Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Qalsody

Active ingredient: Tofersen

Sponsor: Biogen Australia Pty Ltd

October 2026

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List of abbreviations

Abbreviation	Meaning
aCSF	Artificial cerebrospinal fluid
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASO	Anti-sense oligonucleotide
AST	Aspartate transaminase
AUC	Area under the curve
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CMI	Consumer medicines information
CNET	Cyanoethyl
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GoF	Gain of function
HHD	Handheld dynamometry
IIV	Interindividual variability
IT	Intrathecal

Abbreviation	Meaning
ITT	Intention to treat
IUI	Individual unknown impurity
JRT	Joint rank test
LMNs	Lower motor neurons
LP	Lumbar puncture
LS	Least square
MI	Multiple imputation
mITT	Modified intention to treat
MMSE	Mini-Mental State Examinations
mRNA	Messenger ribonucleic acid
N/A	Not applicable
Nf	Neurofilament
NfH	Neurofilament heavy chain
NfL	Neurofilament light chain
NfM	Neurofilament medium chain
PADER	Periodic Adverse Drug Experience Report
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PT	Preferred term
QoL	Quality of life
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
RTU	Ready to use
SAE	Serious adverse event
SBP	Systolic blood pressure
SE	Standard error
SOC	System organ classes
SOD1	Superoxide dismutase 1
SOD1-ALS	Superoxide dismutase 1 associated amyotrophic lateral sclerosis
SVC	Slow vital capacity
Tmax	Time to maximum drug concentration
ULN	Upper limit normal

Abbreviation	Meaning
UMNs	Upper motor neurons
V2	Plasma central volume of distribution
V3	Plasma peripheral volume of distribution
WBC	White blood count

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Qalsody 100 mg/15 mL solution for injection vial
Active ingredient:	Tofersen
Decision:	Approved for registration in the Australian Register of Therapeutic Goods (ARTG)
Date of decision:	10 April 2026
Date of entry into ARTG:	17 April 2026
ARTG number:	467305
▼*Black Triangle Scheme for the current submission:*	Yes
Sponsor's name and address:	Biogen Australia Pty Ltd PO Box 380, North Ryde, NSW, 1670 Australia
Dose form:	Solution for injection
Strength:	100 mg
Container:	Vial
Pack size:	1
Approved therapeutic use for the current submission:	Qalsody has provisional approval in Australia for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene. The decision to approve this indication has been made on the totality of evidence including impacts on clinical function, respiratory function, muscle strength, survival, target engagement and reductions in NfL (a marker of axonal injury and neurodegeneration) in SOD1-ALS patients treated with Qalsody. Continued approval of this indication depends on additional data.
Route of administration:	Intrathecal injection
Dosage:	100 mg/15 mL (6.7 mg/mL) of tofersen per treatment. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information (PI) document.
Pregnancy category:	Category B2 Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Biogen Australia Pty Ltd (the sponsor) to register Qalsody (tofersen) 100 mg/15 mL solution for injection intrathecal vial for the following proposed indication:[1]

> *Qalsody is indicated for the treatment of Amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.*

Disease or condition

Amyotrophic lateral sclerosis (ALS) is a rare, progressive, and ultimately fatal neurodegenerative disease that causes loss of upper motor neurons (UMNs) and lower motor neurons (LMNs) and their axons within the cortex, brainstem, spinal cord, and peripheral nervous system. The loss of motor neurons leads to progressive loss of muscle mass, strength, and function in bulbar, respiratory, and limb muscles, typically leading to paralysis and ultimately death from respiratory failure. ALS may present in any anatomical region and spread throughout the body with variable speeds and patterns in different patients. ALS is a disease with limited treatment options.

ALS is a rare disease. The global prevalence of ALS is estimated to be approximately 4.42 per 100,000. In approximately 2% of people living with ALS, the disease is attributed to mutation(s) in the gene encoding the enzyme SOD1. Although the mechanisms by which mutations in the SOD1 gene cause degeneration in ALS are not fully understood, mutations in this gene are thought to cause accumulation of toxic protein via a gain of function (GoF) mechanism. The human SOD1 gene encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), which catalyses the transmutation of superoxide (O2-) into oxygen (O2) and hydrogen peroxide (H2O2). In SOD1-ALS patients, mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein, presumed to lead to axonal injury and neurodegeneration.

There is a significant unmet medical need for effective therapies that preserve function and/or prolong life for people living with ALS. Available approved treatments for ALS in Australia include riluzole and edaravone. To date, there are no approved treatments designed to target the underlying pathophysiology of SOD1-ALS available in Australia. Tofersen (Qalsody) is the only therapy designed to target the underlying pathophysiology of SOD1-ALS.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

Current treatment options

Available approved treatments for ALS in Australia include riluzole and edaravone.

Riluzole received its first global approval for treatment of ALS in 1995 in the United States (US) based on 2 studies that demonstrated that the time to tracheostomy or death was approximately 3 months longer in participants receiving riluzole than in those receiving placebo. Although riluzole improved survival in both studies, no effect on motor function, lung function, or strength was observed.[2] The mode of action of riluzole is unknown, but its pharmacological activities include inhibition of glutamate release, inactivation of voltage-dependent sodium channels, and interference with intracellular events that follow neurotransmitter binding at excitatory amino acid receptors.

Edaravone received its first global approval for the treatment of ALS in 2015 in Japan, based on a single study in Japanese patients with ALS that demonstrated reduction in severity scores compared with placebo. No effect was observed on survival. The mechanism of action of edaravone in ALS is unknown.

Clinical rationale

The current submission related to the development of a new entity, tofersen, to target the underlying disease pathology of ALS associated with a mutation in the SOD1 gene (SOD1-ALS). Tofersen is an intrathecally (IT)-administered antisense oligonucleotide (ASO) designed to degrade SOD1 messenger ribonucleic acid (mRNA) to reduce synthesis of SOD1 protein.

Tofersen is a 20-base residue (20-mer) antisense oligonucleotide complementary to a portion of the 3′ untranslated region of the mRNA for human SOD1, binding by Watson-Crick base pairing (hybridization). This hybridization of tofersen to the cognate mRNA results in RNase-H-mediated degradation of the mRNA for SOD1, which reduces the amount of SOD1 protein synthesis and accumulation.

As tofersen reduces levels of the substrate for protein translation, an event that is upstream of all pathological mechanisms implicated in SOD1-ALS (all of which occur at the post-translation stage), it is anticipated to provide a therapeutic benefit for all SOD1-ALS patients, regardless of the mutation type.

Regulatory status

Australian regulatory status at the time of this assessment

Biogen Australia Pty Ltd was granted Orphan Drug Designation in Australia on 5 July 2024. The TGA approved orphan indication for tofersen is treatment of amyotrophic lateral sclerosis.

Tofersen (Qalsody) was granted a Provisional Determination on 30 September 2024. The provisional determination was made for tofersen (Qalsody) for the *treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene*.

[2] Miller RG, Mitchell JD, Lyon M, Moore DH. *Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).* The Cochrane Database of Systematic Reviews. 2002;(2):CD001447. doi:10.1002/14651858.CD001447.

International regulatory status at the time of this assessment

Tofersen was first approved on 25 April 2023 in the United States (US) under the accelerated approval pathway for the treatment of adults with ALS who have a mutation in the SOD1 gene. Subsequently it was approved in the European Union (EU) (May 2024), China (September 2024), Japan (December 2024), Canada (February 2025), and other countries.

The international regulatory status of tofersen (at the time this submission was assessed) is summarised in tables 1 and 2.

Table 1: International regulatory status at the time of assessment – date of approval

Region	Date of approval
United States	25 April 2023
European Union	29 May 2024
China	8 October 2024
Bahrain	03 December 2024
Japan	27 December 2024
Canada	28 February 2025
United Arab Emirates	30 October 2024
Qatar	24 November 2024
Oman	25 February 2025
Chile	6 March 2025
Kuwait	05 March 2025
United Kingdom	22 July 2025
South Korea	20 August 2025
Kingdom of Saudi Arabia	23 October 2025
Israel	14 December 2025
Switzerland	19 December 2025

Table 2: International regulatory status at the time of assessment – under review

Region	Date of submission
Switzerland	7 March 2024
Israel	3 June 2024
Kuwait	17 September 2024
Kingdom of Saudi Arabia	19 September 2024
Taiwan	20 September 2024
Columbia	30 September 2024
South Korea	30 September 2024

The sponsor noted that a Brazil marketing authorization application was rejected by ANVISA on 24 Mar 2025 based on their view on the limitations of the efficacy data as the VALOR study did not reach its primary endpoint. An appeal for this rejection is currently under review (at the time this submission was assessed). Since the time of the TGA approval, the appeal has been accepted, and the application is back under review by ANVISA.

Registration timeline

Table 3 captures the key assessment steps and dates for this submission.

The active ingredient with its proposed indication was given orphan drug designation. The submission was assessed under the provisional registration process.

Table 3: Assessment timeline for Submission PM-2024-04852-1-6

Description	Date
Designation (Orphan)	5 July 2024
Determination (Provisional)	30 September 2024
Submission dossier accepted and first round evaluation commenced	2 January 2025
Evaluation completed (End of round 2)	16 December 2025
Registration decision (Outcome)	10 April 2026
Registration in the ARTG completed	17 April 2026
Number of working days from submission dossier acceptance to registration decision*	239 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

The subsequent sections provide a summary of the TGA's assessment for this submission.

Quality evaluation summary

Tofersen is an antisense oligonucleotide designed to degrade superoxide dismutase (SOD1) m ribonucleic acid (mRNA) to reduce the synthesis of SOD1 protein. This is expected to preserve motor neuron integrity (or prevent motor neuron degradation) resulting in reduced levels of neurofilament in cerebrospinal fluid and blood (a biomarker of axonal injury and neurodegeneration), followed by a slowing of disease progression over time.

The product is administered as an intrathecal injection via lumbar puncture, with a recommended dosage of 100 mg/15 mL (6.7 mg/mL) of tofersen per treatment, with treatment initiated with three loading doses administered at 14-day intervals. Maintenance doses are then to be administered every 28 days thereafter.

Drug substance

The drug substance is synthesised via solid phase synthesis, is highly soluble in water and is manufactured as an aqueous solution. Particle size and polymorphism are not considered critical factors due to the manufacture of the drug substance as an aqueous solution.

The impurities are adequately controlled by both the drug substance manufacturer and finished product manufacturer. However, it should be noted that oligonucleotide drug substances are not covered by the International Council for Harmonisation (ICH) Impurities in New Drug Substances - Scientific Guideline (ICH Q3A). Acceptability of impurity limits were determined based on advice from the Toxicology section.

The proposed specifications adequately control the identity, purity, and chemical/physical properties of the drug substance relevant to the dosage form.

The analytical methods used to analyse the drug substance were adequately described and appropriately validated.

Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed. No significant risk was identified.

Stability data provided supports a retest period of 36 months when stored at 5 ± 3 °C.

Drug product

The drug product is an aqueous solution for injection, packaged in 20 mL Type I glass vials closed with a rubber stopper and sealed with a flip-off lid. The proposed product is sterile, non-pyrogenic, and does not contain any antimicrobial preservatives. Container safety was found to be acceptable.

The specifications and limits of the finished drug product are suitable to control the quality of the product and includes adequate control of degradation products, pH/osmolality and extractable volume.

The analytical methods used to analyse the product were adequately described and validated.

Stability data did not show any significant degradation trends or changes for any of the specification parameters tested. The data supports a shelf-life of 42 months when stored at 2-8 °C.

Biopharmaceutics

The drug product formulation used in the clinical studies is the same as the product formulation proposed for registration. Minor differences were declared between the manufacturing of the product used for clinical development and that for commercial purposes. However, these changes were determined to have no impact on the final drug product.

Other information

The PI is considered acceptable from a pharmaceutical quality perspective. The labelling is considered acceptable from a pharmaceutical quality perspective.

The provisional ARTG records are finalised.

The GMP clearances for all manufacturing sites are current until 10/02/2026.

Approval for registration is recommended from a pharmaceutical chemistry perspective. There are no outstanding issues.

Nonclinical evaluation summary

The overall quality of the nonclinical dossier was satisfactory. All pivotal safety-related studies were good laboratory practice (GLP) compliant. While tofersen is pharmacologically inactive in rat, mouse, or rabbit, this did not preclude its toxicological assessment in these species in repeat-dose toxicity and reproductive toxicity studies.

In vitro, tofersen decreased SOD1 mRNA levels in human neuroblastoma and epidermal carcinoma cell lines at clinically relevant concentrations, In the humanised mouse model of ALS, tofersen reduced human SOD1 mRNA and the SOD1 protein in CNS tissues. Prophylactic administration of tofersen, initiated prior to symptom onset, demonstrated beneficial effects in the ALS mouse model, including delayed symptom onset, extended survival, and reduced muscle and neuronal degeneration.

In total, 27 potential off-targets were identified by in silico analyses using a transcriptome database. Tofersen was shown to be highly specific for SOD1 mRNA and over 100-fold more potent for the on-target SOD1m RNA than for any of the assessed off-target mRNAs. Off-target effects are considered unlikely.

Safety pharmacology analysis indicated potential for neurobehavioral effects such as hind-limb impairment, tremors and/or reduced sensorimotor activity at 3 to 15x clinical exposure at 100 mg dose. No cardiovascular or respiratory concerns were noted.

Tofersen rapidly distributed into CNS tissues following IT administration. The half-life of tofersen in CNS tissues was very long, supporting the proposed treatment regimen. Tofersen was cleared from the CSF via CSF turnover resulting in systemic exposure where significant distribution was observed in the kidney and liver. Metabolism of tofersen is largely via exonuclease. No specific excretion studies were submitted, but it is likely to be primarily via the urinary route as metabolites.

Based on the *in vitro* data, pharmacokinetic drug interactions involving CYP450 enzymes or transporters are not predicted.

One dedicated acute toxicity study was conducted in rats, to which tofersen is pharmacologically inactive. Thus, acute toxicity was determined based on the monkey repeat-dose toxicity studies, which indicated a moderate order of acute toxicity.

Repeat-dose toxicity studies conducted in wild type mice (up to 6 months) and Cynomolgus monkeys (up to 9 months) did not indicate organ-specific adverse toxicities at clinical exposures. Findings such as increased vacuolisation in macrophages or neurons were likely related to the accumulation of oligonucleotides resulting class effects such as proinflammatory responses or process-related artefacts.

Tofersen was not mutagenic in a bacterial mutation assay and in *in vitro* (in Chinese hamster lung cells) and *in vivo* (in the mouse micronucleus test) clastogenic assays. Carcinogenicity studies were not conducted.

No effects on fertility were seen in tofersen treated mice, and no adverse fetal effects were seen in mouse and rabbit studies. However, the pharmacological activity of tofersen in these two species is limited. While tofersen was detected in milk, no tofersen was detected in liver and brain tissue of nursing pups. Published Sod1 knockout studies indicate potential for impaired fertility, thus potential for adverse effects on reproductive parameters exist during clinical use.

Outstanding concerns about the mutagenic potential of some of the oligonucleotide impurities were addressed by additional information provided by the sponsor and are considered resolved. The proposed specification limits for drug substance and drug product impurities are acceptable.

Conclusions and recommendation

The pharmacology studies collectively support the intrathecal injection of tofersen as a means by which to initiate RNase-H1-mediated degradation of the mRNA for SOD1 and thus, reduce *in vivo* SOD1 protein synthesis. To this end, the *in vivo* pharmacology studies reported delayed disease onset, improved survival, reduced neurodegeneration and some improvement in motor function when tofersen was administered prior to symptom onset in the mouse model. However, the efficacy of tofersen when administered after disease onset was not substantively investigated.

Based on the combined safety studies, the following have been identified as potential safety concerns:

- Transient neurobehavioral effects (for example, tremors and episodes of limited or uncontrolled lower limb movements) were observed in rats at 15-fold and monkeys at 3.5-fold the clinical dose, following clinical administration route.
- The proposed Pregnancy Category B1 was amended to Pregnancy Category B2 due to the limited predictive value of the embryofetal development toxicity studies arising from the attenuated pharmacological activity of tofersen in mice and rabbits.
- Nonclinical support for registration is acceptable following data presented by the sponsor to address concerns about the genotoxic potential of cyanoethyl (CNET) and individual unknown impurity (IUI) impurities.

Clinical evaluation summary

Summary of clinical studies

The submitted dossier documented a clinical development program of pharmacology, efficacy and safety studies.

The clinical development program consisted of 2 completed and 2 ongoing clinical studies:

- Study 233AS101 Parts A, B, and C (complete)
- Study 233AS102 (ongoing open-label extension) in participants with SOD1-ALS
- Study 233HV101 (complete) in healthy volunteers
- Study 233AS303 (ongoing) in presymptomatic SOD1 mutation carriers.

A completed population pharmacokinetics (PK) analysis was also submitted – Study CPP-21-004.

A clinical study report following anticipated completion of an ongoing open-label extension study for participants who previously completed a prior study to further investigate the long-term efficacy and safety of tofersen in the treatment of SOD1-ALS (Study 233AS102) was also submitted.

Pharmacology

Pharmacokinetics

Clinical pharmacology data submitted in the dossier were drawn from Study 233AS101 Parts A, B, and C (final data), and Study 233AS102 (2 interim analyses: data cuts taken on 16 July 2021 and 16 January 2022).

Study 233AS101 Part A

This was a randomised, double-blind, placebo-controlled, single ascending dose study, evaluated four doses (10mg, 20mg, 40mg and 60mg) of tofersen administered once intrathecally.

Study 233AS101 Part B

This was a randomised, double-blind, placebo- controlled, multiple ascending dose study, evaluated four doses (20mg, 40mg, 60mg and 100mg) of tofersen administered intrathecally multiple times with three loading doses administered at two-week intervals and two maintenance doses administered every four weeks.

Study 233AS101 Part C

This was a randomised double-blind, placebo-controlled, Phase 3 study in SOD1-ALS participants, which assessed the efficacy and safety of tofersen 100mg.

Cerebrospinal fluid

Tofersen exposures (troughs) increased with dose level. The increase was less than dose proportional from 20 to 100 mg. Steady-state concentrations in cerebrospinal fluid (CSF) were achieved immediately after the 4-week loading dose period (3 doses administered every 2 weeks). Minimal accumulation of tofersen in CSF was observed after the loading phase. The effective half-life of tofersen in CSF was approximately 1 month. There was moderate to high inter- and intra-individual variability in the tofersen CSF concentration profiles, with the majority of the coefficients of variation exceeding 50%.

Plasma

Following IT bolus administration, tofersen was rapidly transferred from CSF into the CNS tissue and systemic circulation, with a median time to maximum concentration (T_{max}) of 2 to 6 hours. After reaching the peak level, plasma concentrations of tofersen declined rapidly, likely due to extensive distribution to systemic tissues. Minimal to no accumulation of tofersen was evident in plasma after multiple doses, consistent with nonclinical PK of tofersen in nonhuman primates. The majority of the plasma concentrations were below the quantifiable limit at Day 8 and after; therefore, no meaningful estimate of the terminal plasma t½ could be provided. Significant tofersen plasma PK variability was observed; however, there seemed to be a roughly dose-proportional increase in C_{max} and AUC values over the evaluated dose range.

Integrated analysis of Parts A, B and C of Study 233AS101 provided further data. Steady state in both CSF and plasma was established immediately after the loading dose period.

The accumulation of drug in CSF with monthly dosing was consistent with an effective half-life of approximately 4 weeks. The plasma T_{max} is typically between 4 and 6 hours post dose.

Absorption

Tofersen is only for intrathecal administration.

Distribution

Tofersen is distributed extensively in CNS tissues with highest concentrations present close to the site of administration (spinal cord tissues). Tofersen is highly bound to human plasma proteins (≥ 95% bound) at clinically relevant or higher plasma concentrations (0.1 and 30 µg/mL) [Study 666853-IS03], which limits glomerular filtration and reduces urinary excretion of the drug. However, protein binding in plasma for this class of ASOs is relatively weak, and the

binding sites for this type of hydrophilic drug differs from the binding sites of low molecular weight hydrophobic drugs.

Metabolism

Tofersen is rapidly transferred from CSF into the systemic circulation, with a median T_{max} of 2 to 6 hours. After reaching the peak levels, plasma concentrations of tofersen decline rapidly. The dossier states that tofersen is metabolised slowly by exonuclease-mediated hydrolysis, which is not dependent on liver function; the primary route of elimination is likely via urinary excretion.

Excretion

The sponsor proposes that renal clearance is the likely route of elimination based on non-clinical data. However, no clinical urine samples were collected for measurement of tofersen.

No studies were conducted in patients with impaired hepatic function or impaired renal function.

Population PK data

There is moderate to high intra- and inter- individual variability in tofersen in CSF concentration profiles and in plasma concentration profiles demonstrated across all the studies submitted, that is also evident through the population PK analysis. This is likely compounded by the small sample size.

The population PK analysis added further information on the pharmacokinetic profile of tofersen, identifying three significant covariates for plasma PK: ADA status, baseline body surface area on CL, and sex on central volume of distribution. However, the analysis was based on a small sample size and the results should be considered in this context.

Pharmacodynamics

No specific pharmacodynamic (PD) studies were provided in the dossier. However, all of the submitted studies contained some PD data.

Study 233AS101 Part A, Part B, and Part C in the target population contained some specific PD endpoints, which were effects on SOD1 protein in CSF, deamidated SOD1 peptide in CSF, Neurofilament (Nf) levels in plasma and CSF.

The ongoing study, Study 233AS102, also provided some pharmacodynamic data within the submitted interim data analysis report with regard to effects on SOD1 protein in CSF, Nf levels in plasma and CSF.

Mechanism of action

Tofersen is complementary to a portion of the 3′ untranslated region of the mRNA for human SOD1, binding by Watson-Crick base pairing (hybridization). This hybridisation of tofersen to the cognate mRNA results in RNase-H-mediated degradation of the mRNA for SOD1, which reduces the amount of SOD1 protein synthesis and accumulation.

Given the underlying pathophysiology of SOD1-ALS and tofersen's mechanism of action, total CSF SOD1 protein was assessed as an indirect measure of target engagement in nonclinical and clinical studies. Notably, available assays including the immunoassay utilised in the tofersen development program (Covance Laboratories Inc., Limited Liability Company) are not specific to toxic SOD1 protein and likely reflect a measure of primarily native SOD1 protein.

Given this, levels of total CSF SOD1 are not differentiated between people living with SOD1-ALS and healthy controls and do not correlate with disease progression over time. Therefore, a reduction in total CSF SOD1 is suitable as an indirect measure of target engagement but is not

expected to predict the clinical effect of tofersen (e.g., lowering of NfL or slowing of decline on clinical outcome measures). To supplement the total CSF SOD1 data, the sponsor advanced a novel mass spectrometry assay to measure deamidated (e.g., modified) SOD1 peptide, a species that exists uniquely in SOD1 mutation carriers as a patient specific, indirect marker of target engagement.

Primary pharmacodynamic effects

SOD1 protein concentration in Cerebrospinal Fluid

A target therapeutic threshold for total SOD1 concentration in CSF has not been established. However, reductions of at least 20% were targeted as confirmation of target engagement.

Reductions in total CSF SOD1 protein were observed with administration of tofersen 100 mg for 12 weeks in Study 233AS101 Part B and later initiation of tofersen (placebo/delayed start group) in Study 233AS102. Reductions in total CSF SOD1 were apparent by approximately Week 8 and sustained for over 52 weeks of follow-up in the early-start group integrated analysis of Study 233AS101 Part C and Study 233AS102, and over 104 weeks of follow-up in integrated analysis of Study 233AS101 Parts A and B and Study 233AS102 participants.

In Study 233AS101 Part C participants, a reduction in total CSF SOD1 protein of 35% (geometric mean ratio to baseline) in the tofersen group and 2% in the placebo group were observed in the ITT population at Week 28 (difference in geometric mean ratios for tofersen to placebo: 34%; nominal $p<0.0001$).

Deamidated SOD1 protein concentration in Cerebrospinal Fluid

In the ITT population of Study 233AS101 Part C, changes in levels of deamidated SOD1 protein in CSF were observed, with a reduction of 37% (geometric mean ratio to baseline) in the tofersen group and increase of 2% in the placebo group, at Week 16 (the latest timepoint with adequate samples tested to perform an analysis).

Reductions in deamidated SOD1 peptide in CSF were observed with tofersen administration.

Neurofilament concentration in plasma

Neurofilaments are intermediate filaments that are uniquely expressed in neurons and are a major constituent of the cytoskeletal scaffold of the CNS and PNS neurons. Neurofilaments are heteropolymers composed of the light (NfL), middle (NfM), and heavy chains (NfH), plus α-internexin in the CNS and peripherin in the PNS. When axons are injured or degenerating, neurofilament leaks into the interstitial fluid. From there, it passes into the CSF and blood, where levels can be quantified. Elevated neurofilament levels have been described in a variety of neurological conditions characterised by neuroaxonal damage, including neurodegenerative diseases and diseases with other pathophysiological processes.[3] As such, neurofilaments are considered an unspecific marker of axonal injury and neurodegeneration rather than a pathology-specific marker.[3]

Despite this non-specificity, neurofilament levels in ALS are among the highest across neurodegenerative diseases, with levels 7- to 10-fold higher than in neurologically healthy controls.

Neurofilament light chain has become the preferred neurofilament marker in clinical studies primarily due to availabilty of robust and reliable NfL assays and data sets indicating that the

[3] Verde F, Steinacker P, Weishaupt JH, et al. Neurofilament proteins as biomarkers in neurological disorders and neurodegeneration. *Frontiers in Neuroscie*nce. 2021;15:689938.

stability and preanalytical considerations are similar between heavy and light.[4,5,6] At present, there is no compelling data set or publication to indicate either matrix (blood or CSF) or isoform (heavy or light) has greater utility in clinical trials (or to support clinical testing). The sponsor prioritized plasma NfL for practical reasons including the ease of blood collection versus CSF

In the ITT population of Study 233AS101 Part C, plasma NfL levels were reduced by 55% (geometric mean ratio to baseline) in tofersen-treated participants, compared to a 12% increase in placebo-treated participants from baseline to Week 28 (difference in geometric mean ratios for tofersen to placebo: 60%; post-hoc nominal $p < 0.0001$). Nominally statistically significant reductions in plasma NfL were also observed in the disease progression subgroups (mITT and non-mITT populations). Similar reductions were observed with later initiation of tofersen (placebo/delayed-start group) in Study 102.

Neurofilament levels declined through approximately Week 16 and were sustained over 52 weeks of follow-up in the early-start tofersen group and over 104 weeks of follow-up in Study 233AS101 Parts A and B participants. Similar reductions were observed across matrices (CSF and plasma) and isoforms.

Immunogenicity

The immunogenic response for tofersen in plasma was evaluated in 166 tofersen-treated participants in studies with postbaseline plasma samples for anti-drug antibodies (ADA) including participants in Study 233AS101 [Part A, Part B, and Part C] and Study 233AS102.

Overall, 5 (3.0%) participants were ADA positive prior to their first dose of tofersen. Ninety-seven (58.4%) tofersen-treated participants developed treatment emergent ADAs, of which 14 were transient and 83 were persistent. The impact of ADA was evaluated but not identified as a significant covariate for either the SOD1 protein or NfL PK/PD models. Given ADAs were not found to be a significant covariate for either the SOD1 protein or NfL PK/PD models, no true impact of ADAs on clinical effect is expected. An analysis performed in persistent ADA positive versus other participants suggested that those who were persistent positive experienced less decline on ALSFRS-R over time. However, this is likely confounded by the relatively small number of participants in each group and individual disease heterogeneity, which make it difficult to draw conclusions. Consistently, there were no discernible differences in total CSF SOD1 and plasma NfL reductions in tofersen-treated ADA-positive participants as compared with ADA-negative participants across study visits.

Time course of PD effects

Reductions in total CSF SOD1 were apparent by approximately Week 8-Week 12 and sustained for over 52 weeks of follow-up in the early-start group in the integrated analysis of Study 233AS101 Part C and Study 233AS 102 and over 104 weeks of follow-up in integrated analysis of Study 233AS101 Parts A, B and C and Study 233AS102 participants.

The data submitted were insufficient to fully document a timeline of the effects on deamidated SOD1 protein levels in CSF.

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[4] Koel-Simmelink, M.J.A., Vennegoor, A., Killestein, J., Blankenstein, M.A., Norgren, N., Korth, C., and Teunissen, C.E. *The impact of pre-analytical variables on the stability of neurofilament proteins in CSF, determined by a novel validated SinglePlex Luminex assay and ELISA.* Journal of Immunological Methods. 2014;402(1-2):43-49.

[5] Kuhle J, Plattner K, Bestwick JP, Lindberg RLP, Ramagopalan SV, Norgren N, Nissim A, Malaspina A, Leppert D, Giovannoni G, Kappos L. *A comparative study of CSF neurofilament light and heavy chain protein in multiple sclerosis.* Multiple Sclerosis Journal.

[6] Thebault, S., Booth, R.A., and Freedman, M.S. *Blood Neurofilament Light Chain: The Neurologist's Troponin?* Biomedicines. 2020;8(11):523. doi:10.3390/biomedicines8110523.

In Study 233AS101 Part C participants, reduction in plasma neurofilament light chain (NfL) levels were demonstrated at Week 8 through to Week 16 following tofersen administration. The reduction was sustained to Week 28 in Study 101 Part C and in the integrated analysis of Study 101 Part C and Study 102 at over 104 weeks.

At Round 3 of evaluation updated Population PK and PKPD model data were provided. The CPP-21-004 study was based on data from studies 233AS101 and 233AS102.

The following conclusions can be made based on the developed population PK and population PKPD model for tofersen:

- Following the DBL on November 18, 2024, both plasma and CSF PK models were re-run with the Final Integrated Data. The PK of tofersen in plasma and CSF were characterized by a two-compartment model with depot compartment and first order elimination, and a one compartment bolus model, respectively.
  - The updated PK models demonstrated largely consistent parameter with that of the previous analyses reported in the Report CPP-21-004-BIIB067 V2.1.
  - In the previous analysis, three significant covariates were identified for plasma PK: ADA, BSA baseline on CL, Sex on V2. In the updated model, notable changes from the previous model include the removal of the BSA baseline effect on CL and the additive error term from the plasma model. In this final model, the estimated ADA impact on CL slightly decreased relative to the previous estimate (32.3% vs 37.9%).
- Changes in CSF PK results due to re-testing did not have a significant impact on CSF PK model and exposure-response modeling analysis.
- The pharmacodynamics using the Final Integrated Data were characterized by two indirect response models with exposure in the CSF compartment inhibiting: (1) the production of SOD1 protein in CSF, and (2) the synthesis of NFL in plasma.
  - The updated CSF PK–SOD1 and CSF PK–NFL models demonstrated overall consistency with previously developed models. The only notable difference was the removal of IIV on EC50 in the PK–NFL model, due to imprecise estimation.
- Model-based simulations were used to explore the impact of various dosing schemes on tofersen PD effect.
  - The gains in terms of SOD1 and NFL reduction with increasing doses to 150 mg or 200 mg compared to the current highest dose (100 mg) were shown to be very marginal.

Efficacy

Efficacy summary from Round 1

The dossier contained one pivotal study and interim analysis from one ongoing open-label extension follow-on study. The studies were:

- Pivotal study: Study 233AS101 Part C
- Other efficacy study: Study 233AS102 – ongoing.

Study 233AS101 Part C

Study design, objectives, locations and dates

Study design

This was a randomised, double-blind, placebo-controlled study to examine the efficacy, safety, tolerability, PK, and PD of tofersen administered by intrathecal bolus injection to adult participants with ALS. The study was conducted in 3 parts; however, only Part C, a Phase 3 pivotal study, is detailed in this report. Participants were randomised to receive tofersen 100 mg or placebo in a 2:1 (active:placebo) ratio for 28 weeks (197 days) at 32 sites globally.

Participants who completed the study had the opportunity to be screened for Study 233AS102, an open-label long-term extension study.

Primary objective

- To evaluate the clinical efficacy of tofersen administered to adult participants with ALS and a confirmed SOD1 mutation.

Secondary objective

- To evaluate the safety, tolerability, pharmacodynamics (PD), and biomarker effects of tofersen administered to adult participants with ALS and a confirmed SOD1 mutation.

Exploratory objective

- To evaluate the pharmacokinetics (PK) of tofersen and other potential biomarkers in adult participants with ALS and a confirmed SOD1 mutation and to assess the effect of tofersen on changes in participant quality of life (QoL) and caregiver burden.

Efficacy variables and outcomes

Primary efficacy endpoint

- ALSFRS-R score at Week 28

Secondary efficacy endpoints

- Slow vital capacity (SVC) – direct measure of respiratory function
- Handheld dynamometry (HHD)
- Survival: Time to death or permanent ventilation and Time to death

Exploratory efficacy endpoints

- Motor unit number index (MUNIX)
- QoL measured by the following: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5), Fatigue Severity Scale (FSS), European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI), Zarit Burden Interview (ZBI), 36-Item Short Form Health Survey (SF-36), Patient Global Impression of Change (PGI-C), Clinician Global Impression of Change (CGI-C), Patient Global Impression of Status (PGI-S), and Clinician Global Impression of Status (CGI-S).

ALSFRS-R

ALSFRS-R is a 12-item scale that assesses function in 4 domains, including respiratory, bulbar, gross motor, and fine motor.

Analysis populations

Analysis populations were defined as follows:

- Intent-to-treat (ITT) population: all participants who were randomized and received at least 1 dose of study treatment.
- Modified intent-to-treat (mITT) ['enriched'] population: subset of the population who met prognostic enrichment criteria for rapid disease progression, who were randomized, and received at least 1 dose of study treatment.
- Non-mITT ("other") population: all other eligible participants who were randomized and received at least 1 dose of study treatment.

A total of 108 participants were enrolled and were dosed, and 97 participants completed the study. Treatment discontinuations and study withdrawals were similar in the tofersen group compared to the placebo group: 3 participants (8.3%) in the placebo group and 9 participants (12.5%) in the tofersen group discontinued treatment, and 3 participants (8.3%) in the placebo group and 8 participants (11.1%) in the tofersen group were withdrawn from the study. The discrepancy between treatment discontinuation and study withdrawal in the tofersen group was due to 1 participant who discontinued treatment due to an adverse event (AE) (pulmonary embolism) but continued and completed the study. Treatment discontinuations and study withdrawals were more common in the 'enriched' (mITT) subgroup. Of the 12 participants (11.1%) who discontinued study treatment prematurely, only 1 participant discontinued study treatment due to a COVID-19 pandemic-related reason of the site closing due to the COVID-19 pandemic. The most common reason for discontinuation of study treatment was disease progression (n = 5, 4.6%), all of which occurred in the 'enriched' subgroup, followed by AEs (n = 3, 2.8%). One participant (in the 'enriched' subgroup) died 114 days after being randomized to tofersen 100 mg. The cause of death was reported as congestive cardiac failure, and the Investigator assessed the event to be unrelated to tofersen.

Baseline data

Of the 108 subjects in the ITT population, there was a propensity for White patients (63.9%), and males (57.4%). Percentage of males and females were similar across treatment groups. There was an age difference between the treatment groups with an overall higher mean participant age in the placebo group (51.2 years) compared with the tofersen group (48.1 years).

Baseline and disease characteristics were balanced across treatment groups for use of riluzole and/or edaravone and characteristics related to the stage of disease, including time from onset, total ALSFRS-R score, and SVC. However, baseline plasma NfL levels were approximately 15% to 25% higher in the tofersen group compared to the placebo group, suggesting that these participants were progressing more quickly at baseline.

Results for the primary efficacy outcome

Change in ALSFRS-R Score from baseline to week 28

In the mITT population, a not statistically significant difference of 1.2 favouring tofersen was observed 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; JRT + MI p = 0.9689). The results from the ANCOVA + MI sensitivity analysis support the results from the JRT + MI (p = 0.5998).

The forest plot results for ALSFRS-R total score change from baseline versus placebo at Week 28 showed consistent trends favouring tofersen across sensitivity, additional, and supplementary analyses (figure 1). These results were also observed in the non-mITT and ITT populations

including the ANCOVA analysis in the non-mITT population when excluding assessments of ALSFRS-R by a noncertified rater. No conclusion between subgroups can be drawn from the analyses based on gender, disease duration since symptom onset, site of onset, geographic region, and riluzole or edaravone use, in particular due to imbalances in baseline clinical function and biomarkers. There was little slowing of decline in the subgroup of participants with a pre-randomization ALSFRS-R slope decline of ≥ 0.9 per month.

Figure 1: Forest Plot of ALSFRS-R Total Score Changes from Baseline to Day 197 – mITT Population

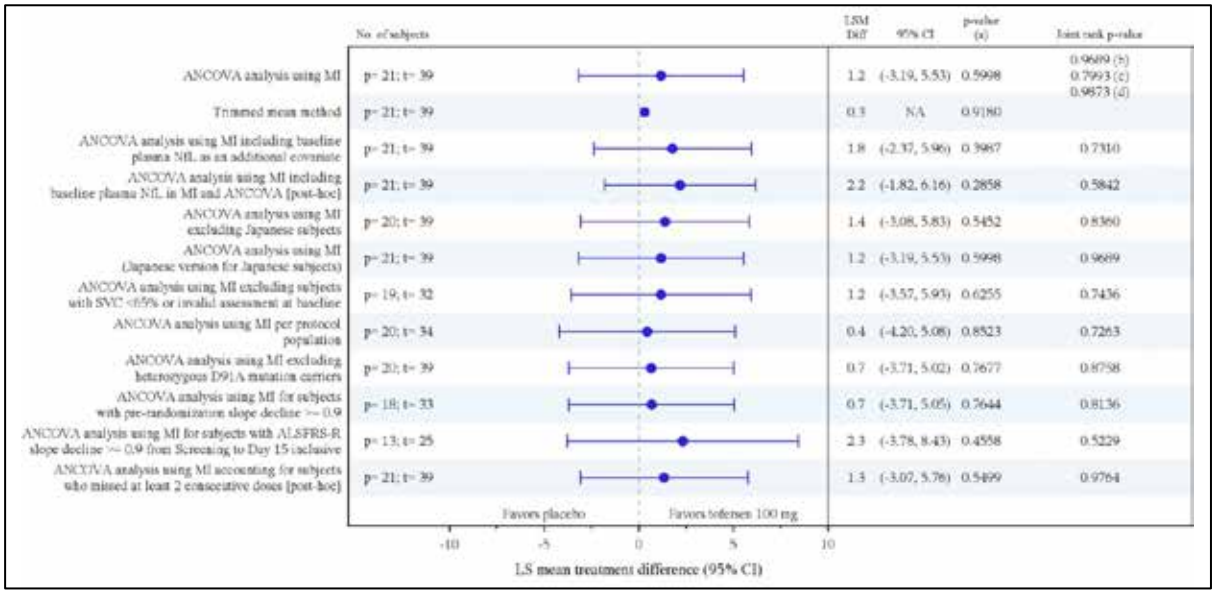
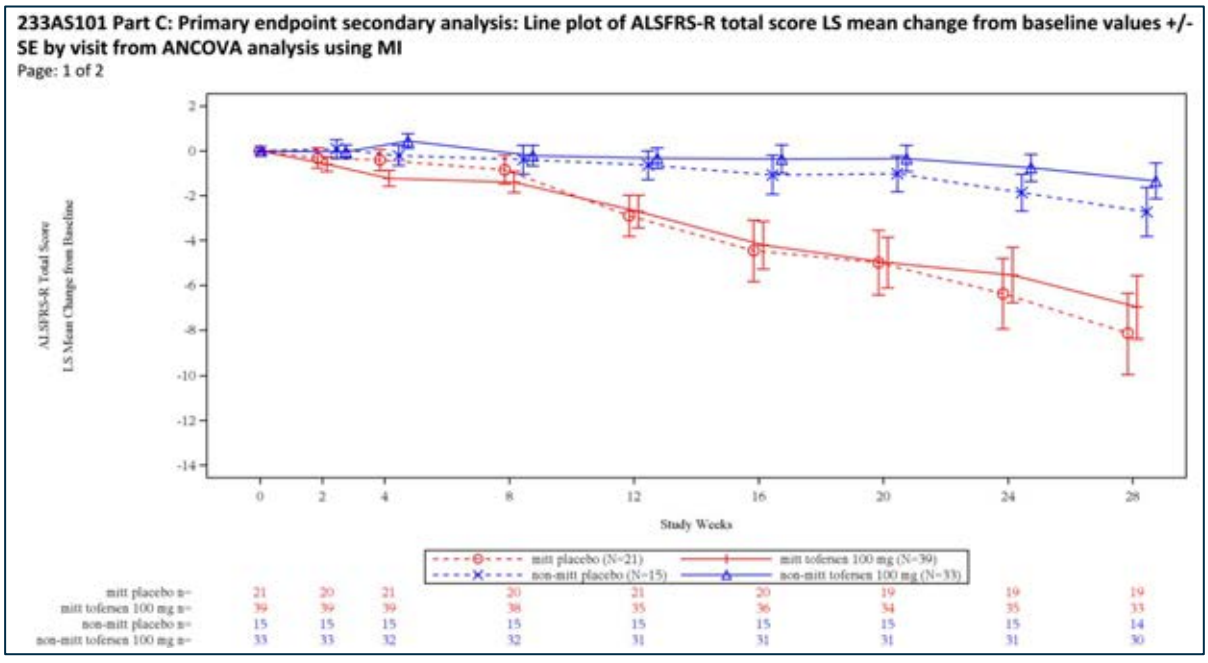


Figure 2: Line Plot of ALSFRS-R Total Score LS Mean Change from Baseline – mITT and non-mITT Populations



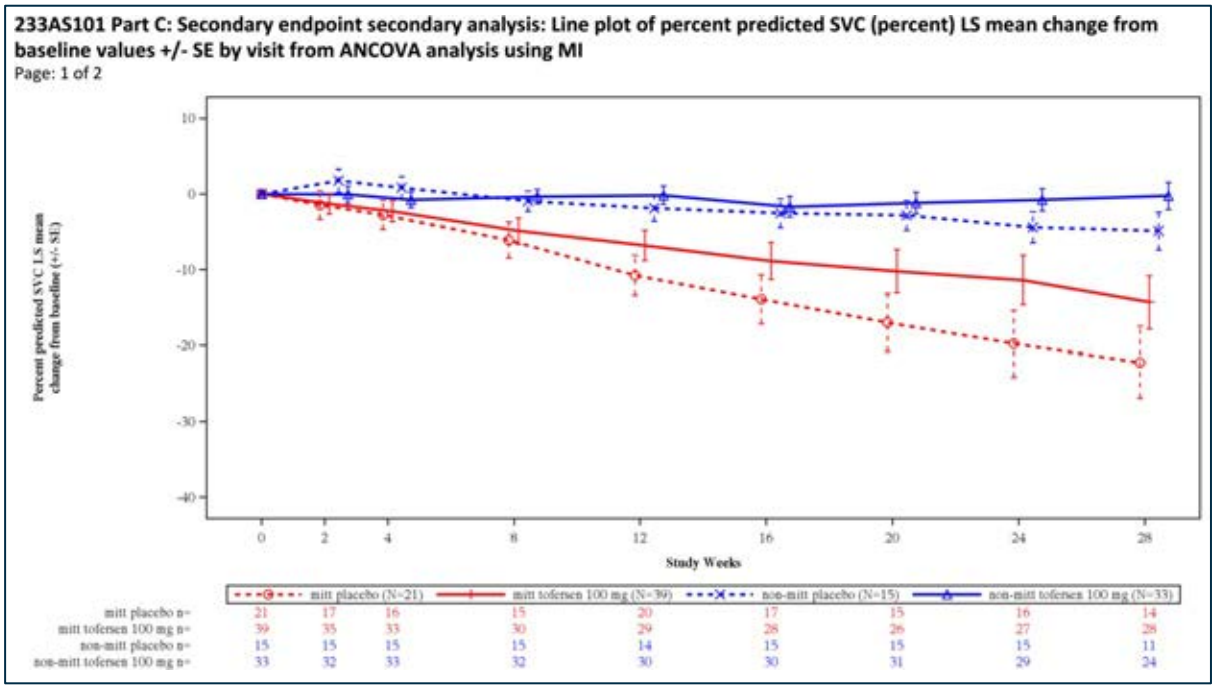
Results for other efficacy outcomes

As the primary efficacy analysis did not meet statistical significance, all subsequent statistical testing of secondary endpoints became nominal.

Change from baseline to day 197 in slow vital capacity (SVC)

Change from baseline to Week 28 in percent predicted SVC showed a lesser decline in the tofersen group compared to the placebo group (7.9% predicted treatment difference, nominal p = 0.3233 [JRT + MI] in the mITT population.

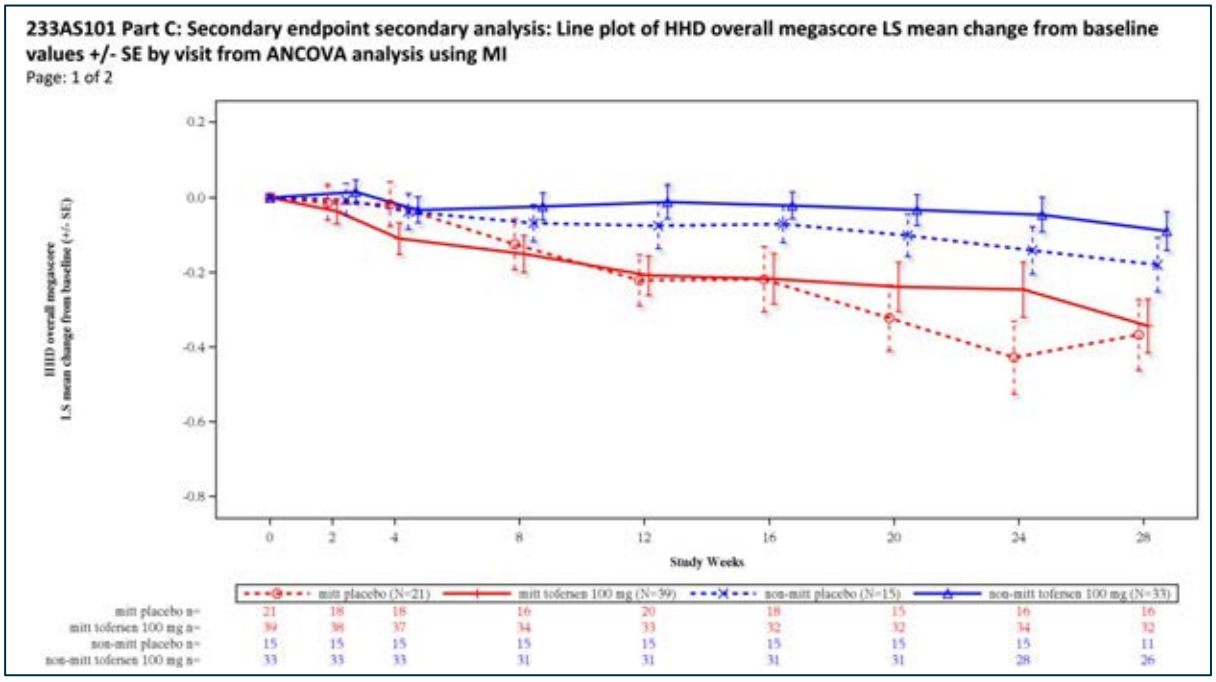
Figure 3: Line Plot of percent predicted SVC LS Mean Change from Baseline – mITT and non-mITT Populations



Change from Baseline to Day 197 in handheld dynamometry (HHD) megascore

A modest trend suggesting slowing of decline in muscle strength in the tofersen group compared to the placebo group (0.02-point treatment difference, nominal p = 0.8390) [ANCOVA + MI] was observed in the mITT population (figure 4).

Figure 4: Line Plot of HHD overall megascore LS Mean Change from Baseline – mITT and non-mITT Populations



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 1 death.

Motor unit number index (MUNIX)

MUNIX was performed at 5 participating sites. In the mITT population, 4 participants in the tofersen group and 3 participants in the placebo group, and in the non-mITT population, 3 participants in the tofersen group and 1 participant in the placebo group had MUNIX evaluated during the study. Participation was too limited to draw conclusions.

Quality of life (QoL) variables

Trends toward slowing of disease progression with tofersen were observed across exploratory measures of clinical function, respiratory function, muscle strength, QoL, and underlying disease activity (table 4). Comparisons between results in the tofersen and placebo group were not nominally significant, except for the change from baseline in the EQ-5D-5L utility scale (p = 0.0043). There were limitations in the collection of SF-36, ZBI, WPAI, and CGI/PGI endpoints, which impact interpretation.

Table 4: Overall summary of exploratory endpoints for QoL measures

233AS101 Part C: Overall summary of exploratory efficacy endpoints at Day 197 – mITT population
Page: 1 of 2

LS mean change from baseline (-/+ SE)	placebo (N=21)	tofersen (N=39)	tofersen – placebo estimated treatment difference (95% CI))	p-value
ALSAQ-5 total score	15.57 (11.414, 19.730)	9.98 (6.794, 13.173)	-5.59 (-15.550, 4.373)	0.2715
FSS total score	10.46 (7.866, 13.063)	5.56 (3.500, 7.617)	-4.91 (-11.231, 1.418)	0.1283
EQ-5D-5L utility scale	-0.35 (-0.411, -0.299)	-0.16 (-0.202, -0.114)	0.20 (0.062, 0.332)	0.0043
EQ-5D-5L VAS	-15.64 (-20.228, -11.050)	-10.75 (-14.227, -7.272)	4.89 (-6.225, 16.004)	0.3885
ZBI total score	-0.31 (-2.808, 2.187)	4.13 (2.155, 6.098)	4.44 (-1.689, 10.564)	0.1557
SF-36 physical component summary	-7.24 (-8.931, -5.558)	-5.48 (-6.797, -4.156)	1.77 (-2.345, 5.880)	0.3995
SF-36 mental component summary	-4.23 (-6.636, -1.828)	-0.45 (-2.358, 1.454)	3.78 (-2.171, 9.731)	0.2131
ALSFRS-R bulbar function domain score	-0.4 (-0.79, -0.01)	-1.0 (-1.35, -0.74)	-0.6 (-1.60, 0.30)	0.1826
ALSFRS-R fine motor skills domain score	-2.8 (-3.38, -2.22)	-1.8 (-2.29, -1.39)	1.0 (-0.44, 2.36)	0.1785

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: Missing data is imputed using multiple imputation.
NOTE 3: A positive change in the following endpoints indicates an improvement: EQ-5D-5L utility scale/VAS, SF-36 component summaries, ALSFRS-R domain scores. A negative change in the following endpoints indicates an improvement: ALSAQ-5, FSS total/average scores, ZBI total score.
NOTE 4: LS mean and the corresponding 95% CI estimates are obtained from the ANCOVA model which includes treatment as a fixed effect and adjusts for the following covariates: baseline values for the endpoint, disease duration since symptom onset, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; FSS = Fatigue Severity Scale; EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ZBI = Zarit Burden Interview; SF-36 = 36 Item Short Form Health Survey; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/233as101-partc/csr/t-cf-exp-sum.sas:t-cf-exp-sum-mitt.rtf **Run Date:** 22SEP2021

Other efficacy studies/data

Study 233AS102

This is an ongoing, multicentre, open-label, long-term extension study to assess long-term safety, tolerability, PK, PD, and efficacy of tofersen administered by intrathecal (IT) injection to participants with SOD1-ALS who completed Part A, B, or C of Study 233AS101. This was an uncontrolled study. Two interim analyses have been submitted in the dossier.

A total of 139 participants were enrolled in Study 233AS102 including 44 participants from Study 233AS101 Parts A + B, 63 participants who received tofersen in Study 233AS101 Part C, and 32 participants who received placebo in Study 233AS101 Part C.

The planned duration of treatment is up to 360 weeks with a planned follow-up period of 4 weeks.

Efficacy analysis/endpoints

- Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R).
- Slow vital capacity (SVC).
- Handheld dynamometry (HHD).
- Participant diary/eDiary to record ventilation use. Time to death or permanent ventilation was not summarized or analysed as part of this interim CSR; it was integrated with data from Study 233AS101 and reported separately.
- Time to death.
- Quality of life as measured by the following: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5), Fatigue Severity Scale (FSS), European QOL Five Dimension Five Level, Questionnaire (EQ 5D-5L), Work Productivity and Activity Impairment (WPAI), Zarit

Burden Interview (ZBI), 36-Item Short Form Health Survey (SF-36), Patient Global Impression of Change (PGI-C), Clinician Global Impression of Change (CGI-C), Patient Global Impression of Status (PGIS), and Clinician Global Impression of Status (CGI-S). These endpoints were not summarised or analysed as part of the interim CSR; they were integrated with data from Study 233AS101 and reported separately.

- Total SOD1 protein in cerebrospinal fluid (CSF) was also evaluated and contributed to pharmacodynamic data evaluation. Tofersen concentrations in plasma and CSF were determined using validated assays for pharmacokinetic data evaluation. NfL levels were also measured in plasma and CSF. Clinical safety and laboratory safety assessments were also performed.

In the initial Australia provisional application, two standalone interim analyses for Study 233AS102, Interim 1 V1 dated 22 April 2022 and Interim 2 V1 dated 9 May 2022, and an additional data cut for both efficacy and safety dated 28 February 2023 were provided. The additional data cut was requested by EMA for the EU application. The objective was an integrated analysis of Study 233AS101 and Study 233AS102. The sponsor advises that analyses of efficacy, QoL, and biomarker endpoints previously conducted for interim data highlighted the limitations of conducting standalone analyses of these endpoints for Study 233AS102, including the following.

- Standalone analyses of Study 233AS102 are based on data selected using post randomization factors and therefore break the original randomisation.
- The window to observe an effect on biomarkers (CSF SOD1 protein levels and plasma NfL levels) will not be available in Study 233AS102 for participants who received tofersen treatment in Study 233AS101 Part C given the impact of tofersen on these biomarkers during Study 233AS101 Part C has already occurred.
- Comparison of the treatment groups from Study 233AS102 fails to reflect the overall treatment effect due to early tofersen initiation that is evident in Study 233AS101.
- Imbalances at Baseline of Study 233AS102, as expected due to the effect of tofersen in Study 233AS101, thus confounding the interpretation of Study 233AS102 analyses.
- Incorporation of baseline NfL as a covariate is the most objective mechanism to control disease heterogeneity at Baseline. However, baseline neurofilament in Study 233AS102 cannot be incorporated as a covariate due to the confounding effect of tofersen administration during Study 233AS101.

As such, the sponsor analysed the longitudinal efficacy, biomarker, and QoL data from Study 233AS102 as part of an integrated analysis of Study 233AS101 and Study 233AS102.

The sponsor advises that analysis of treatment effect in the full ITT population from baseline in the randomised portion of the study is the most valid approach to analysis.

Results

Biomarker data from participants who received tofersen in Study 233AS101 Part C and continued tofersen in Study 233AS102 demonstrated that longer-term treatment with tofersen 100 mg results in a sustained biological effect, as measured by maintenance of previously lowered total CSF SOD1 protein, plasma and CSF NfL, and plasma and CSF NfH over 24 to 52 weeks of treatment in Study 233AS102. In participants who received placebo in Study 233AS101 Part C and initiated tofersen 100 mg in Study 233AS102, initiation of treatment with tofersen 100 mg produced a robust biological effect, as measured by reduction of total CSF SOD1 protein, plasma and CSF NfL, and plasma and CSF NfH, even when started 6 months later in disease.

ALSFRS-R scores

Participants who previously received tofersen in Study 233AS101 Part C had higher baseline ALSFRS-R total scores than participants who previously received placebo in Study 233AS101 Part C. Over 24 weeks of open-label tofersen treatment in Study 233AS102, ALSFRS-R total scores had modest declines of similar magnitude, regardless of prior treatment group. For participants who enrolled in Study 233AS102 from Study 233AS101 Parts A and B, the baseline mean (SD) ALSFRS-R total score was similar to the baseline of participants from Study 233AS101 Part C. Data were available for 44 participants at Baseline, with an ALSFRS-R score ranging from 3 to 48. The mean ALSFRS-R total score remained fairly consistent over 196 weeks of open-label tofersen treatment.

SVC

Participants who previously received tofersen in Study 233AS101 Part C had higher percent predicted SVC baseline values in Study 233AS102 than participants who received placebo in Study 233AS101 Part C. Over 24 weeks of open-label tofersen treatment in Study 233AS102, percent predicted SVC values had modest declines of similar magnitude regardless of prior treatment group. Participants who enrolled in Study 233AS102 from Study 233AS101 Parts A and B, the baseline mean (SD) vital capacity as measured by percent predicted SVC was similar to that in participants from Study 233AS101 Part C. The mean (SD) change from baseline in percent predicted SVC remained fairly consistent over 196 weeks of open-label tofersen treatment.

HHD

Baseline mean HHD megascore values in Study 233AS102 were similar between participants who received tofersen in Study 233AS101 Part C and participants who received placebo in Study 233AS101 Part C. Over 24 weeks of open-label tofersen treatment in Study 233AS102, HHD megascore values remained fairly consistent regardless of prior treatment group. At the end of 24 weeks in Study 233AS102, participants who previously received tofersen in Study 233AS101 Part C had higher HHD megascores than participants who previously received placebo. Participants who enrolled in Study 233AS102 from Study 233AS101 Parts A and B, the baseline mean (SD) HHD megascore was similar to participants from Study 233AS101 Part C. The mean (SD) change from baseline in HHD megascore remained consistent over 196 weeks of open label tofersen treatment.

Time to death

Thirteen participants from Study 233AS101 Part C and 4 participants from Study 233AS101 Parts A and B died during Study 233AS102. Median survival time was not estimable due to the limited number of events.

Final integrated efficacy data from Study 233AS101 Part C and Study 233AS102

Analyses of efficacy, QoL, and biomarker endpoints previously conducted for Study 233AS102 interim data highlighted the limitations of conducting standalone analyses of these endpoints for Study 233AS102, such as:

- In contrast to the prespecified integrated analyses of Study 233AS101 Part C and Study 233AS102, the standalone analyses of Study 233AS102 are based on data selected using postrandomization factors and therefore break the original randomization. Conversely, the overall ITT analysis with the original Study 233AS101 Part C baseline provides an objective comparison of the 2 treatment regimens.

- Rate of progression is variable over time. Comparison of the treatment groups from Study 233AS102 fails to reflect the overall treatment effect due to early tofersen initiation that is evident in Study 233AS101. For example, in a hypothetical scenario with 2 periods, if the rate of progression is faster for the delayed-start group in period 1 and then becomes comparable to the rate for the early-start group, then a comparison using only period 2 data would be misleading.
- There are imbalances at baseline of Study 233AS102, as expected due to the effect of tofersen in Study 233AS101, thus confounding the interpretation of Study 233AS102 standalone analyses.
- Incorporation of baseline NfL as a covariate is the most objective mechanism to control for disease heterogeneity at Baseline. However, baseline Nf in Study 233AS102 cannot be incorporated as a covariate due to the confounding effect of tofersen administration during Study 101.

Based on these learnings, the Sponsor prespecified analysis of the longitudinal efficacy and biomarker data from Study 233AS102 as part of an integrated analysis of Study 101 and Study 102 only.

To further inform the longer-term effectiveness of tofersen, final Study 233AS102 data for efficacy and biomarkers are presented only in an integrated manner using data from Study 233AS101 and Study 233AS102.

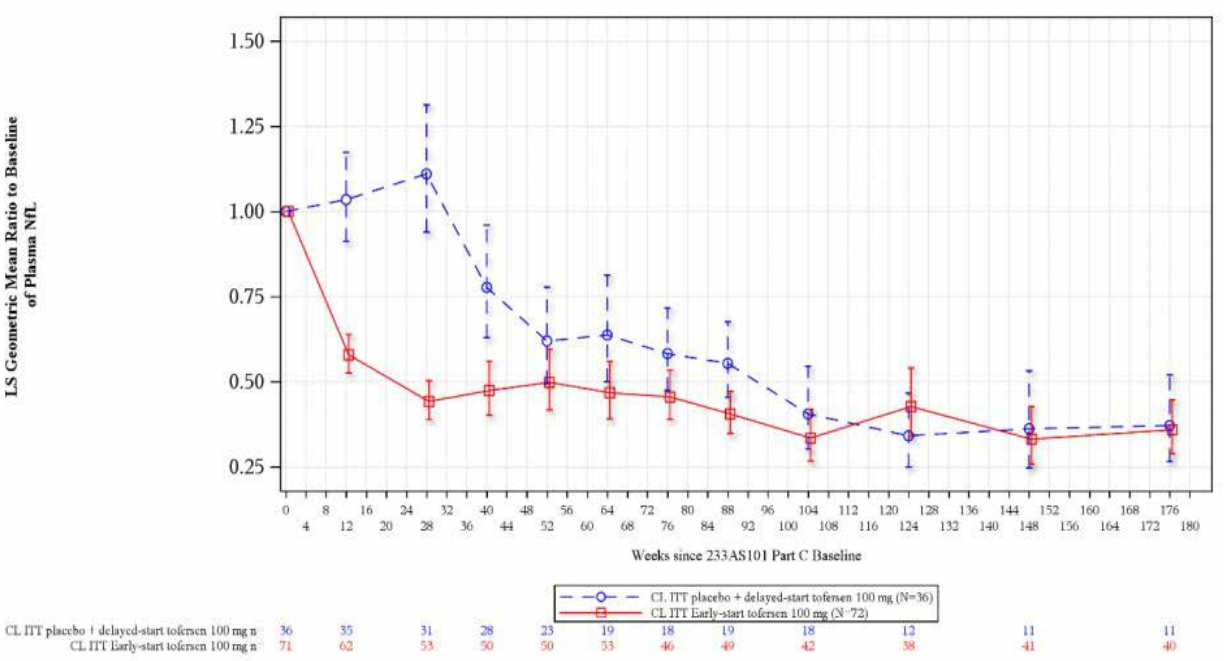
CSF SOD1 protein levels

Reductions in total CSF SOD1 protein, an indirect measure of target engagement, became apparent by ~8 weeks of treatment, consistent with the estimated time to steady-state concentrations of tofersen in CSF and estimated half-life of SOD1 protein (each ~1 month). Early reductions in CSF SOD1 concentrations were sustained at Week 148, with a reduction of 21% in the early-start group and 25% in the placebo/delayed-start group. Owing to a lack of a certified reference material to determine an absolute concentration of SOD1 protein across assay plates and inherent assay analytical variability, SOD1 protein levels for a given observation may vary up to 12.3%.

Plasma NfL levels

Maximal reductions in plasma NfL, a marker of the speed of axonal injury and neurodegeneration, were observed by ~16 weeks after treatment initiation and sustained over time. Specifically, reductions (geometric mean ratio to baseline) in plasma NfL from baseline to Week 148 were 67% in the early-start group and 64% in the placebo/delayed-start group (Figure 14). These data illustrate that tofersen robustly slowed the pace of neuronal injury and neurodegeneration, with no evidence of attenuation of effect over time.

Figure 5: Studies 233AS101 Part C and 233AS102 - Integrated Study Efficacy: Geometric Mean Ratio (95% CI) to Baseline of Plasma NfL over time

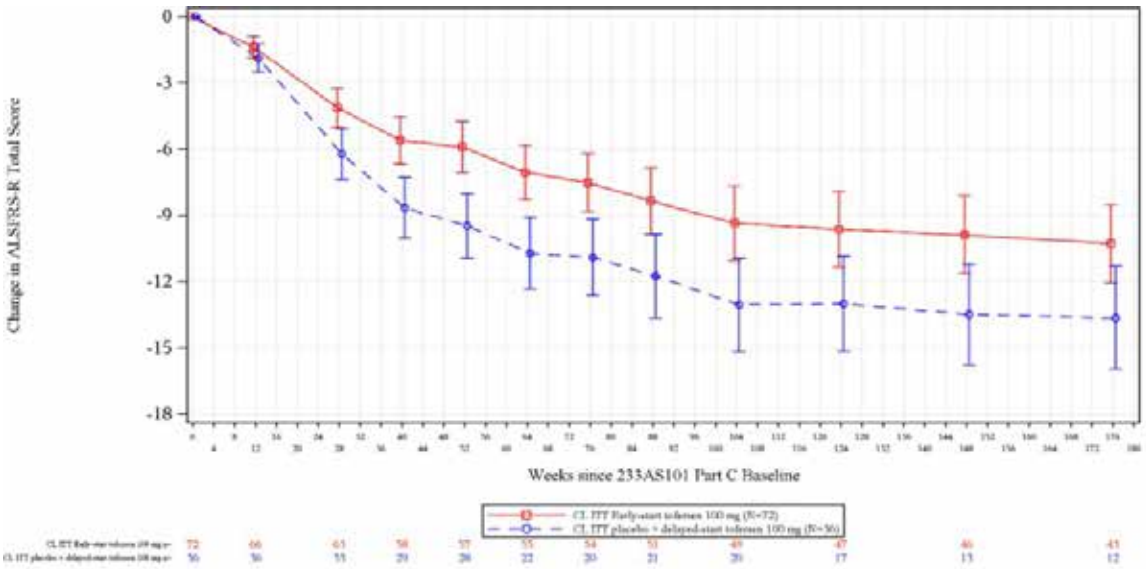


ALSFRS-R scores

Over 148 weeks, the sponsor considered earlier initiation of tofersen was associated with less decline across measures of clinical function, breathing, and strength. The sponsor considered the *early-start group* as the group that started in 233AS101 Part C on tofersen treatment and considered the *delayed-start group* as the group that received placebo in 233AS101 Part C. The sponsor reported results in their integrated analyses in favour of the *early-start group* were observed across populations (ITT, faster-progressing subgroup [NfL > median] and slower-progressing subgroup [NfL < median]) and regardless of which covariates were incorporated into the analyses.

The *early-start group* experienced a 9.9-point decline on ALSFRS-R from baseline to Week 148, as compared with a 13.5-point decline in the *placebo/delayed-start group* (adjusted mean difference, 3.6 points; 95% CI: –1.2 to 8.4; ANCOVA+MI: p = 0.1432; JRT: p = 0.1064; alternative JRT: p = 0.0541) (Figure 15). A larger proportion of participants in the *early-start group* experienced improvement on clinical function (21.0%) as compared with the *delayed-start group* (17.3%). In the *early-start group*, the proportion of participants that gained function from baseline was even greater in the slower-progressing subgroup (26.5%) than the faster-progressing subgroup (16.2%).

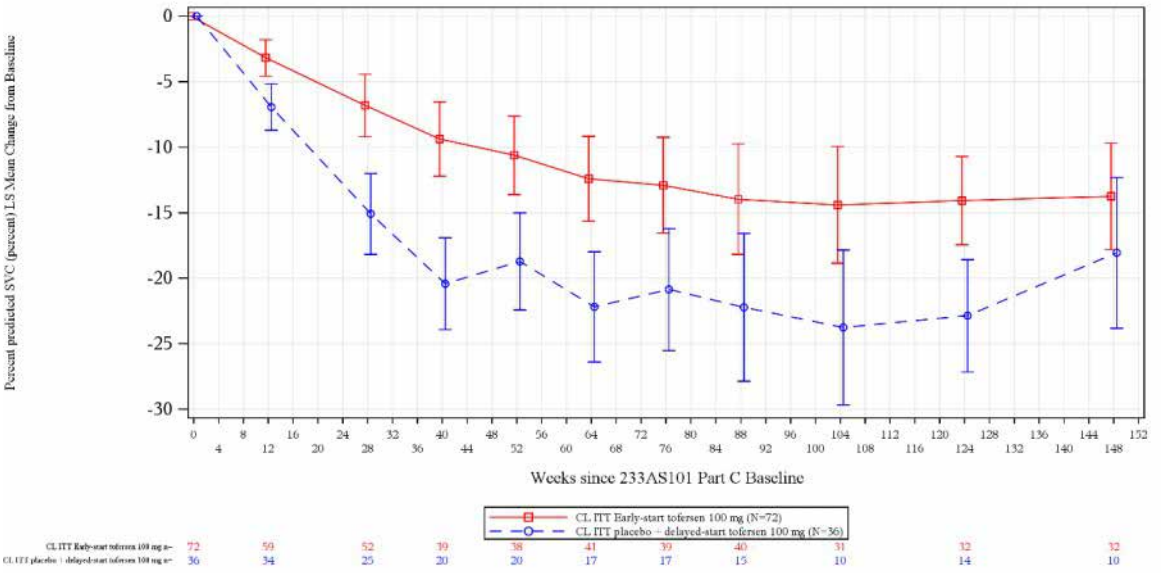
Figure 6: Studies 233AS101 Part C and 233AS102 - Integrated Study Efficacy: Least Squares Mean Change from Baseline in ALSFRS-R over time



SVC

The *early-start group* experienced a 13.8%-predicted decline on SVC from baseline to Week 148 (least squares mean change), as compared with an 18.1%-predicted decline in the *placebo/delayed-start group* (adjusted mean difference, 4.3; 95% CI: –6.6 to 15.2; ANCOVA+MI p = 0.4388) (Figure 16). Consistently, a larger proportion of participants in the *early-start group* experienced improvement (23.1%) in SVC from baseline to Week 148 as compared with the *delayed-start group* (15.8%). In the *early-start group*, the proportion of participants who gained respiratory function from baseline was even greater in the slower-progressing subgroup (35.5%) than the faster-progressing subgroup (12.5%).

Figure 7: Studies 233AS101 Part C and 233AS102 - Integrated Study Efficacy: Least Squares Mean Change from Baseline in percent-predicted SVC over time

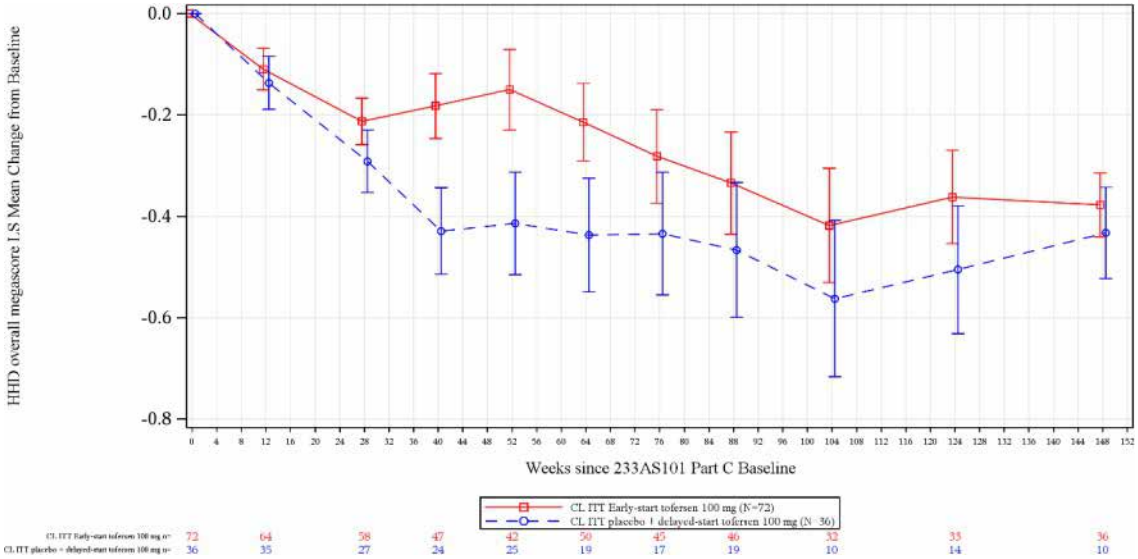


HHD

The *early-start group* experienced a 0.38-point decline on HHD megascore from baseline to Week 148, as compared with a 0.43-point decline in the *placebo/delayed-start group* (adjusted

mean difference, 0.06; 95% CI: –0.124 to 0.234; ANCOVA+MI: p = 0.5452) (figure 8). A larger proportion of participants in the *early-start group* exhibited improvement (27.3%) on HHD from baseline to Week 148 compared with the *delayed-start group* (10.7%). Notably, half (50.0%) of participants in the early-start slower-progressing subgroup gained strength from baseline to Week 148 compared with 6.9% in the early-start faster-progressing subgroup.

Figure 8: Studies 233AS101 Part C and 233AS102 - Integrated Study Efficacy: Least Squares Mean Change from Baseline in HHD Megascore over time



Time to death or permanent ventilation

Despite all participants enrolled in Study 233AS101 Part C having the opportunity for ≥ 3.5 years of follow-up at the completion of the study, there were a limited number of death-equivalent events, thus precluding estimation of median time to death or PV or time to death in both the early-start and placebo/delayed-start groups of the full ITT population. Median time to death, PV, or withdrawal due to disease progression was met in the early-start group, estimated at 260.7 weeks. In the faster-progressing subgroup (defined by median baseline plasma NfL level), those on early-start tofersen experienced a 3.4-year extension of event-free survival compared with those who initiated tofersen 6 months later.

The *early-start group* experienced a 36% reduction in the risk of death or PV (HR: 0.64; 95% CI: 0.282, 1.461); a 48% reduction in the risk of death (HR: 0.52; 95% CI: 0.199, 1.357); and a 39% reduction in the risk of death, PV, or withdrawal due to disease progression (HR: 0.61; 95% CI: 0.312, 1.185) as compared with the *placebo/delayed-start group*.

Summary

Clear differences favouring early-start tofersen (as compared with delayed-start tofersen) were observed across clinical outcome measures of function (ALSFRS-R), respiratory strength (percentage of predicted SVC), muscle strength (HHD megascore), and patient-reported outcomes of disease severity and QoL (including ALSAQ-5, EQ-5D-5L, and SF-36). Comparing the effects of tofersen in the early-start relative to the delayed-start group is a conservative approach to quantifying the effects of tofersen, given that both groups received the treatment for ≥ 3 years (as the placebo/delayed-start group had the opportunity to transition to active treatment after the first 6 months). As such, it is important to also consider that the effects observed in both groups are vastly different from the expected natural history of the disease, which is uniformly progressive. For example, on a population basis, individuals with ALS are

estimated to decline by an average of 0.6 to 1 point per month on the ALSFRS-R scale,[7,8,9] which would equate to ~22 to 34 points over a 148-week follow-up period. While these data are from the broad ALS population as there are limited natural history data in the SOD1-ALS population, the Study 233AS101 Part C population was enriched for faster progressing individuals and thus would be expected to progress at least as quickly absent an effective treatment. In contrast, participants in the early-start group declined by only 9.9 points, and those in the placebo/delayed-start group by 13.5 points over this period.

Evidence of improvement in strength and/or function was observed over ~3 years in ~21-27% and ~11-17% of participants in the early-start and placebo/delayed-start groups, respectively, which is highly inconsistent with the progressive decline expected from the natural history of the disease. Sustained recovery of strength and function does not occur in people living with ALS. For comparison, < 70 reports of sustained symptom improvement in people with ALS have been documented in the history of the disease, with no known documented ALS reversals in people living with SOD1-ALS.[10,11]

The median survival for SOD1-ALS is estimated to be ~2.3 years from symptom onset.[12] As participants in the placebo/delayed-start group initiated tofersen at ~28 weeks in Study 233AS102, it is not possible to precisely estimate survival outcomes without the impact of tofersen treatment. However, the sponsor proposes that the data presented here suggest tofersen is having a substantial impact on survival. Despite the extensive duration of follow-up (median of 4.9 years with a range of 3.6 to 5.4 years), the limited number of death-equivalent events precluded estimation of the median time to death or PV in the full ITT population. However, in the faster-progressing subgroup (where a larger number of events occurred), the median time to death or PV was met in both the delayed-start and early-start groups, allowing for a straightforward and precise estimate of survival. In this faster-progressing subgroup, those on early-start tofersen experienced a 3.4-year extension of event-free survival compared with those who initiated tofersen 6 months later. Importantly, for the ITT population, earlier initiation of tofersen was associated with a 36% reduction in the risk of death or PV and a 48% reduction in the risk of death relative to initiation of tofersen 6 months later in the placebo/delayed-start group.

The clinical evaluator noted the primary efficacy endpoint that was not reached in Study 233AS101 Part C, change in ALSFRS-R scores, continued to show a numerical difference between the randomised groups from 233AS101 Part C and that there was less of a decline on ALSFRS-R from baseline to Week 148 in those who commenced on tofersen in 233AS101 Part C (9.9 points), as compared with those who were in the placebo group in 233AS101 Part C and subsequently commenced tofersen in 233AS102 approximately 6 months later (13.5-point decline). This finding is not statistically significant. Notably the numerical discrepancy in the

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[8] van Eijk RPA, Weemering DN, Opie-Martin S, et al. Natural history of the revised ALS functional rating scale and its association with survival: the PRECISION-ALS Extant Study. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2025; 26(sup1):30-40.

[9] Westeneng HJ, Debray TPA, Visser AE, et al. *Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model.* Lancet Neurology. 2018;17(5):423-433.

[10] Crayle, J., Lutz, M., Raymond, J., Mehta, P., & Bedlack, R. (2023). *Study of "ALS reversals": LifeTime environmental exposures (StARLiTE).* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 24(1-2), 54-62. DOI: 10.1080/21678421.2022.2090846.

[11] Crayle JI, Rampersaud E, Myers JR, Wuu J, Taylor JP, Wu G, Benatar M, Bedlack RS. Genetic associations with an amyotrophic lateral sclerosis reversal phenotype. *Neurology*. 2024;103:e209696. doi:10.1212/WNL.0000000000209696.

[12] Opie-Martin S, Al Khleifat A, Kiernan MC, et al. The SOD1-mediated ALS phenotype shows a decoupling between age of symptom onset and disease duration. *Nature Communications*. 2022;13:7653. doi:10.1038/s41467-022-34620-y.

decline of ALSFRS-R scores between the groups have also widened compared to that evaluated at the Week 28 timepoint of Study 233AS101 Part C (the primary efficacy endpoint).

The clinical evaluator accepted and agreed with the sponsor that in spite of limited natural history data, the expected decline in those enrolled in the tofersen clinical studies would be estimated to be similar to the populational basis without any treatment, quoted as a decline by an average of 0.6 to 1 point per month on the ALSFRS-R scale, which would equate to ~22 to 34 points over a 148-week follow-up period. Taken in this context, the overall study population (both the early start treatment group and placebo/delayed start treatment group) is considered to be fairing significantly better than expected with much less decline in ALSFRS-R scores compared to the expected general ALS population.

The secondary efficacy endpoints in predicted SVC and HHD megascores both exhibited less decline in those who commenced on tofersen in 233AS101 Part C, as compared with those who were in the placebo group in 233AS101 Part C and subsequently commenced tofersen in Study 233AS102 approximately 6 months later. Again, these endpoints do not demonstrate statistical significance. However, there was evidence of improvement in strength and/or function observed over ~3 years in ~21-27% and ~11-17% of participants in the early-start and placebo/delayed-start groups, respectively, which is highly inconsistent with the progressive neurological decline expected from the natural history of the disease.

Study 233AS303 is an ongoing study investigating tofersen in presymptomatic SOD1 mutation carriers. Cumulative enrolment to Part A of the study is complete with 158 participants enrolled (target 150). Part B, Part C and Part D are still enrolling participants. The anticipated trial completion date is December 2027 at the earlier, with a final study report anticipated for Quarter 4 2028.

The sponsor considers that this study will address the following information gaps:

- whether initiation of tofersen at an earlier point in the disease spectrum can halt or slow disease progression
- improved definition of the early disease spectrum and markers of earlier disease activity.

The sponsor is confident Study 233AS303 will provide additional efficacy data.

Safety

All completed and ongoing studies provided data for the assessment of safety.

Patient exposure

A total of 166 participants with ALS received tofersen through intrathecal administration in clinical studies. All except 4 had SOD1-ALS, the proposed indication for this application, were exposed to any dose of tofersen for 352.55 participant-years. The median exposure to tofersen for this group was 112.4 weeks.

A total of 147 participants from Studies 233AS101 and 233AS102 with ALS were exposed to 100 mg of tofersen for 312.56 participant-years. The median exposure to tofersen 100 mg for this group was 119.4 weeks. The 4 participants who did not have SOD1-ALS were treated with tofersen in Study 101 Part A (SAD) only.

Pivotal efficacy study – Study 233AS101 Part C

Adverse events

The percentage of participants experiencing at least one adverse event (AE) was similar across groups. AEs were experienced by the majority of participants (95.8% in the tofersen group and 94.4% in the placebo group).

AEs were reported most commonly (>10% of the tofersen treated group) in the following system organ classes (SOCs). Data are presented as tofersen treated versus placebo group, and SOCs. Those classes in which the incidence in the tofersen group is at least 5% discrepant when compared with the control group are shown in italics:

- *Injury, poisoning, and procedural complications (68.1% versus 80.6%)*
- Nervous system disorders (65.3% versus 61.1%)
- *Musculoskeletal and connective tissue disorders (55.6% versus 50.0%)*
- *General disorders and administration site conditions (33.3% versus 25%)*
- *Gastrointestinal disorders (30.6% versus 44.4%)*
- *Respiratory, thoracic and mediastinal disorders (25% versus 36.1%)*
- *Infections and infestations (20.8% versus 41.7%)*
- *Investigations (20.8% versus 8.3%)*
- *Skin and subcutaneous tissue disorder (15.3% versus 8.3%)*
- Psychiatric disorders (12.5% versus 16.7%)

In the overall safety population, differences in the profile of AEs between the tofersen group and the placebo group were also observed at preferred term (PT) level. The most commonly reported AEs by preferred term (reported in 10% or more *in either* the tofersen treated or placebo group) as follows. Data are presented as tofersen treated versus placebo group, and PTs. Those classes in which the incidence in the tofersen group is at least 10% discrepant when compared with the control group are shown in italics:

- Procedural pain (56.9% versus 58.3%)
- Headache (45.8% versus 44.4%)
- *Pain in extremity (26.4% versus 16.7%)*
- *Fall (23.6% versus 41.7%)*
- *Back pain (20.8% versus 5.6%)*
- *Post-LP syndrome (18.1% versus 30.6%)*
- *Fatigue (16.7% versus 5.6%)*
- Arthralgia (13.9% versus 5.6%)
- Myalgia (13.9% versus 5.6%)
- Nausea (12.5% versus 16.7%)
- Constipation (8.3% versus 11.1%)

- Paraesthesia (8.3% versus 16.7%)
- Dyspnoea (5.6% versus 13.9%)
- Muscular weakness (5.6% versus 11.1%)
- Neck pain (5.6% versus 11.1%)
- Post procedural complication (4.2% versus 11.1%)
- *Nasopharyngitis (2.8% versus 19.4%)*
- *Diarrhea (1.4% versus 13.9%)*

Most AEs were mild or moderate in severity. There was a higher incidence of AEs that were

Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 in the tofersen group (16.7%) compared to the placebo group (11.1%). Serious AEs (SAEs) were reported more frequently in the tofersen 100 mg-treated participants than the placebo-treated participants. The incidence of SAEs was higher in the tofersen group (18.1%) compared with the placebo group (5.6%). The most frequently reported SAEs (≥ 2%) were dyspnoea, pulmonary embolism, pneumonia aspiration, dehydration, and atelectasis.

Treatment related adverse events (adverse drug reactions)

AEs related to the LP were experienced by the majority of participants in both the tofersen group (80.6%) and placebo group (80.6%).

Overall, in the safety population, the incidence of AEs that were considered related to study treatment by the Investigator was higher in the tofersen group (28/72 participants [38.9%]) compared with the placebo group (2/36 participants [5.6%]). There was a higher (≥ 5% difference) incidence of AEs that were considered by the Investigator as related to study treatment in the tofersen group compared with the placebo group for the following AEs by preferred term (PT):

- Headache (6/72 participants [8.3%] in the tofersen group and 0% in the placebo group),
- Myalgia (5/72 participants [6.9%] in the tofersen group and 0% in the placebo group)
- Pain in extremity (5/72 participants [6.9%] in the tofersen group and 0% in the placebo group)
- Procedural pain (4/72 participants [5.6%] in the tofersen group and 0% in the placebo group)

Four SAEs, lumbar radiculopathy, myelitis transverse, myelitis, and chemical meningitis (1.4% each), were considered tofersen-treatment–related by the Investigator. Myelitis was reported in the 'other' subgroup, and the other SAEs were reported in the 'enriched' subgroup. These 4 events were serious neurological events.

Deaths and other serious adverse events

One participant in the tofersen 100 mg-treated group had a fatal AE of cardiac failure congestive which was assessed as unrelated to tofersen. No other deaths occurred in the main efficacy study.

Overall, in the safety population, the incidence of SAEs was higher in the tofersen group (13/72 participants [18.1%]) compared with the placebo group (5/36 participants [13.9%]).

The most frequently reported (≥ 2%) SAEs by PT were:

- dyspnoea (0% of participants in the tofersen group and 2/26 participants [5.6%] in the placebo group)
- pulmonary embolism (3/72 participants [4.2%] in the tofersen group and 1/36 participants [2.8%] in the placebo group)
- aspiration pneumonia (2/72 participants [2.8%] in the tofersen group and 0% in the placebo group)
- dehydration (0% in the tofersen group and1/36 participants [2.8%] in the placebo group)
- atelectasis (0% in the tofersen group and1/36 participants [2.8%] in the placebo group).

There were three deaths that occurred in Study 233AS101 Part B. None of these deaths were considered to be related to study treatment. All deaths were considered associated with underlying disease or comorbidities by the Investigator.

There were no deaths or SAEs in Study 233AS101 Part A.

Issues with possible regulatory impact

Treatment with tofersen was not associated with any clinically meaningful changes or percent changes over time in liver function parameters, and the values were similar to those for placebo. Overall, there was no case of potential serious hepatotoxicity.

Treatment with tofersen was not associated with any clinically meaningful changes or percent changes over time for the blood chemistry analytes, and the values were similar to those for placebo. No clinically meaningful changes were seen in urinalysis parameters.

Treatment with tofersen was not associated with any clinically meaningful changes or percent changes over time for the hematology analytes and the values were similar to placebo. The incidence of shifts to high values and shifts to low values for hematology parameters was generally similar between the tofersen and placebo groups.

Treatment with tofersen was not associated with any clinically meaningful changes or percent changes over time for coagulation parameters and the values were similar to placebo.

Multiple participants were observed to have abnormalities in CSF protein and/or leukocyte count. Some of these were reported as AEs by the Investigator. However, additional participants had abnormalities in these CSF parameters that were not reported as AEs. CSF protein levels were noted to be elevated at baseline in some participants, which may be related to ALS disease.

Shifts from normal to high, low to high, and unknown to high protein were higher in the tofersen group (31/46 participants [67.4%]) compared with the placebo group (6/20 participants [25.0%]). Shifts from normal to high, low to high, and unknown to high leukocytes were higher in the tofersen group (54/69 participants [78.3%]) compared with the placebo group (9/36 participants [25.0%]). The proportion of participants with at least one CSF leukocyte value >10 x 106/L was 42/72 participants (58.3%) in the tofersen group compared to 2/36 participants (5.6%) in the placebo group. There was the same trend for participants with at least one CSF leukocyte value >5 x 106/L.

None of these AEs or non-AE abnormalities led to treatment discontinuation, and in some cases the laboratory abnormalities stabilised or improved despite continued study treatment. The clinical significance of these abnormalities remains uncertain.

The incidence of abnormalities in ECG measurements was slightly higher in the tofersen group compared to the placebo group, with 8 participants (11.3%) displaying a maximum increase from baseline in QTcF > 30 to 60 ms in the tofersen group compared to 2 participants (5.6%) in

the placebo group. No participants in the tofersen or placebo group displayed an increase from baseline in QTcF > 60 ms, and no participants displayed maximum postbaseline QTcF > 480 ms.

Treatment with tofersen was not associated with meaningful changes over time for the vital sign measurements and the values were similar to placebo.

Any clinically meaningful abnormalities on physical examinations were reported by the Investigators as AEs. These were predominantly neurological examination findings. Changes to neurological examination findings over time were considered generally consistent with ALS disease progression and were suggestive of a slowing in decline in participants in the tofersen group compared to participants in the placebo group.

Most participants (70/72 participants [97.2%] in the tofersen group and 36/36 participants [100%] in the placebo group) were anti-drug antibody (ADA)-negative at Baseline. Of the participants with a negative baseline result, 21/72 participants (29.2%) in the tofersen group and 2/36 participants (5.6%) in the placebo group had a positive treatment-emergent sample. Overall, 19/72 participants (26.4%) in the tofersen group and 2/36 participants (5.6%) in the placebo group were persistently positive for anti-tofersen antibodies during the study, defined as more than 1 postbaseline positive evaluation occurring ≥ 112 days (≥ 16 weeks) apart, or one or more postbaseline positive evaluations, but occurring < 112 days of evaluable data after the first positive timepoint. The presence of anti-tofersen antibodies did not have a significant effect on PK parameters (AUC0-24h and C_{max}) of tofersen. Based on medical review (no formal analysis was conducted), no impact of ADA was observed on serious neurological events (lumbar radiculopathy, chemical meningitis, myelitis, and transverse myelitis).

Safety in special populations

SOD1-ALS is exceedingly rare in people younger than 18 years of age. The total tofersen population ranged in age from 23 to 78 years. Evaluation of the overall summary of AEs showed that within each of the 2 age subgroups (participants <65 and ≥65 years), participants generally had similar proportions of participants experiencing AEs in each AE category.

Evaluation of the overall summary of AEs showed that each of the 2 subgroups (females or males) generally had similar proportions of participants experiencing AEs in each AE category.

Overall, in relation to race, no notable concerns were identified through medical review of AEs by SOC and individual PTs.

There are no data available on the potential effects of tofersen on fertility, impact on pregnancy, and during lactation in humans.

No drug-drug interaction studies have been performed.

Study 233AS102 additional safety data

Adverse events

Overall, 137 participants (98.6%) experienced an AE. The most commonly reported AEs (reported by > 20% of participants overall) by PT were headache (59.7%), procedural pain (54.0%), fall (51.1%), back pain (48.2%), arthralgia (34.5%), COVID-19 (34.5%), pain in extremity (34.5%), fatigue (28.1%), CSF protein increased (26.6%), nasopharyngitis (26.6%), nausea (26.6%), post-lumbar puncture syndrome (24.5%), constipation (23.7%),dizziness (22.3%), muscle spasms (21.6%), myalgia (21.6%), pyrexia (21.6%), CSF white blood cell count increased (20.1%), and contusion (20.1%).

A total of 129 participants (92.8%) experienced AEs that occurred within 24 hours of dosing.

The most common AEs (> 20%) that occurred within 24 hours of dosing by PT were procedural pain (50.4%), headache (43.2%), and back pain (32.4%).

Overall, most participants experienced AEs that were CTCAE Grade 2 (moderate) (35.3%) or Grade 3 (severe) (29.5%) in severity

Adverse events related to study treatment

AEs considered by the Investigator to be related to study treatment were reported in 94 participants (67.6%). The most commonly reported AEs considered by the Investigator to be related to study treatment (reported by >10% of participants overall) were CSF protein increased (33 participants [23.7%]), CSF white blood cell count increased (26 participants [18.7%]), pain in extremity (22 participants [15.8%]), headache (19 participants [13.7%]),

and pleocytosis (15 participants [10.8%]).

Adverse events related to lumbar puncture

Overall, AEs considered by the Investigator to be related to the LP were reported in

113 participants (81.3%). The most commonly reported AEs (> 20% participants overall) considered by the Investigator to be related to the LP by PT were procedural pain (71 participants [51.1%]), headache (60 participants [43.2%]), back pain (48 participants [34.5%]), and post-lumbar puncture syndrome (34 participants [24.5%]).

Deaths

Twenty-six participants (18.7%) died. Most deaths reported in this study were consistent with and considered related to the expected course of ALS. The most common

AEs that resulted in deaths were in the SOC Respiratory, thoracic and mediastinal disorders with a fatal AE of respiratory failure (12 participants [8.6%]); this was followed by the SOCs Infections and infestations with a fatal AE of pneumonia aspiration (3 participants [2.2%]) and Cardiac disorders with a fatal AE of cardiac arrest (3 participants [2.2%]). All AEs leading to death were considered by the Investigators to be unrelated to tofersen.

Serious adverse events

Overall, 71 participants (51.1%) experienced SAEs. The most common SAEs by PT included respiratory failure (17 participants [12.2%]), pneumonia aspiration (13 participants

[9.4%]), dysphagia (11 participants [7.9%]), acute respiratory failure (7 participants

[5.0%]), pneumonia (5 participants [3.6%]), pulmonary embolism (5 participants [3.6%]), and fall (5 participants [3.6%]); all other SAEs were each reported for ≤ 3 participants overall.

Adverse events related to study treatment

Nine participants experienced a total of 13 SAEs considered by the Investigator to be related to study treatment.

- Intracranial pressure increased in 2 participants (1 participant previously receiving placebo and 1 participant previously receiving tofersen in Study 233AS101).
- Neuromyelitis optica spectrum disorder was reported in 1 participant previously receiving placebo in Study 233AS101.
- Myelitis was reported in 2 participants (1 participant previously receiving placebo and 1 participant previously receiving tofersen in Study 233AS101).

- Meningitis aseptic, headache, and papilloedema were reported in 1 participant previously receiving placebo in Study 233AS101.
- Intracranial pressure increase and myelitis were reported in 1 participant.
- Radiculopathy was reported in 1 participant.
- Gastritis and pancreatitis were reported in 1 participant.

There were no AEs of special interest identified for this study.

Neurological events

A total of 8 participants (5.8%) experienced serious neurologic events, and a total of 11 participants (7.9%) experienced nonserious neurologic events. An ADR of 'myelitis' included the PTs of myelitis, myelitis transverse, and neurosarcoidosis. Serious events of myelitis were reported in 4 participants (2.9%). The events of myelitis in all 4 participants were Grade 3 severity, assessed as related to study treatment by the investigator, did not lead to treatment discontinuation, and all resolved.

An ADR of 'radiculitis' included the PTs of radiculopathy and lumbar radiculopathy. One participant (0.7%) had a serious event of radiculopathy (previously in Study 233AS101 Part A and B). The event of radiculopathy was of Grade 3 severity, assessed as related to tofersen by the Investigator, and did not lead to discontinuation of tofersen.

An ADR of 'papilloedema' included the PTs of papilloedema and intracranial pressure increased. One participant (0.7%) had a serious event of papilloedema. The event was of Grade 3 severity, assessed as related to study treatment by the Investigator, and did not lead to discontinuation of study treatment. The event of papilloedema resolved.

No serious events of intracranial pressure increased lead to treatment discontinuation, and all resolved.

Five participants reported only nonserious events of papilloedema and/or increased intracranial pressure, two participants had events that were Grade 3 in severity; the rest had events that were of Grade < 3. All events were assessed as related to study treatment by the Investigator. No events led to study withdrawal. Three events with papilloedema resolved while 3 did not resolve. Three events of intracranial pressure increased resolved whereas 3 did not resolve.

The neurologic ADR of 'aseptic meningitis' included the PTs of meningitis chemical and meningitis aseptic. One participant (0.7%) had a serious event of meningitis aseptic. The event of meningitis aseptic was of Grade 2 severity, was assessed as related to study treatment by the Investigator and did not lead to discontinuation of study treatment.

Nonserious adverse drug reactions

There were nonserious adverse drug reactions (ADRs) reported in Study 233AS102, including CSF white blood cell increased, CSF protein increased, pain, neuralgia, arthralgia, myalgia, musculoskeletal stiffness, pyrexia, and fatigue.

Laboratory parameters

Overall, treatment with tofersen was not associated with meaningful changes or percent changes over time for the hematology analyte or blood chemistry analytes.

Liver function test abnormalities reported as AEs (and overall proportion of participants reporting) included alanine aminotransferase increased (8 participants [5.8%]), aspartate aminotransferase increased (6 participants [4.3%]), hepatic enzyme increased (6 participants

[4.3%]), gamma-glutamyl transferase increased (2 participants [1.4%]), transaminases increased (1 participant [0.7%]), liver function test abnormal (1 participant [0.7%]), and liver function test increased (1 participant [0.7%]). None of these AEs were of ≥ Grade 3 severity. Most of these AEs were unrelated to the study drug.

Although abnormal values were reported, no clinically meaningful changes in urinalysis parameters were observed.

CSF parameters

CSF protein levels were noted to be elevated at Baseline in some participants, which may be related to ALS disease. Multiple participants were observed to have abnormalities in CSF protein and/or WBC counts, 3.6% had shift to low protein, 92.3% had shift to high leukocytes, and 93.5% had shift to high protein, compared with their corresponding baseline values. The majority of abnormalities in these CSF parameters were not reported as AEs.

Vital signs

Treatment with tofersen was not associated with changes over time in vital signs.

Electrocardiograph findings

Treatment with tofersen was not associated with clinically meaningful changes over time for ECG measurements.

Physical findings and neurological examination findings

Any clinically meaningful abnormalities on physical examinations were reported by the Investigator as AEs. Events reported included weight decreased (3.6% of participants overall) and weight increased (0.7% of participants overall). By PT, AEs due to abnormal neurological findings included balance disorder (8 participants [5.8%]), coordination abnormal (1 participant [0.7%]), decreased vibratory sense (1 participant [0.7%]), gait apraxia (1 participant [0.7%]), action tremor (1 participant [0.7%]), and essential tremor (2 participants [1.4%]). One AE of balance disorder led to study drug interruption and was assessed as related to study drug. There were no clinically relevant findings considered to be related to study treatment in MMSE. Changes to neurological examination findings over time were generally consistent with ALS disease progression.

Immunogenicity and immunological findings

Most participants (87.0%) were antibody-negative at Baseline. Overall, 61.6% of participants were considered ADA-positive (a participant was considered to have a positive ADA result if they had at least 1 postbaseline sample with a ≥ 2-fold increase in titer compared with a positive baseline result or if they had at least 1 confirmed postbaseline positive result with a negative baseline result).

Overall, 52.2% of participants were persistently positive for anti-tofersen antibodies during the study, defined as more than 1 postbaseline positive time point ≥ 112 days (≥ 16 weeks) apart or 1 or more postbaseline positive time points when < 112 days of evaluable data post first positive time point are available; and 9.4% of participants had a transient anti-tofersen antibody response, defined as a single postbaseline positive time point, followed by results after ≥ 112 days that were all negative or 2 or more positive data points < 112

days apart, with later negative samples ≥ 112 days from the first positive result. In participants enrolled from Study 233AS101 Part C, 59.4% of participants who previously received placebo were persistently positive for anti-tofersen antibodies while none were transiently positive; and

50.0% of participants who previously received tofersen were persistently positive while 11.3% were transiently positive. In participants enrolled from Study 233AS101 Parts A and B, 50.0% of participants who previously received tofersen were persistently positive while 13.6% were transiently positive.

Round 3 – Integrated summary of safety

A topline summary of the final integrated data from studies 233AS101 and 233AS102 was submitted with the response to s31 questions [on 13 August 2025, e007818 (0002-)] and all data in the topline summary had already been reviewed within the Round 2 clinical evaluation.

Adverse events, adverse events related to study treatment, adverse events related to lumbar puncture, deaths, serious adverse events, serious adverse events related to study treatment, and discontinuation or disruption of treatment or study withdrawal were reviewed previously (refer above). The integrated information is not dissimilar to the previously reviewed data.

Neurological Adverse Drug Reactions were also reviewed previously.

Additionally, laboratory parameters and CSF parameters impacted by tofersen were reviewed previously.

Suicide-related events were reviewed previously in response to evaluator questions and the additional information provided with the response. In the previous response, the clinical evaluator noted the following in relation to suicidal behaviours within the dossier:

- There were 2 participants with an AE of suicidal ideation (ABCL1 – pooled participants for safety analysis who have received at least one dose of 100mg tofersen intrathecally) and 1 participant with a fatal SAE of euthanasia in Belgium where voluntary euthanasia is legal [Roehr 2021]; each was assessed as unrelated to study treatment. One participant in the tofersen-treated group at any dose (ABCL2) demonstrated treatment-emergent suicidal preparatory acts or behaviour based upon C-SSRS results, but there were no suicide attempts or events of suicide, reported in Summary of Clinical Safety Report.
- There were no participants who engaged in preparatory acts or behaviour or attempted to commit suicide at any point during Study 233AS101 Part C, as reported in the Study Report.
- Parts A and B, as reported in the Study Report.
- No specific suicidal behaviour was reported during Study 233AS102, as reported in the Study Report.

The sponsor has committed to continuing monitoring suicidal ideation, suicidal behaviours and hallucinations through routine pharmacovigilance activities.

The sponsor advised that there were no clinically meaningful differences or trends in MMSE score change from baseline by visit, and there were no significant declines in MMSE with increasing tofersen exposure across the clinical program. There was insufficient data to establish a causal relationship between tofersen and changes in cognition.

AEs and SAEs were examined by intrinsic factor subgroups.

There was an increased frequency of SAEs in the participants with baseline NFL at or above median though the sponsor considered this likely due to those participants experiencing a more progressive stage of SOD1-ALS and not due to the effects of tofersen.

When reviewed by age, the sponsor advised the following:

- SOD1-ALS is exceedingly rare in people younger than 18 years of age.

- Review of individual AEs within each age subgroup (participants <65 years old and participants ≥ 65 years old) were generally consistent with those of the overall population.

There were no notable differences between males and females.

There was limited representation of races other than White which restricted comparison of AEs across race.

Site of onset of disease was specified as a subgroup of interest. However, given the small number of participants, no clear difference between site of onset subgroups were identified.

AEs and SAEs were also examined by extrinsic factor subgroups.

No regional differences were identified across commonly reported AEs or serious neurological AEs. No regional variation was observed that might suggest a difference in safety profile in participants in different geographical locations.

No clinical studies of interactions of tofersen with other medicines have been performed. There was no noticeable potentiation of other common side effects to concomitant medication. There were also no AEs observed suggestive of any potential drug-drug interaction with tofersen.

There are no data available on potential effects of tofersen on fertility in humans. There are no data on the use of tofersen during lactation in humans.

Extended Access Program

As of 30 April 2025, approximately 700 patients have been shipped tofersen 100 mg doses in the Extended Access Program (EAP).

As of 30 April 2025, AEs were reported in a total of 373 cases in the EAP. These 373 cases included 257 nonserious AEs and 169 SAEs; 152 AEs were assessed as possibly related, probably related, or related to tofersen. Eighty-eight AEs led to treatment discontinuation or interruption, and 56 events were fatal.

Serious neurological events were reported, including 11 events in 10 cases of papilledema, 10 events of myelitis, 7 events of aseptic meningitis, and 3 events in 2 cases of radiculitis. The characteristics of these serious neurologic events were consistent with what was observed in clinical trials.

The profile of common AEs reported, and AEs assessed as related to or probably/possibly related to tofersen, were similar to what was reported in the clinical trials.

Serious AEs assessed as tofersen related included: 7 serious events of meningitis aseptic, 6 serious events of myelitis, 2 serious events of radiculopathy and 4 nonserious events of radiculopathy, 2 serious events of papilledema, and 1 nonserious event of lumbar radiculopathy. One serious event of intervertebral discitis was assessed as possibly related to tofersen by the HCP. Tofersen treatment was interrupted as a result of the event. The event was resolved on an unknown date.

A total of 79 fatal events were reported in 56 cases from the EAP. One fatal event (PT: death) was recorded as related to tofersen in the global safety database. However, causality to tofersen was not assessed by the HCP in the CIOMS or in the GSD. This case involved a 59-year-old female patient who received her first dose of tofersen for SOD1-ALS on 02 February 2023. At the time of the event, the patient had received an unknown number of doses, with the most recent dose, prior to event onset, administered on 24 August 2023. The patient was hospitalised on 26 August 2023 for an unknown duration due to severe pulmonary embolism, which was also considered as a life-threatening event. The patient passed away on 31 August 2023. The cause of death was not provided. It is unknown whether treatment was provided prior to death or if an autopsy was performed. Causality of the event was not assessed by the HCP (conservatively captured as

related in the field for reporting purposes). It was unknown if tofersen therapy was ongoing at the time of death.

The most common SOCs with fatal events (≥ 5 events) were the SOC of General disorders and administration site conditions, with PT of death (18 events); the SOC of Nervous system disorders, with PTs of amyotrophic lateral sclerosis (14 events), hypoxic-ischemic encephalopathy and motor neuron disease (1 event each); the SOC of Respiratory, thoracic, and mediastinal disorders, with PTs of respiratory failure (6 events), acute respiratory failure (4 events), hypoventilation and pulmonary embolism (2 events, each) followed by bronchial secretion retention, dyspnoea, lung disorder, pleurisy, respiratory disorder, and respiratory distress (1 event, each); the SOC of Infections and infestations, with PTs of pneumonia aspiration (5 events), pulmonary sepsis and sepsis (2 events each), and haematological infection, parotitis, pneumonia, and septic shock (1 event each); the SOC of cardiac disorders, with PTs cardiac arrest, cardio-respiratory arrest, and cardiovascular disorder (2 events each), cardiac failure, cardiac failure congestive, and myocardial infarction (1 event each).

Non serious ADRs reported through the EAP again had a similar profile to those reported through the clinical trials.

The following are serious neurological ADRs of tofersen: myelitis (PTs myelitis, myelitis transverse, and neurosarcoidosis [verbatim term: neurosarcoid transverse myelitis), radiculitis (PTs radiculopathy and lumbar radiculopathy), aseptic meningitis (PTs meningitis aseptic and meningitis chemical), and papilledema (PTs papilledema and intracranial pressure increased).

In the EAP, as of 30 April 2025, SAEs were reported for the serious neurological ADR PTs as follows: papilledema (11 events in 10 cases), myelitis (10 events), meningitis aseptic (7 events), and radiculitis (3 events in 2 cases).

Of note, 1 myelitis case (Case 2022BI01126701) was incorrectly captured as multiple sclerosis in the outputs and is accurately and correctly captured as an event of myelitis in the Integrated Summary of Safety Addendum.

Again, the characteristics of these serious neurologic ADRs were consistent with those observed in clinical trials.

Post marketing experience

Periodic Adverse Drug Experience Reports (PADERs) were provided in sequence e007818-0001 as part of supplementary information submitted to the TGA.

There were 5 PADERs submitted that covered a 15-month reporting period. A total of 14 fatal events. In 9 of these events, the majority were related to respiratory decline or failure considered to be in keeping with progression of ALS disease. Two events were related directly to a fall sustained. In the remaining 5 events, the cause of death is unknown.

There were serious safety events that were also reported during this 15-month reporting period. Where there was enough information submitted, the sponsor considered these serious events either consistent with progression of ALS disease, pre-existing conditions, general population events, or consistent with known ADRs of tofersen or tofersen administration.

The known ADRs of tofersen that have been reported in the PADERs include neuromyelitis optica and papilloedema. One serious event of encephalitis was reported though there was not enough information provided to evaluate the relationship between the event and tofersen administration. There was one serious event of pancreatitis where the event was compounded by the concomitant administration of ramipril and therefore the relationship between the event and tofersen administration could not be assessed.

Notably there were events of hallucinations and raised intracranial pressure (2 events and 1 event respectively). Neither are listed as known ADRs of tofersen. It is unclear if either are related to tofersen administration and longer-term safety data may be required.

No new ADRs have been identified in the postmarketing setting with tofersen as of 30 April 2025.

Risk management plan evaluation summary

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in table 5.

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myelitis and/or radiculitis	✓*	✓†‡§	✓	–
	Increased intracranial pressure and/or papilloedema	✓*	✓†‡§	✓	–
Important potential risks	None	–	–	–	–
Missing information	None	–	–	–	–

*Specific adverse reaction follow-up questionnaires, a Data Collection Tool (DCT)
†Observational registry-based study
‡Extension Study
§Yearly updates

The summary of safety concerns in the ASA aligns with the EU-RMP and is acceptable from an RMP perspective.

- Routine and additional pharmacovigilance activities are proposed. Routine pharmacovigilance includes specific adverse reaction follow-up questionnaires, a Data Collection Tool (DCT), for the important, identified risks of 'Myelitis and/or radiculitis' and 'Increased intracranial pressure and/or papilloedema'.
- Additional pharmacovigilance includes an observational registry-based and a long-term extension PASS study, as well as yearly updates on safety and efficacy of tofersen. The pharmacovigilance plan in the ASA aligns with the EU-RMP. A clinical study plan has been provided and will be assessed by the Delegate.
- Routine risk minimisation activities only are proposed. The CMI and PI will be available on the company's website with a link to it on the product packaging.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

ALS is a rare, progressive, and ultimately fatal neurodegenerative disease. ALS is a disease with limited treatment options that typically results in progressive muscle loss leading to paralysis

and ultimately respiratory failure and death, with a short median survival from time of disease onset of less than 3 years.

Tofersen (Qalsody) is the first novel treatment directly targeting the underlying pathophysiology of SOD1-ALS. Tofersen has been shown to reduce plasma NfL levels and deamidated SOD1 protein levels in CSF, that together confirm target engagement. The prognostic and predictive value of NfL in ALS is not fully established yet and NfL is not yet considered a validated surrogate endpoint for predicting efficacy though is increasingly recognised as important in this field.

Although the pivotal efficacy study presented did not confirm the clinical efficacy of tofersen in its treatment of adults with SOD1-ALS, there were notably some consistent trends in favour for tofersen compared to placebo, which is further demonstrated with longer treatment and longer follow-up in the open-label extension study. Again, the additional data submitted do not demonstrate statistical significance in the outcomes assessed. However, in contrast to expected natural history of those with ALS (or SOD1-ALS), the study participants all recorded better outcomes when compared to projected untreated general ALS population averages across a median 4.9 year follow-up (ALSFRS-R decline, respiratory function, and muscle strength), with marginal advantage and survival benefit exhibited in those who commenced on tofersen 6 months earlier, that is those who were randomised to receive tofersen in the pivotal randomised controlled efficacy study. Taken as a whole, there is evidence to support the benefits of tofersen in those with SOD1-ALS.

Safety concerns with tofersen in relation to neuro-inflammatory ADRs, listed as lumbar radiculopathy, myelitis transverse, myelitis, chemical meningitis and papilloedema, remain. A serious adverse event of neurosarcoidosis was recorded and may be in keeping with the neuro-inflammatory side effect profile of tofersen. Adverse events related to the intrathecal mode of administration continue to be reported in a majority of study participants which included headaches, procedural pain, and post-lumbar puncture syndrome.

Additional possible safety signals relate to muscle cramping, involuntary muscle contractions, muscle spasticity, hallucinations and suicide-related events however these have not been reported to be a direct concern or directly related to treatment. Nonetheless, it is prudent that pharmacovigilance activities remain to monitor these events along with known ADRs and other SAEs which may be more common with increased exposure to the compound. Further, kidney toxicity has been recorded with another intrathecal ASO molecule and while not reported thus far across the clinical development program of tofersen, pharmacovigilance activities remain vital for surveillance of such safety signals.

Pharmacovigilance activities remain vital for surveillance of possible additional safety signals including those previously raised but not verified subsequently to be directly related to tofersen (such as events related to muscle cramping, involuntary muscle contractions, muscle spasticity, hallucinations and suicide-related events) as well as other ADRs recognised with other ASO use though not previously noted with tofersen use.

The risks with tofersen use are not negligible but considered acceptable in the context of the severe, debilitating, and fatal disease affecting this population.

The clinical evaluator noted that as part of the provisional determination application and assessment for tofersen, the Sponsor submitted a clinical study plan aiming to generate further comprehensive clinical data through Study 233AS303 which is a placebo-controlled study in presymptomatic adults with SOD1 mutation and an Integrated Analysis of Variant-Specific Survival, to support the transition of tofersen from provisional registration status to full marketing authorisation status.

Proposed action

Based on the evaluation of the data provided, the Delegate proposes to recommend provisional approval of tofersen (Qalsody) for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

The recommendation for provisional approval is based on the totality of evidence in respiratory function, muscle strength and survival in patients with SOD1-ALS treated with tofersen, in the context of a cohort of patients with a rare progressive, ultimately fatal, neurodegenerative disease, short median survival, poor outcomes and limited treatment options.

Exposure to tofersen has been limited and ongoing post-marketing surveillance will contribute to better understanding of the safety profile and detection of any safety signals as outlined above. These issues can be continually addressed with ongoing post-marketing surveillance.

The Delegate considers that data generation through the ongoing clinical study plan would provide further affirmation of tofersen.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Qalsody (tofersen) 100 mg/15 mL solution for injection intrathecal vial. The provisionally approved indication for the medicine is:

> *Qalsody has provisional approval in Australia for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene. The decision to approve this indication has been made on the totality of evidence including impacts on clinical function, respiratory function, muscle strength, survival, target engagement and reductions in NfL (a marker of axonal injury and neurodegeneration) in SOD1-ALS patients treated with Qalsody. Continued approval of this indication depends on additional data.*

Specific conditions of registration

- Qalsody (tofersen) is to be included in the Black Triangle Scheme. The PI and CMI for Qalsody must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.
- The Qalsody EU-Risk Management Plan (RMP) (version 1.0, dated 21 February 2024, data lock point 28 February 2023), with Australia-Specific Annex (ASA) (version 1.0, dated October 2024), included with submission PM-2024-04852-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
  - Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer. Each report must be submitted within ninety calendar days of the data lock point for that report.

  - The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- The sponsor must conduct studies as described in the Clinical Study Plan provided to address Criterion 5 of the Provisional determination in September 2025.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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