▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION –

QALSODY™ (TOFERSEN) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Tofersen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 ml vial contains 100 mg of tofersen.

Each ml contains 6.7 mg of tofersen.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

QALSODY is administered intrathecally using lumbar puncture by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Dosage

The recommended dosage is 100 mg/15 mL (6.7 mg/mL) of tofersen per treatment.

QALSODY treatment should be initiated with three (3) loading doses administered at 14-day intervals.

A maintenance dose should be administered every 28 days thereafter.

Missed or delayed doses

If the second loading dose is delayed or missed, QALSODY should be administered as soon as possible, and the third loading dose should be administered 14 days later.

If the third loading dose is delayed or missed, QALSODY should be administered as soon as possible, and the first maintenance dose should be administered 28 days later.

If a maintenance dose is delayed or missed, QALSODY should be administered as soon as possible. Subsequent maintenance doses should be administered every 28 days from the last dose.

Method of administration

Aseptic technique must be used when preparing and administering QALSODY intrathecally.

Preparation

Vial preparation instructions:

The refrigerated vial should be allowed to warm to room temperature (25°C) prior to administration without external heat sources (see section 6.3).

The vial containing QALSODY should not be shaken.

Solution should be visually inspected prior to removal of QALSODY from the vial. The solution should be essentially free of visible particles. Only clear and colourless to slightly yellow solution should be administered. If not, the vial must not be used.

Procedural preparation instructions

If indicated by the clinical condition of the patient, sedation can be considered.

If indicated by the clinical condition of the patient, imaging to guide intrathecal administration of QALSODY can be considered.

Prior to removing the vial's cap on the aluminium overseal, readiness of patient should be confirmed. Unopened vial can be returned to the refrigerator; see section 6.3 for total time permitted.

Patients should be evaluated prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture to avoid serious procedural complications.

Administration

Just prior to administration, the plastic cap should be removed from the vial and a non-spinal anaesthesia needle attached to the syringe for the purpose of withdrawing tofersen from the vial. The syringe needle is inserted into the vial through the centre of the overseal to withdraw the required dose of 15 mL (equivalent to 100 mg) from the vial.

QALSODY must not be diluted.

External filters are not required.

It is recommended that approximately 10 mL of cerebrospinal spinal fluid (CSF) is removed using a lumbar puncture needle prior to administration of QALSODY.

QALSODY is administered as an intrathecal bolus injection using a lumbar puncture needle over 1 to 3 minutes.

QALSODY contains no preservatives. Once drawn into the syringe, the solution should be administered immediately (within 4 hours since removal from refrigeration) at room temperature; otherwise, it must be discarded.

QALSODY is for single use in one patient only. Discard any residue.

Following injection, no additional monitoring procedures are recommended apart from standard post-lumbar-puncture care.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lumbar puncture procedure

There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. headache, back pain, post lumbar puncture syndrome, infection).

Myelitis and/or radiculitis

Serious events of myelitis (including myelitis transverse and neurosarcoidosis) and radiculitis (including radiculopathy and lumbar radiculopathy) have been reported in patients treated with tofersen. If symptoms consistent with these adverse events develop, diagnostic workup and treatment should be initiated according to the standard of care.

Increased intracranial pressure and/or papilloedema

Serious events of increased intracranial pressure and/or papilloedema have been reported in patients treated with tofersen. If symptoms consistent with these adverse reactions develop, diagnostic workup and treatment should be initiated according to the standard of care.

Thrombocytopenia and coagulation abnormalities

Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of subcutaneously or intravenously administered antisense oligonucleotides. If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of tofersen.

Renal toxicity

Renal toxicity has been observed after administration of subcutaneously and intravenously administered antisense oligonucleotides. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.

Aseptic/Chemical Meningitis:

Serious events of aseptic meningitis have been reported. Monitor for symptoms. If symptoms are consistent with this adverse event, diagnostic workup and treatment should be initiated according to standard of care.

Special populations

Use in hepatic impairment

QALSODY has not been studied in patients with hepatic impairment.

Use in renal impairment

QALSODY has not been studied in patients with renal impairment.

Use in the elderly

A total of 13.3% (22/166) ALS patients were 65 years of age and older and 1.2% (2/166) subjects were 75 years of age and older at initiation of treatment in clinical studies. There is no evidence for special dosage considerations based on age when QALSODY is administered.

Paediatric use

Safety and effectiveness in paediatric patients below the age of 18 years has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

The co-administration of other intrathecal medicinal products with tofersen has not been evaluated and the safety of these combinations is not known.

Tofersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism; therefore, it should not interfere with other medicinal products that interact with these metabolic pathways.

In vitro studies indicated that the likelihood for interactions with tofersen due to competition with or inhibition of transporters is low. Tofersen is not a substrate of BCRP and MDR1 efflux or MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters, nor is it an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC, BCRP, BSEP, and MDR1 transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data available on the potential effects on fertility in humans. Reproductive toxicology studies were conducted using subcutaneous administration of tofersen (up to 30 mg/kg, every 2 days) in mice. Male mice in the high dose group of 30 mg/kg (3.7- times the clinical AUC) had minimal to mild seminiferous tubular degeneration, seminiferous tubule dilatation, spermatid retention, apoptosis of epithelial cells, increased cellular debris in the testes, and hypospermia in the epididymis. However, there were no tofersen-related adverse effects on mating and fertility or sperm parameters. In female mice, there was no tofersen-related effects on mating or fertility up to the highest dose tested (30 mg/kg/every 2 days; 3.7- times the clinical AUC). Translation of mouse

fertility data to humans is limited based on the lack of cross-reactivity of tofersen to SOD1 in rodents. Microscopic evaluation of reproductive tissues from both males and females in the 13-week and 39-week NHP toxicology studies revealed no treatment-related changes to reproductive tissues.

Use in pregnancy – Category B2

There are no data from the use of tofersen in pregnant women. Studies in animals in which tofersen is not pharmacologically active do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Tofersen is not recommended during pregnancy and in women of childbearing potential not using contraception.

Animal data

Developmental toxicity studies in mice and rabbit using subcutaneous administration of tofersen did not identify any effects on embryo-fetal development at up to the highest dose tested (30 mg/kg every 2 days at 3.7- and 21- times the clinical AUC in mice and rabbits, respectively). In a mouse perinatal/postnatal reproduction study, there were no adverse effects on dosed dams or on the growth and the development of their pups at the highest dose evaluated (30 mg/kg every 2 days SC).

Translation of mouse and rabbit data on embryofetal development to humans is limited based on > 4 sequence mismatches within the tofersen binding site in both species, such that tofersen is not pharmacologically active in mice and rabbits.

Use in lactation

There are no data on the use of QALSODY during lactation in humans. It is unknown whether tofersen or its metabolites are excreted in human milk. A risk to the newborn or infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from tofersen therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Animal data

Tofersen was detected in mouse milk samples from all tofersen-dosed animals. There were no tofersen-related effects on either the maternal dams or offspring at doses up to 30 mg/kg/every 2 days SC (up to 3.7-times the clinical AUC).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tofersen has minor influence on the ability to drive and use machines. Patients who develop visual disturbance under tofersen should be cautioned to avoid driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of safety profile

The safety of QALSODY 100 mg was evaluated in 147 SOD1-ALS subjects. The median patient exposure was 199.7 weeks (range 4 to 321 weeks). QALSODY was evaluated in the placebo-controlled study (Study 101, Part C (VALOR)) and in the open label extension study (Study 102). Of these patients, approximately 44.2% were female; 55.8% were male; 59.9% were White; 6.8% were Asian. The mean age at study entry was 49.8 years (range 23 to 78 years).

Tabulated list of adverse reactions

Very common adverse reactions (≥ 10%) by preferred term reported in tofersen-treated subjects were pain, myalgia, arthralgia, fatigue, CSF white blood cell increased, CSF protein increased, and pyrexia.

The corresponding frequency category for each adverse drug reaction (ADR) is based on the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from available data). ADRs are presented by MedDRA system organ class (SOC), frequency, and ADR.

Table 1. Adverse Drug Reactions (ADRs) with Tofersen Treated Patients in Study 101 and Study 102

System Organ Class (SOC)	Preferred term	Study 101 Part C		Study 101 and Study 102	
		Placebo (n = 36) n/N (%)	QALSODY 100 mg (n = 72) n/N (%)	QALSODY 100 mg (n = 147) n/N (%)	Frequency
Nervous system disorders	CSF white blood cell increased*	0/36 (0)	10/72 (13.9)	41/147 (27.9)	Very common
	CSF protein increased	1/36 (2.8)	6/72 (8.3)	39/147 (26.5)	Very common
	Papilloedema‡	0	0	9/147 (6.1)	Common
	Neuralgia	0/36 (0)	4/72 (5.6)	7/147 (4.8)	Common
	Aseptic Meningitis††	0/36 (0)	1/72 (1.4)	6/147 (4.1)	Common
	Radiculitis†	0/36 (0)	1/72 (1.4)	6/147 (4.1)	Common
	Myelitis§	0/36 (0)	2/72 (2.8)	6/147 (4.1)	Common
Musculoskeletal and connective tissue disorders	Arthralgia	2/36 (5.6)	10/72 (13.9)	54/147 (36.7)	Very common
	Myalgia	2/36 (5.6)	10/72 (13.9)	33/147 (22.4)	Very common
	Musculoskeletal stiffness	0/36 (0)	4/72 (5.6)	11/147 (7.5)	Common

System Organ Class (SOC)	Preferred term	Study 101 Part C		Study 101 and Study 102	
		Placebo (n = 36) n/N (%)	QALSODY 100 mg (n = 72) n/N (%)	QALSODY 100 mg (n = 147) n/N (%)	Frequency
General disorders and administration site conditions	Pain‡‡	8/36 (22.2)	30/72 (41.7)	101/147 (68.7)	Very common
	Fatigue	2/36 (5.6)	12/72 (16.7)	45/147 (30.6)	Very common
	Pyrexia	1/36 (2.8)	3/72 (4.2)	30/147 (20.4)	Very common

* CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis.
† Radiculitis includes preferred terms of radiculopathy and lumbar radiculopathy.
‡ Papilloedema includes preferred terms of papilloedema and intracranial pressure increased. See discussion in Description of selected adverse events (AEs).
§ Myelitis includes preferred terms of myelitis, myelitis transverse, and neurosarcoidosis. See discussion in Description of selected adverse events.
†† Aseptic meningitis includes preferred terms of meningitis chemical and meningitis aseptic. See discussion in Description of selected adverse events.
‡‡ Pain includes preferred terms of pain, back pain, and pain in extremity.
Note: Table 1 represents cases of serious and non-serious ADRs.

Description of selected adverse events

Lumbar-puncture-related events

Adverse events associated with the administration of QALSODY by lumbar puncture, such as headache, back pain, and post lumbar puncture syndrome, have been observed. The incidence and severity of these events were consistent with events expected to occur with lumbar puncture.

Myelitis and/or radiculitis

Eight tofersen-treated subjects experienced serious events of myelitis or radiculitis while receiving tofersen 100 mg treatment in the clinical studies. Two subjects discontinued treatment, and both events resolved. In the remaining six subjects, the events did not lead to discontinuation of treatment, see section 4.4.

Increased intracranial pressure and/or papilloedema

A total of 4 serious events in tofersen-treated subjects involving elevated intracranial pressure and/or papilloedema were reported in Study 102. No events led to discontinuation of tofersen, and all were manageable with standard of care, see section 4.4.

Aseptic or chemical meningitis

One subject experienced a serious event of chemical meningitis which led to discontinuation of tofersen. One additional serious event of aseptic meningitis occurred in Study 102 and did not lead to discontinuation of tofersen. Nonserious ADRs of CSF white blood cell increased and CSF protein increased have also been reported with tofersen, see section 4.4.

4.9 OVERDOSE

No cases of overdose associated with QALSODY were reported in clinical studies.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX22

Mechanism of action

The human SOD1 gene encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), which catalyses the transmutation of superoxide (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2). In SOD1-ALS patients, mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein, resulting in axonal injury and neurodegeneration. Tofersen is antisense oligonucleotide that is complementary to a portion of the 3' untranslated region (3'UTR) of the mRNA for human SOD1 and binds to the mRNA 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.

Pharmacodynamics Effects

Total CSF SOD1 protein biomarker

Total CSF SOD1, an indirect measure of target engagement, was formally tested in Study 101 Part C (VALOR) in the mITT and non-mITT populations and informally in the ITT population. The results were consistent in all populations analysed.

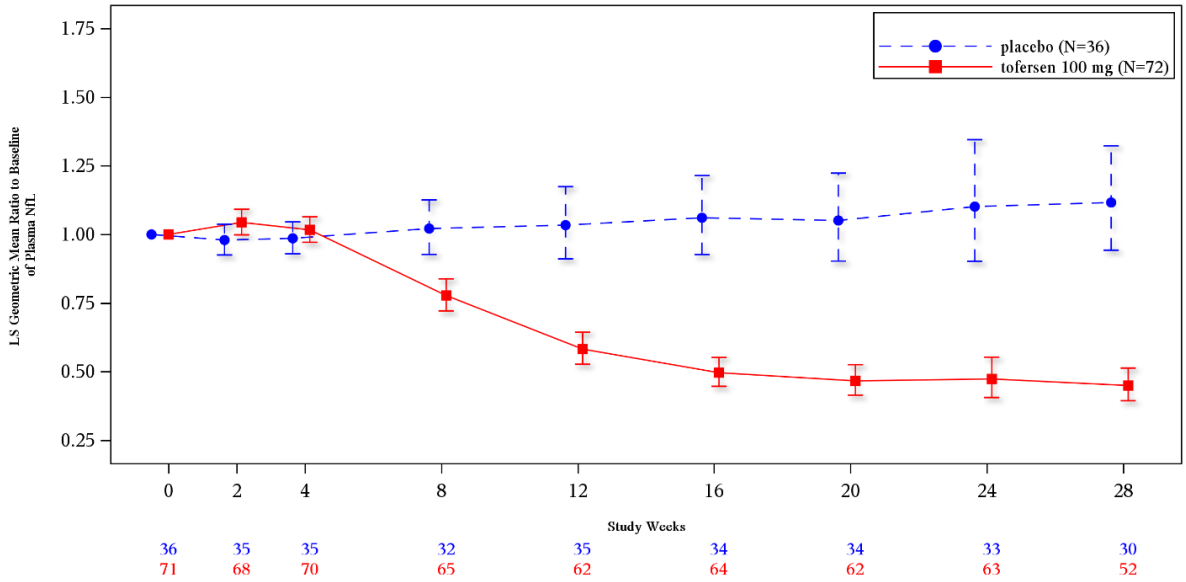
At Week 28 in Study 101 Part C, a reduction in total CSF SOD1 protein of 35% (geometric mean ratio to baseline) in the tofersen-treated group versus a 2% decrease from baseline in the corresponding placebo subjects in the ITT population was observed (difference in geometric mean ratios for tofersen to placebo: 34%; nominal $p < 0.0001$). Total CSF SOD1 declined until approximately Day 56, after which the reductions were sustained.

Plasma NfL (neurofilament light chain) biomarker

Plasma NfL, a blood-based biomarker of axonal injury and neurodegeneration, was formally tested as a secondary endpoint in Study 101 Part C in the mITT population and informally in the non mITT and ITT populations. The results were consistent in all populations analysed.

At Week 28 in Study 101 Part C, mean plasma NfL was reduced 55% (geometric mean ratio to baseline) in the tofersen-treated subjects (ITT), compared to a 12% increase with placebo (difference in geometric mean ratios for tofersen to placebo: 60%; nominal $p < 0.0001$). Plasma NfL declined until approximately Day 113, after which the reductions were sustained. The reductions in phosphorylated neurofilament heavy chain (pNfH) were consistent compared to NfL as were reductions in CSF compared to plasma. At the time of the final integrated analysis across Study 101 Part C and Study 102, the reductions in NfL were sustained at Week 148 and Week 176. Similar reductions in NfL were observed in the placebo/delayed start group after initiating tofersen in Study 102.

Figure 1. Study 101 Part C: plasma NfL adjusted geometric mean ratio to baseline values by study week for the ITT population



Abbreviations: NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

Note 1: Baseline is defined as day 1 value prior to the clinical 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: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 4.9 pg/mL) in calculations. Multiple imputation is used for missing data.

Note 3: The analysis is based on ANCOVA model with natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, baseline disease duration since symptom onset, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.

Note 4: The table at the bottom presents the number of subjects with observed non-missing data at each visit.

Cardiac Electrophysiology

ECG (electrocardiogram) measurements and the values for the tofersen 100 mg group (n = 41) were similar to placebo group (n = 34) in Study 101 Part C. The incidence of abnormalities in ECG measurements was slightly higher in the tofersen group compared to the placebo group, with 8 subjects (11.3%) displaying a maximum increase from baseline in Fridericia formula (QTcF) > 30 to 60 ms in the tofersen group compared to 2 subjects (5.6%) in the placebo group. No subjects in the tofersen or placebo group displayed an increase from baseline in QTcF > 60 ms, and no subjects displayed maximum postbaseline QTcF > 480 ms. Results of this analysis suggested the absence of a concentration dependent QTcF prolongation with tofersen by demonstrating that there is a lack of QTcF prolongation for the 5th to 95th percentiles of the observed tofersen concentration range (1.14 to 1440 ng/mL). The slope of the tofersen concentration effect was estimated to be approximately zero, indicating the tofersen concentration is not a clinically relevant predictor of QTcF and tofersen is not anticipated to prolong the QTcF interval.

Clinical studies

Efficacy

The efficacy of QALSODY was assessed in a 28-week randomised, double-blind, placebo-controlled clinical study (Study 101, Part C) in subjects aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation confirmed by central laboratory. One hundred eight (108) subjects were

randomised 2:1 to receive treatment with either QALSODY 100 mg or placebo for 24 weeks (3 loading doses followed by 5 maintenance doses). Forty-two (42) unique SOD1 mutations were evaluated, with the most common being p.Ile114Thr (n = 20), p.Ala5Val (n = 17), p.Gly94Cys (n = 6), and p.His47Arg (n = 5). Concomitant riluzole and/or edaravone use was permitted for subjects who were on a stable dose for at least 30 or 60 days prior to study baseline, respectively.

The prespecified primary analysis population (n = 60, modified intent to treat [mITT]) had a Study 101 SVC (slow vital capacity) ≥ 65% of predicted value as adjusted for sex, age, and height (from the sitting position) at screening and met prognostic enrichment criteria for rapid disease progression, defined based on their pre-randomisation ALS Functional Rating Scale–Revised (ALSFRS-R) decline slope and SOD1 mutation type as follows:

One of the following SOD1 mutations and a pre-randomisation ALSFRS R decline slope ≥ 0.2 points per month (calculated as [48 minus baseline ALSFRS-R total score]/time since symptom onset):

p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly

OR

SOD1 mutation other than those listed above with pre-randomisation ALSFRS R decline slope ≥ 0.9 points per month (calculated as [48 minus baseline ALSFRS-R total score]/time since symptom onset)

The non-mITT population (n = 48) had an SVC ≥ 50% of predicted value as adjusted for sex, age, and height (from the sitting position) at screening.
Baseline disease characteristics in the overall intent to treat (ITT) population were generally similar in the QALSODY-treated subjects and placebo treated subjects, with slightly shorter time from symptom onset and higher plasma NfL at baseline in the tofersen group (Table 2).

Table 2. Baseline and disease characteristics in Study 101 Part C

	ITT (n = 108)			**ITT (n = 108)**	
Baseline and disease characteristics*	**Placebo (n = 36)**	**Tofersen 100 mg (n = 72)**	**Baseline and disease characteristics**	**Placebo (n = 36)**	**Tofersen 100 mg (n = 72)**
Site of onset n(%)			**ALSFRS-R baseline total score:**		
Bulbar	3 (8)	3 (4)	mean (SD)	37.3 (5.81)	36.9 (5.91)
Lower limbs	26 (72)	46 (64)	Range: min, max	24, 47	15, 48
Upper limbs	7 (19)	20 (28)			
Respiratory	0	1 (1)			
Multiple sites	0	2 (3)			
Riluzole Use‡ Yes n (%)	22 (61)	45 (63)	**% predicted SVC at baseline:**		
			mean (SD)	85.1 (16.53)	82.1 (16.59)
			Range: min, max	54.8, 120.4	46.7, 134.7

Baseline and disease characteristics*	ITT (n = 108)		Baseline and disease characteristics	ITT (n = 108)	
	Placebo (n = 36)	Tofersen 100 mg (n = 72)		Placebo (n = 36)	Tofersen 100 mg (n = 72)
Edaravone Use[†,‡] Yes n (%)	3 (8)	6 (8)	**Plasma NfL at baseline (pg/mL)**		
Time from symptom onset (months): median (min, max)	14.6 (2.4, 103.2)	11.4 (1.7, 145.7)	mean (SD) Geometric mean Range: min, max	89.7 (86.5) 56.6 8, 370	100.4 (82.8) 66.6 5, 329

ALSFRS-R =Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; SVC = Slow Vital Capacity; NfL = neurofilament light

* Most common mutations i.e. N > 4 subjects: a total of 42 SOD1 mutations in 108 subjects were studied with the most common being p.Ile114Thr (N = 20), p.Ala5Val (N = 17), p.Gly94Cys (N = 6) and p.His47Arg (N = 5).

† All subjects receiving edaravone were also receiving riluzole.

‡ Concomitant use of riluzole and/or edaravone were allowed assuming the individual was on a stable dose for at least 30 or 60 days prior to Day 1, respectively, and expected to remain on that dose through end of study. Randomization was stratified within each of the subgroups for disease progression based on the use of edaravone and the use of riluzole at baseline to balance across treatment arms.

The primary efficacy analysis was the change from baseline to Week 28 in the ALSFRS-R total score in the mITT population, analysed using the joint rank test to account for mortality in conjunction with multiple imputation (MI) to handle missing data for withdrawals other than death. The results numerically favoured tofersen but were not statistically significant (tofersen-placebo adjusted mean difference [95% CI]: 1.2 [-3.2, 5.5]).

In the ITT population during the 28 week follow up period, the median time to death and/or permanent ventilation was not estimable due to the limited number of events observed. In the QALSODY group, 1.4% of subjects died compared to 0.0% in the placebo group. In the QALSODY and placebo groups, 5.6% of subjects died or had an event of permanent ventilation.

In post hoc analyses in the ITT population, trends favouring tofersen over placebo were observed across measures of clinical function (ALSFRS-R), respiratory function (SVC), and strength (handheld dynamometry [HHD] megascore) over 28 weeks (Table 3).

Table 3. Effect of tofersen from Study 101 Part C baseline for the ITT population

Endpoint	**Study 101 Part C*** Change from baseline to Week 28 Tofersen (n = 72) versus placebo (n = 36)
Change from baseline on ALSFRS-R total score	
Adjusted means: Tofersen; Placebo	-4.1; -6.2
Tofersen-placebo: adjusted mean difference (95% CI)	2.1 (-0.3, 4.5)
Nominal p-value (ANCOVA+MI)	0.0904
Change from baseline on %-predicted SVC	
Adjusted means: Tofersen; placebo	-7.3; -15.8
Tofersen-placebo: adjusted mean difference (95% CI)	8.5 (1.8, 15.2)
Nominal p-value (ANCOVA+MI)	0.0128
Change from baseline on HHD megascore	
Adjusted means: Tofersen; placebo	-0.23; -0.32
Tofersen-placebo: adjusted mean difference (95% CI)	0.10 (-0.04, 0.23)
Nominal p-value (ANCOVA+MI)	0.1547

* Post-hoc analyses adjusting for baseline plasma NfL

Notes:

A negative change from baseline indicates a worsening in function. Interpretation of these results are limited due to short duration of treatment and small number of subjects. Nominal p-values are presented.

For ITT analyses adjusted for baseline plasma NfL the multiple imputation (MI) model is based on all subjects in the ITT population and includes baseline plasma NfL, treatment, use of riluzole or edaravone, relevant baseline score and post-baseline values.

Adjusted means, treatment difference and corresponding 95% CIs and nominal p-values are obtained from the ANCOVA model for change from baseline in conjunction with multiple imputation. The ANCOVA models for include treatment as a fixed effect and adjust for the following covariates: baseline plasma NfL, relevant baseline score, and the use of riluzole or edaravone.

Integrated results of Study 101 Part C and Study 102

To allow for long-term follow up of these subjects, at the end of Study 101 Part C, 88% of subjects (95/108) (QALSODY 100 mg: n = 63; placebo: n = 32) enrolled in Study 102, an open-label extension study with a blinded loading dose period for subjects who previously participated in Study 101 Part C. In Study 102, all subjects received QALSODY 100 mg. At the time of tofersen initiation, subjects in the placebo/delayed-start group had a mean percent-predicted SVC value of 68.7 (SD: 25.8; range 21.6 to 113.7) and total ALSFRS-R score of 30.9 (SD: 9.2; range: 12 to 44). The median follow-up across the 2 studies at the time of the interim analysis (cut-off date 16 January 2022) for subjects who participated in Study 101 Part C, was 1.7 years (range: 0.08 to 2.82 years). At the time of the interim analysis, 62% (67/108) of subjects remained ongoing in Study 102. At the time of the final integrated analysis of Study 101 Part C and Study 102, 33.3% (12/36) of subjects in the placebo/delayed-start group and 47.2% (34/72) of subjects in the early-start group completed Study 102. The median opportunity for follow-up across the two studies was 4.9 years (range: 3.6 to 5.4 years). An accounting of subject disposition at the time of the final integrated analysis is provided in Table 4.

Table 4. Subject disposition as of the final integrated analysis of Study 101 Part C and Study 102 for the ITT population

Subjects	Early-start Tofersen 100 mg (n = 72)	Placebo/delayed-start Tofersen 100 mg (n = 36)
Dosed in Study 101 Part C n (%)	72 (100)	36 (100)
Dosed in Study 102 n (%)	63 (88)	32 (89)
Completed Study 101 Part C but not enrolled in Study 102 n (%)	1 (1.4)	1 (2.8)
Completed in Study 102 n (%)	34 (47.2)	12 (33.3)
Died while on study n (%)	15 (20.8)	7 (19.4)
Withdrew from study n (%) AE Consent withdrawn Death Disease progression	37 (51.4) 2 (2.8) 7 (9.7) 15 (20.8) 10 (13.9)	23 (63.9) 0 7 (19.4) 7 (19.4) 7 (19.4)

Note: Percentages are based on overall ITT population (i.e., all participants randomized and dosed in Study 101 Part C)

Interim Integrated Analysis

At the time of the interim analysis, across Study 101 Part C and Study 102 combined, there were 12 (16.7%) subjects with death or permanent ventilation in those who initiated QALSODY 100 mg in Study 101 Part C ('early-start' (ES) group) in the ITT population and 8 (22.2%) in those who initiated QALSODY 100 mg in Study 102 ('placebo/delayed-start' (DS) group). Earlier initiation of tofersen (ES group) was associated with an apparent reduction in the risk of death or permanent ventilation (HR [95% CI]: 0.36 [0.14, 0.94]) and risk of death (HR [95% CI]: 0.27 [0.08, 0.89]). Median time to event was not estimable.

Earlier initiation of tofersen (ES group) was associated with a reduction of decline on ALSFRS-R, SVC percent predicted, and HHD megascore over 52 weeks from the start of Study 101 Part C as compared to placebo/delayed initiation of tofersen (DS group); see Table 5, Figure 2, Figure 3, and Figure 4.

Table 5. Analyses of clinical outcome measures for Study 101 Part C and Study 102* integrated data at Week 52 for the ITT population

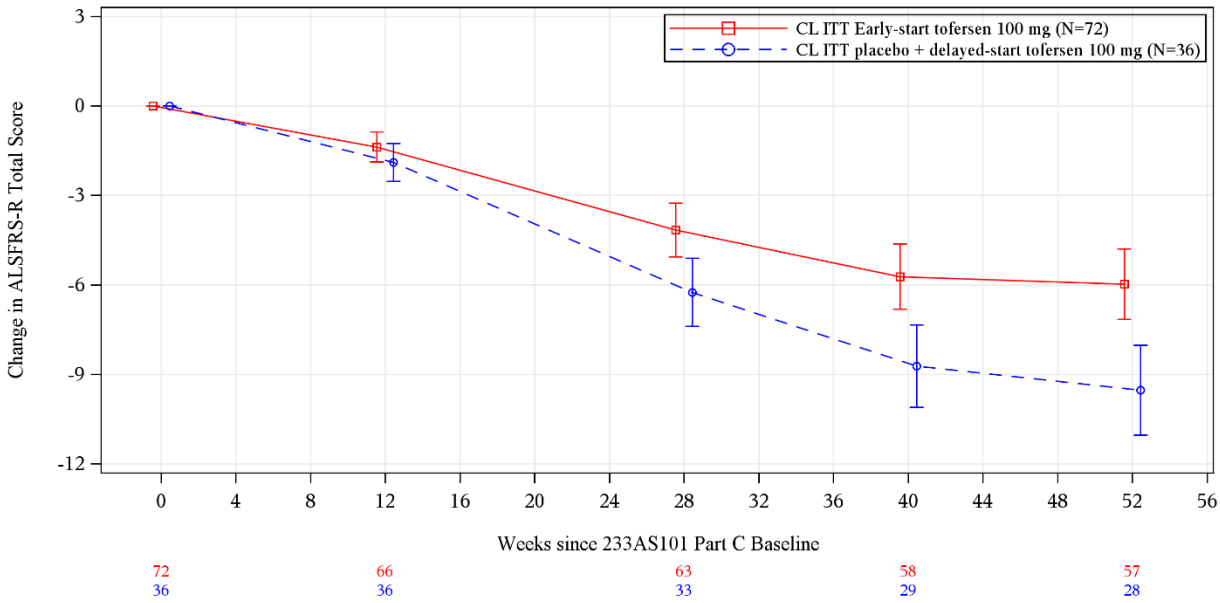
Endpoint	Study 101 Part C & Study 102†		
	Early-start tofersen 100 mg (n = 72) Adjusted mean	Placebo/delayed-start tofersen 100 mg (n = 36) Adjusted mean	Adjusted mean difference (95% CI) Nominal p-value
ALSFRS-R total score change from Study 101 Part C baseline to Week 52	-6.0	-9.5	3.5 (0.4, 6.7) 0.0272
SVC %-predicted change from Study 101 Part C baseline to Week 52	-9.4	-18.6	9.2 (1.7, 16.6) 0.0159
HHD megascore change from Study 101 Part C baseline to Week 52	-0.17	-0.45	0.28 (0.05, 0.52) 0.0186

* Interim analysis for Study 102

† Adjusted means, treatment difference and corresponding 95% CIs and nominal p-values are obtained from the ANCOVA model for change from baseline in conjunction with multiple imputation. The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, relevant baseline value, and use of riluzole or edaravone.

Notes: Baseline is defined using Study 101 Part C baseline. For ITT analyses the multiple imputation model is based on all subjects in the ITT population and includes baseline plasma NfL, treatment, use of riluzole or edaravone, relevant baseline value and post-baseline values.

Figure 2. Adjusted mean change from baseline ± SE in ALSFRS-R total score over time – ANCOVA + MI (ITT)



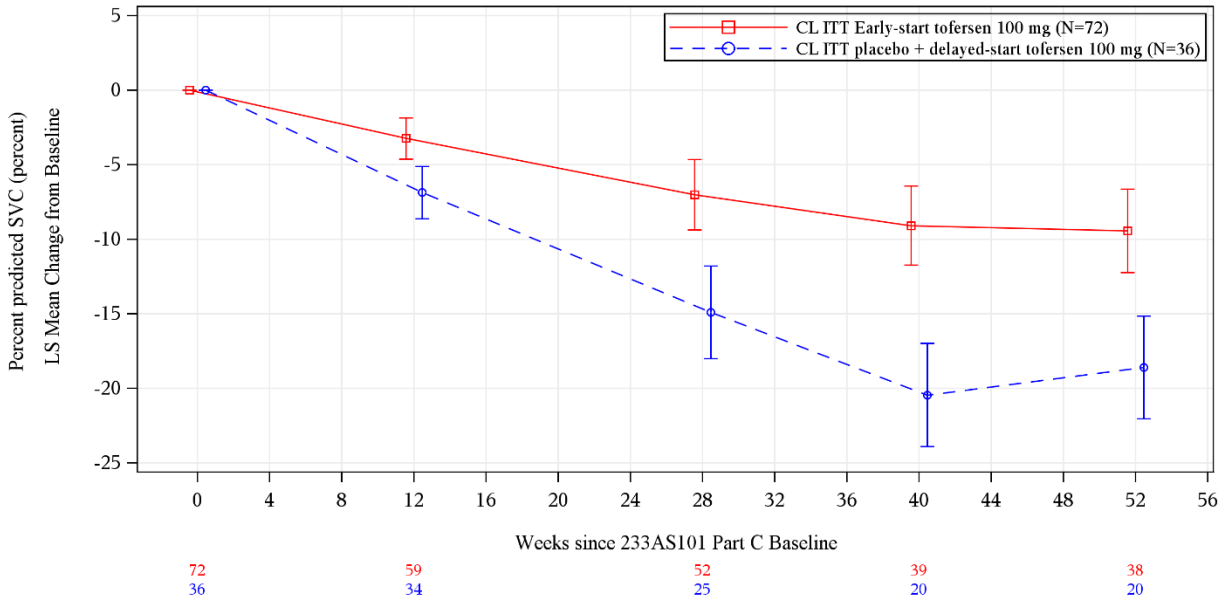
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

Note 1: Baseline is defined as day 1 value prior to the clinical study drug and presented as Day 1. 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: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

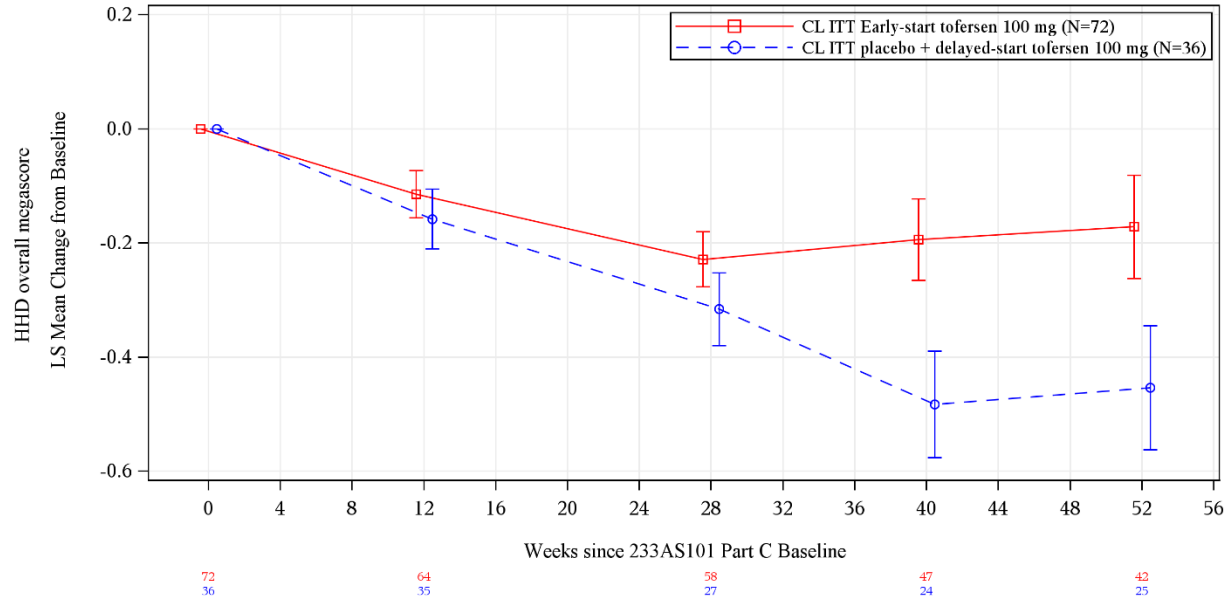
Note 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Note 5: Subjects that were randomised to placebo in Study 101 Part C and continued to Study 102 received tofersen after Week 28.

Figure 3. Adjusted mean change from baseline ± SE in % Predicted SVC over time – ANCOVA + MI (ITT)



Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square; ATS = the American Thoracic Society.
Note 1: Baseline is defined as day 1 value prior to the clinical study drug and presented as Day 1. 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: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
Note 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Note 5: Subjects that were randomised to placebo in Study 101 Part C and continued to Study 102 received tofersen after Week 28.

Figure 4. Adjusted mean change from baseline ±SE in HHD megascore over time – ANCOVA + MI (ITT)



Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

Note 1: Baseline is defined as day 1 value prior to the clinical study drug and presented as Day 1. 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: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

Note 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.

Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.

Note 5: Subjects that were randomised to placebo in Study 101 Part C and continued to Study 102 received tofersen after Week 28.

Final Integrated Analysis

At the time of the final integrated analysis across Study 101 Part C and Study 102 combined, earlier initiation of tofersen compared to placebo/delayed initiation of tofersen was associated with continued trends for reduction of decline in ALSFRS-R, SVC percent-predicted, and hand-held dynamometry (HHD) megascore, although the differences were not statistically significant. Earlier initiation of tofersen (ES group) was associated with an apparent reduction in the risk of death or permanent ventilation (HR [95% CI]: 0.64 [0.28, 1.46]) and risk of death (HR [95% CI]: 0.52 [0.20, 1.36]). Median time-to-event was not estimable in the ITT population. In the faster-progressing subgroup (defined according to baseline plasma NfL level equal to or above the median [75.6 pg/mL]), the median time to death or permanent ventilation in the early-start group was 253.6 weeks compared with 76.0 weeks in the placebo/delayed-start group, representing an approximately 3.4-year extension of event-free-survival compared with initiation of tofersen 6 months later (DS group).

5.2 PHARMACOKINETIC PROPERTIES

The single and multidose pharmacokinetics of tofersen, administered via intrathecal injection, were characterised in plasma and CSF of adult ALS patients with a SOD1 mutation and in autopsy tissue from deceased clinical study subjects. PK analysis demonstrate that IT administered tofersen is widely distributed into CNS tissues and is rapidly transferred from CSF to the systemic circulation.

Absorption

The maximum CSF trough concentration occurred at the third dose, which was the last dose of the loading period. There was little to no accumulation with monthly dosing after the loading phase; the accumulation ratio appears to be less than 2-fold. Tofersen is rapidly transferred from CSF into the systemic circulation, with a median time to maximum concentration (T_{max}) plasma values ranged from 2 to 6 hours post IT administration. There was no accumulation in plasma exposure measures (C_{max} and AUC) after monthly maintenance dosing.

Distribution

Autopsy tissue from tofersen-treated patients (n = 3) showed that tofersen administered intrathecally was extensively distributed within the CNS, achieving therapeutic levels in the target spinal cord tissues. The CNS maintained therapeutic levels in the target tissues at a steady state level within the estimated pharmacologically active range which were attained immediately after the loading phase, with little to no accumulation with monthly maintenance dosing.

Metabolism

Tofersen is metabolised predominantly through exonuclease (3' and 5')-mediated hydrolysis and is not a substrate for or inhibitor or inducer of CYP450 enzymes.

Excretion

The primary route of elimination is expected via urinary excretion of unchanged tofersen and its metabolites. Although CNS tissue half-life cannot be measured in humans, the mean terminal elimination half-life was measured in the CNS tissue of cynomolgus monkeys and found to be 31 to 40 days. The effective half-life in CSF of approximately 4 weeks supports a monthly maintenance dosing interval.

Immunogenicity

The presence of anti-drug antibodies (ADAs) decreased plasma clearance by 37.9% but had no effect on drug concentrations in the CSF. The impact of ADAs was evaluated but was not identified as a significant covariate for either the SOD1 protein or NfL PKPD models.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tofersen demonstrated no evidence of mutagenicity based on nonclinical genotoxicity studies (*in vitro* Ames bacterial mutagenicity, *in vitro* chromosome aberration, and *in vivo* mouse micronucleus assays).

Carcinogenicity

Carcinogenicity studies with tofersen have not been performed.

Toxicology

Evidence of myelitis was not observed in the repeat-dose nonclinical toxicology studies for tofersen in mouse (up to 150 mg/kg, SC) and cynomolgus monkey (up to 35 mg/body, IT). However, vacuolation of neurons in brain and spinal cord as well as mononuclear cell infiltrates in spinal cord/nerve roots were seen in monkeys treated with tofersen at CSF exposures that were 6-times the clinical exposure. These findings have been observed with other antisense oligonucleotide (ASO) treatments. None of these findings were associated with degenerative changes in the brain or spinal cord. Tofersen was not detected in mouse brain following SC administration.

Tofersen demonstrated a very low potential for cardiac IKR (hERG channel) inhibition (IC_{50} > 34 µM) in vitro and did not produce adverse effects on cardiovascular safety pharmacology endpoints in nonhuman primates at the highest dose tested (35 mg/body, IT) which is 13-times the clinical AUC.

In a repeat-dose toxicology study (9 months), IT administration of tofersen to adult cynomolgus monkeys was generally well-tolerated. The exception was one out of four females in the high dose group (35 mg) that had behaviour described as muscle cramping, head/neck dorsiflexion, and opisthotonos-like-back-arching posture after IT dosing, with CSF and AUC exposures that were 3 and 13 times, respectively, the exposures observed clinically. Electroencephalogram (EEG) indicated the absence of seizure. The no observed adverse effect levels (NOAELs) in the repeat dose chronic toxicology studies were 150 mg/kg subcutaneous administration in the mouse (28-times the clinical AUC) and 12 mg intrathecal administration in the 9-month nonhuman primate (with CSF and AUC exposures that were 1.3- and 2.2- times the respective clinical exposures).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate
Potassium chloride
Calcium chloride dihydrate
Magnesium chloride hexahydrate
Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed.

6.3 SHELF LIFE

42 months.

<u>In-use Shelf Life</u>

The vial of QALSODY in its original carton to protect from light can be stored for up to 14 days at room temperature (not to exceed 30°C).

Unopened vials of QALSODY can be removed from and returned to the refrigerator, if necessary. Unopened vials can be removed from the original carton for not more than 6 hours per day at room temperature for a maximum of 6 days.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store refrigerated at 2°C to 8°C.
Do not freeze.
Store in the original package in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

15 mL of solution for intrathecal injection in a 20 mL neutral borosilicate clear Type I glass vial with latex-free chlorobutyl rubber stopper and an aluminium overseal with flip-off plastic button.

Product in container closure system is sterile and non-pyrogenic.

QALSODY is available in pack of 1 vial.

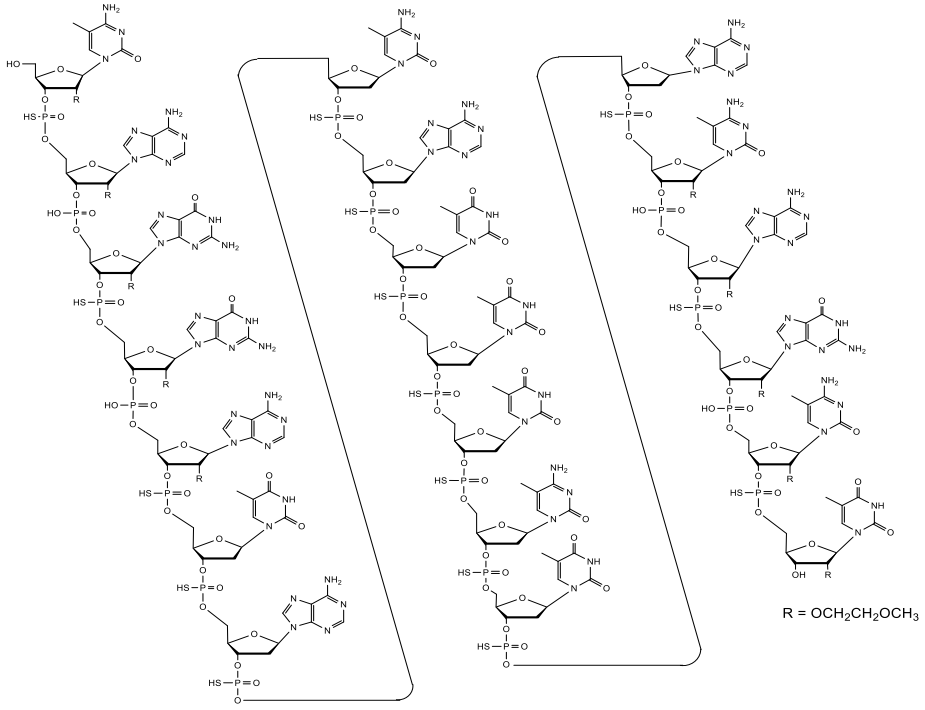
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

QALSODY is for single use in one patient only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Long form for chemical name:

Tofersen is named based on accepted oligonucleotide nomenclature, showing each 3′-O to 5′-O-linked phosphorothioate or phosphorodiester internucleotide linkage as follows:

2-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(*3′-O→5′-O*) -2′-*O*-(2-methoxyethyl)-adenylyl-(*3′-O→5′-O*)-2′-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(*3′-O→5′-O*) -2′-*O*-(2-methoxyethyl)-guanylyl-(*3′-O→5′-O*)-2′-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thiothymidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thioadenylyl-(*3′-O→5′-O*) -2′-deoxy-5-methyl-*P*-thiocytidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thioadenylyl-(*3′-O→5′-O*) -2′-deoxy-*P*-thiothymidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thiothymidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thiothymidylyl-(*3′-O→5′-O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thiothymidylyl-(*3′-O→5′-O*)-2′-deoxy-*P*-thioadenylyl-(*3′-O→5′-O*) -2′-*O*-(2-methoxyethyl)-5-methylcytidylyl-(*3′-O→5′-O*)-2′-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(*3′-O→5′-O*) -2′-*O*-(2-methoxyethyl)-guanylyl-(*3′-O→5′-O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(*3′-O→5′-O*) -2′-*O*-(2-methoxyethyl)-5-methyluridine

Short form for chemical name:

5′ - ^{Me}CsAoGsGoAsTsAs^{Me}CsAsTsTsTs^{Me}CsTsAs^{Me}CoAsGo^{Me}Cs^{Me}U- 3′

The underlined residues are 2′-O-(2-methoxyethyl) nucleosides and the other residues are deoxy nucleosides. The locations of phosphorothioate and phosphate diester linkages are designated by s and o, respectively.

Australian approved name: tofersen

Molecular formula: $C_{230}\ H_{317}\ N_{72}\ O_{123}\ P_{19}\ S_{15}$ (free acid form)

Exact mass: 7123.1589 - (free acid form)

Molecular weight (Molar mass): 7127.86 atomic mass units (amu)

CAS number: 2088232-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Biogen Australia Pty Ltd
ABN 30 095 760 115
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Macquarie Park NSW 2113
Australia
Website: www.biogen.com.au

9 DATE OF FIRST APPROVAL

17 April 2026

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information