

None of the subjects experienced a QRS interval of >120 ms and a 25% increase over baseline.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

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

Inspection 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: August 9, 2022 to August 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 and # (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. The records reviewed included, but were not limited to, source documents, monitoring documents, Institutional Review Board/Applicant communications, financial disclosure, test article accountability, inclusion/exclusion criteria, AE 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 Applicant data line listings. No discrepancies were identified. Plasma NfL concentrations, the biological efficacy data, were not available at the site. The Applicant stated that these data were not sent to clinical sites in order to maintain the blinding of the study.

Therefore, NfL concentration data were verified during the Applicant inspection (see the inspection summary below). There was no evidence of under-reporting of AEs.

Inspection 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: August 9 2022 to August 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. The records reviewed included, but were not limited to, source documents, monitoring documents, Institutional Review Board/Applicant communications, financial disclosure, test article accountability, inclusion/exclusion criteria, AE reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (ALSFRS-R). The primary efficacy data, ALSFRS-R scores recorded on paper, were verified against Applicant data line listings. No discrepancies were identified. Plasma NfL data, the biological efficacy data, were not available at the site. The Applicant stated that these data were not sent to clinical sites to maintain the blinding of the study. Therefore, NfL concentration data were verified during the Applicant inspection (see the inspection summary below). There was no evidence of under-reporting of AEs.

Inspection 3: Angela Genge, M.D.
Site #130
Montreal Neurological Institute & Hospital
3801 University Street, Room 207
Montréal, PQ, Canada
Inspection Dates: September 19 2022 to September 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. The records reviewed included, but were not limited to, source documents, monitoring documents, Research Ethics Board/Applicant communications, financial disclosure, test article accountability, inclusion/exclusion criteria, AE reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (ALSFRS-R). The primary efficacy data, ALSFRS-R scores recorded on paper, were verified against Applicant data line listings. No discrepancies were identified. Plasma NfL data, the biological efficacy data, were not available at the site. The Applicant stated that these data were not sent to clinical

sites to maintain the blinding of the study. Therefore, NfL concentration data were verified during the Applicant inspection (see the inspection summary below).

On four occasions, in 4 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 the impact of the coronavirus disease 2019 pandemic. These protocol deviations were included in the Applicant data line listings and affected 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 Applicant is seeking accelerated approval based on a biological endpoint, reduction in plasma NfL, not on the ALSFRS-R ratings.

The inspection identified six unreported AEs in 3 of 15 randomized subjects. The majority of these AEs was reported during the telephone contact the day after lumbar puncture for intrathecal administration of study drug.

- Subject # (b) (6), randomized to tofersen, reported feeling tired (Day 15).
- Subject # (b) (6), randomized to placebo, reported feeling weak (Day 29), lightheaded (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 AEs were reported to the site during the telephone contact visit 24 h after lumbar puncture/study drug administration. No further information is available on these AEs. These unreported AEs occurred in subjects randomized to placebo and tofersen; their omission is unlikely to affect the overall safety assessment.

Inspection 4: Biogen, Inc.
225 Binney St
Cambridge, MA 02142-1031
Inspection Dates: November 1 2022 to November 4 2022

The inspection covered Applicant 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, standard operating procedures, organizational charts, monitoring plans and reports, site selection/qualification, monitor qualification, vendor list, contracts, investigator agreements and 1572s, investigator compliance/corrective actions, Institutional Review Board approvals, Independent Data Monitoring Committee charter and meeting minutes, Endpoint Adjudication Committee charter, electronic case report forms, data management, financial disclosure forms, Investigational

Product 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 noncompliance 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 CSF NfL samples. Laboratory 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 are 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 Applicant. The Applicant did not send the certified copies to the clinical sites for data verification to maintain the blinding of the study. The certified copies, obtained from (b) (4), were available at the Applicant site in addition to being submitted with the NDA. NfL plasma and CSF data were verified during the Applicant inspection for all randomized subjects at the three clinical sites selected for inspections. No discrepancies were identified.

A note-to-file written by the Applicant and dated August 25, 2022 stated that there were six 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). Testing of the vials yielded values of 19 pg/mL and <4.9 pg/mL. According to the Applicant, the two results were not within the 22% coefficient of variation of the assay and should have undergone reanalysis to confirm the results or to be reported as not determinable. The sample with a value of 19 pg/mL was reported. The Applicant noted that this issue was investigated by (b) (4); although the root cause was not identified it was thought to be site error.

Reviewer's Comment: Only one of the duplicate plasma/CSF NfL samples was 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 Applicant, these samples should have been reanalyzed to confirm the results. This isolated event is unlikely to affect the overall results of the study.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted in an amendment on October 7, 2022 (Table 116). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Carton
- Vial container label

24. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) will be imposed:

Clinical

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

Draft Protocol Submission: February 2021 (submitted)
Final Protocol Submission: July 2021 (submitted)
Study Completion: December 2027
Final Report Submission: June 2028

Nonclinical

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

Draft Protocol Submission: July 2024
Final Protocol Submission: September 2024
Study Completion: November 2027
Final Report Submission: February 2028

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

Draft Protocol Submission: September 2023
Final Protocol Submission: December 2023
Study Completion: December 2026
Final Report Submission: June 2027

The following postmarketing commitments will also be imposed:

Clinical Pharmacology

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

Draft Protocol Submission: February 2021 (submitted)
Final Protocol Submission: July 2021 (submitted)
Study Completion: December 2027
Final Report Submission: June 2028

Product Quality

4436-5 Conduct an extractable study for the rubber stopper. The aqueous extractions should use pH adjusted waters that bracket the pH of tofersen drug product as extracting solvents. The extraction should be conducted by heating at reflux conditions to ensure they represent worst-case scenarios for extractable impurities. Full extractable reports, including analytical method qualification, should be submitted to the Agency.
Final Report Submission: June 2023

4436-6 Conduct a leachable study using at least three batches of tofersen drug product. The leachables should be tested at multiple time points on stability storage - from release through the proposed shelf-life. Full study reports, including analytical method validation, should be submitted to the Agency.
Interim Report Submission: December 2024
Final Report Submission: March 2024

25. Financial Disclosure

Table 117. Covered Clinical Studies: 233AS101

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 385			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4			
	If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0			
Is an attachment provided with details of the disclosable financial interests/arrangements:			Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:			Yes ☒	No ☐ (Request information from Applicant)
	Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0			
Is an attachment provided with the reason:			Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

See footnotes throughout the document.

27. Review Team

Table 118. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Michelle Mathers/IA; Heather Bullock/IA (CPMS)
Nonclinical reviewer	David (Dave) Carbone/IA
Nonclinical team leader	Lois Freed/IA
OCP reviewer(s)	Xiaohan Cai/IA; Sreedharan Sabarinth/IA; Sharma Vishnu/IA; Hobart Rogers/IA; Sarah Dorff/IA
OCP team leader(s)	Bilal AbuAsal/IA; Atul Bhattaram/IA
Clinical reviewers	Rainer Paine/IA; Kevin Krudys/IA
Clinical team leader	Emily Freilich/IA
Biometrics reviewers	Jinnan Liu/IA; Tristan Massie/IA
Biometrics team leader	John Lawrence (Acting)/IA
Cross-disciplinary team leader	Emily Freilich/IA
Division director (pharm/tox)	Lois Freed/IA
Division director (OCP)	Mehul Mehta/IA; Hao Zhu/IA
Division director (OB)	Jim Hung/IA
Division director (clinical)	Emily Freilich/IA (Acting)
Office director (or designated signatory authority)	Teresa Buracchio

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; IA, Interdisciplinary Assessment

Table 119. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Martha Heimann (ATL)/IA
Drug Substance	Katherine Duncan; Gaetan Ladouceur (TL)
Drug Product	Mariappan Chelliah; Martha Heimann (TL)
OPMA-Manufacturing	Suzanne Hudak; Lane Christensen (TL)
Environmental Assessment	Xiaoquin Wu; James (Jim) Laurenson (TL)
Microbiology	Jianli Xue; Nandini Bhattacharya (TL)
OPDP	Sam Fasanmi; Aline Moukhtara (TL)
OSI	Cara Alfaro; Philip Kronstein (TL)
OSE/DEPI	Danielle Abraham; Kira Leishear
OSE/DMEPA	John (Chad) Morris; Stephanie DeGraw (TL)
OSE/DRM	Jacqueline Sheppard (TL)/Sarah (Katie) Holman
OSE/DPV	Dave Croteau; Suprat Saely; Allen Brinker (TL)
Other	OBP Consult: Seth Thacker; DDS: Sally Jo Yasuda; Medical Editor: James Ebersole; Clinical Data Scientist: Elizabeth Booth; Tracy Peters: Associate Director of Labeling/IA

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRM, Division of Risk Management; DPV, Division of Pharmacovigilance; IA, Interdisciplinary Assessment

26.1. Reviewer Signatures

Table 27-120 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Martha Heimann ONDP DNDPII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Martha Heimann**

Digitally signed by Martha Heimann

Date: 4/24/2023 5:16 PM EDT
GUID: 202342421169

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Martha Heimann ONDP DNDPII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Martha Heimann**

Digitally signed by Martha Heimann

Date: 4/24/2023 5:16 PM EDT
GUID: 2023424211650

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Michelle Mathers ORO DRON	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Michelle Mathers

Digitally signed by Michelle Mathers

Date: 4/24/2023 5:17 PM EDT
GUID: 2023424211716

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Hsien Ming Hung OB DBI	Sections: 6.2.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Hsien Ming Hung

Digitally signed by Hsien Ming Hung

Date: 4/24/2023 5:18 PM EDT
GUID: 202342421182

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Tracy Peters ON DNI	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Tracy Peters**

Digitally signed by Tracy Peters

Date: 4/24/2023 5:33 PM EDT
GUID: 2023424213327

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Tracy Peters ON DNI	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Tracy Peters**

Digitally signed by Tracy Peters

Date: 4/24/2023 5:34 PM EDT
GUID: 2023424213436

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hobart Rogers OCP DTPM	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Hobart Rogers

Digitally signed by Hobart Rogers

Date: 4/24/2023 5:39 PM EDT
GUID: 2023424213931

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Heather Bullock ORO DRON	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Heather Bullock

Digitally signed by Heather Bullock

Date: 4/24/2023 5:40 PM EDT
GUID: 2023424214035

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Hao Zhu OCP DPM	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Hao Zhu

Digitally signed by Hao Zhu

Date: 4/24/2023 5:41 PM EDT
GUID: 2023424214133

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Rainer Paine ON DNI	Sections: 2, 3, 4, 6, 7, 10, 11, 17, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Rainer Paine

Digitally signed by Rainer Paine

Date: 4/24/2023 6:01 PM EDT
GUID: 202342422133

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Mehul Mehta OCP DNP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Mehul Mehta

Digitally signed by Mehul Mehta

Date: 4/24/2023 6:33 PM EDT
GUID: 2023424223351

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Vishnu Sharma OCP DPM	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Vishnu Sharma

Digitally signed by Vishnu Sharma

Date: 4/24/2023 6:35 PM EDT
GUID: 2023424223545

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Jinnan Liu OB DBI	Sections: 6.2.2	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Jinnan Liu

Digitally signed by Jinnan Liu

Date: 4/24/2023 6:46 PM EDT
GUID: 202342422465

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Bilal Abuasal OCP DNP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Bilal Abuasal

Digitally signed by Bilal Abuasal

Date: 4/24/2023 7:54 PM EDT
GUID: 2023424235413

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Emily Freilich ON DNI	Sections: 1, 2, 3, 4, 6, 7, 11, 16, 17	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Emily Freilich

Digitally signed by Emily Freilich

Date: 4/24/2023 8:31 PM EDT
GUID: 202342503129

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sarah Dorff OCP DTPM	Sections: 14.8.2	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Sarah Dorff

Digitally signed by Sarah Dorff

Date: 4/24/2023 8:57 PM EDT
GUID: 20234250575

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	David Carbone ON DPTN	Sections: 13.1, 13.2, 5.1, 7.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: David Carbone

Digitally signed by David Carbone

Date: 4/25/2023 6:37 AM EDT
GUID: 202342510376

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	John Lawrence OB DBI	Sections: 6.2.2	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: John Lawrence

Digitally signed by John Lawrence

Date: 4/25/2023 8:43 AM EDT
GUID: 2023425124329

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Venkatesh Bhattaram OCP DPM	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Venkatesh Bhattaram

Digitally signed by Venkatesh Bhattaram

Date: 4/25/2023 9:30 AM EDT
GUID: 2023425133042

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Sreedharan Sabarinath OCP DNP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sreedharan Sabarinath

Digitally signed by Sreedharan Sabarinath

Date: 4/25/2023 9:31 AM EDT
GUID: 202342513313

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Reviewer	Kevin Krudys ON	Sections: 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kevin Krudys

Digitally signed by Kevin Krudys

Date: 4/25/2023 9:31 AM EDT
GUID: 2023425133145

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Reviewer	Xiulian Du OCP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Xiulian Du

Digitally signed by Xiulian Du

Date: 4/25/2023 9:36 AM EDT
GUID: 2023425133640

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Xiaohan Cai OCP DNP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Xiaohan Cai

Digitally signed by Xiaohan Cai

Date: 4/25/2023 9:38 AM EDT
GUID: 2023425133828

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Tristan Massie OB DBI	Sections: 6.2.2	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Tristan Massie

Digitally signed by Tristan Massie

Date: 4/25/2023 9:44 AM EDT
GUID: 202342513443

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Lois Freed ON DPTN	Sections: 13.1, 13.2, 5.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Lois Freed

Digitally signed by Lois Freed

Date: 4/25/2023 10:06 AM EDT
GUID: 202342514636

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Yow-Ming Wang OCP OCP-IO	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Yow-Ming Wang

Digitally signed by Yow-Ming Wang

Date: 4/25/2023 10:21 AM EDT
GUID: 2023425142137

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Ramana Uppoor OCP DNP	Sections: 5.2, 8.1; 8.2, 14, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Ramana Uppoor**

Digitally signed by Ramana Uppoor

Date: 4/25/2023 10:30 AM EDT
GUID: 2023425143031

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

/s/

EMILY R FREILICH
04/25/2023 11:04:45 AM

TERESA J BURACCHIO
04/25/2023 11:10:59 AM