Report on the Deliberation Results

December 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Qalsody Intrathecal Injection 100 mg
Non-proprietary Name	Tofersen (JAN*)
Applicant	Biogen Japan Ltd.
Date of Application	May 21, 2024

Results of Deliberation

In its meeting held on December 2, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients have been gathered.

**Japanese Accepted Name (modified INN)*

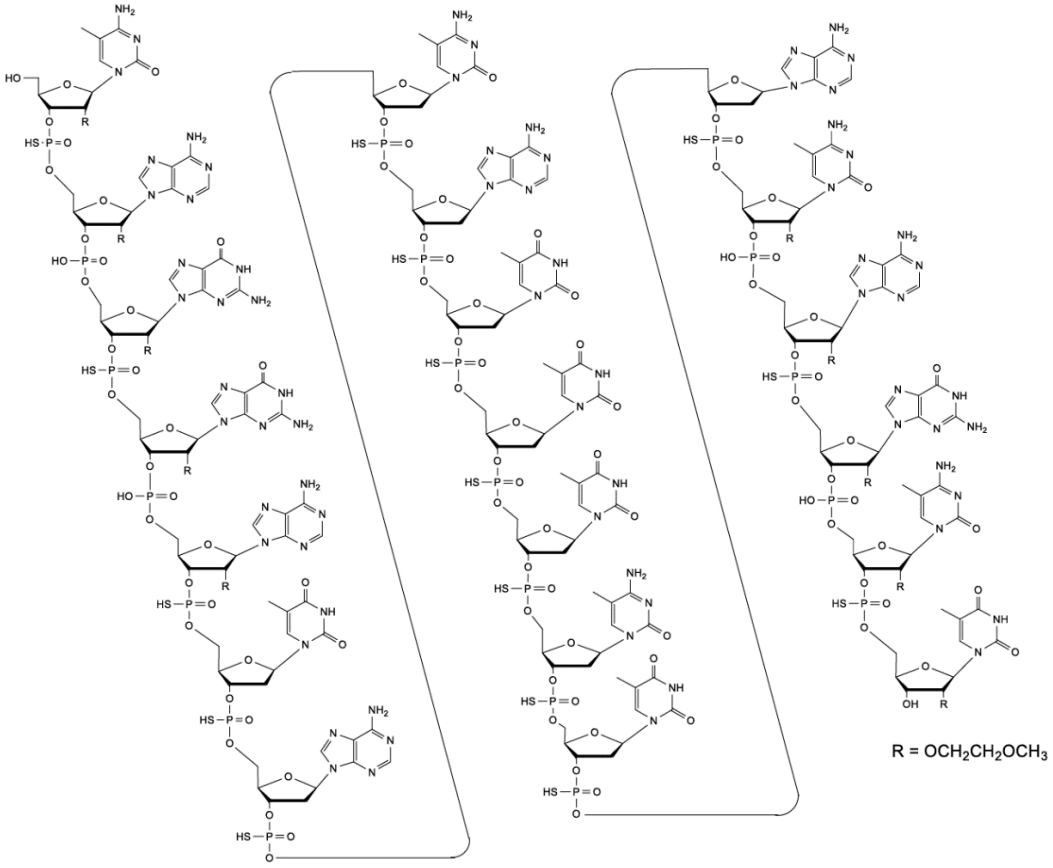
Review Report

November 20, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Qalsody Intrathecal Injection 100 mg
Non-proprietary Name	Tofersen
Applicant	Biogen Japan Ltd.
Date of Application	May 21, 2024
Dosage Form/Strength	Aqueous injection in a vial (15 mL): Each vial contains 100 mg of tofersen.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{230}H_{317}N_{72}O_{123}P_{19}S_{15}$

Molecular weight: 7127.86

Chemical name: *all-P-ambo*-2'-*O*-(2-Methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)adenylyl-(3' → 5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)guanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3' → 5')-*P*-thiothymidylyl-(3' → 5')-2'-deoxy-*P*-thioadenylyl-(3' → 5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3' → 5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3' → 5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3' → 5')-*P*-thiothymidylyl-(3' → 5')-2'-deoxy-*P*-thioadenylyl-(3' → 5')-2'-*O*-(2-methoxyethyl)-5-methylcytidylyl-(3' → 5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3' → 5')-2'-*O*-(2-methoxyethyl)guanylyl-(3' → 5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyluridine

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 489 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 1125-9 dated November 25, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in slowing the progression of functional impairment in patients with amyotrophic lateral sclerosis associated with a mutation in the *SOD1* gene, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Slowing the progression of functional impairment in patients with amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene

Dosage and Administration

The usual adult dosage is 100 mg of tofersen administered intrathecally over 1 to 3 minutes. The first 3 doses are administered every 2 weeks, and the subsequent doses are administered every 4 weeks.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients have been gathered.

Attachment

Review Report (1)

October 23, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Qalsody Intrathecal Injection 100 mg
Non-proprietary Name	Tofersen
Applicant	Biogen Japan Ltd.
Date of Application	May 21, 2024
Dosage Form/Strength	Aqueous injection in a vial (15 mL): Each vial contains 100 mg of tofersen.

Proposed Indication

Amyotrophic lateral sclerosis associated with a mutation in the *SOD1* gene (SOD1-ALS)

Proposed Dosage and Administration

The usual dosage is 100 mg of tofersen administered as an intrathecal injection of 15 mL. The first 3 doses are administered every 2 weeks, and the subsequent doses are administered every 4 weeks. Each dose is administered intrathecally over 1 to 3 minutes.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons and classified as a designated intractable disease (Public Notice No. 393-2 of the Ministry of Health, Labour and Welfare dated October 21, 2014). The major symptoms are progressive muscular weakness and muscle atrophy affecting skeletal muscles throughout the body. As the disease advances, the ability to perform activities of daily living declines progressively, and bulbar palsy and respiratory muscle paralysis may develop, potentially leading to pneumonia aspiration and respiratory failure, respectively. In Japan, the 1-year prevalence of ALS is 9.9 per 100,000 people (Practical Guideline for Amyotrophic Lateral Sclerosis 2023, Drafting Committee for Practical Guideline for Amyotrophic Lateral Sclerosis ed.), and approximately 2% of ALS cases are deemed to be caused by a mutation of the superoxide dismutase 1 (*SOD1*) gene (*Neuroepidemiology.* 2021;10:1-12, J *Neurol Neurosurg Psychiatry.* 2017;88:540-9, etc.). The SOD1 protein, encoded by the*SOD1* gene, is localized in cytoplasm and an enzyme that catalyzes degradation of superoxide, oxygen radical, into oxygen and hydrogen peroxide *(J Biol Chem.* 1969;244:6049-55). More than 200 *SOD1* gene mutations related to ALS have been identified to date, and depending on the type of gene mutation, the progression rate and duration of the disease greatly vary (*J Neurol Neurosurg Psychiatry.* 2017;88:99-105, *Nat Commun.* 2022;13:6901). The natural history of ALS attributable to an *SOD1* gene mutation extremely varies, and the mechanism of onset remains to be fully elucidated, but accumulation of SOD1 protein with abnormal functions caused by an *SOD1* gene mutation is considered responsible for the onset (*Proc Natl Acid Sci USA.* 2000;97:12571-6, *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2000;1:163-84).

Tofersen, which was discovered by Ionis Pharmaceuticals, is an antisense oligonucleotide (ASO) that targets the 3'-untranslated region of *SOD1* messenger ribonucleic acid (mRNA) and, by binding to *SOD1* mRNA, enhances degradation of mRNA catalyzed by ribonuclease H (RNase-H). The enhanced degradation is expected to reduce synthesis and accumulation of SOD1 protein and thereby prevent degeneration of motor neurons. Outside Japan, tofersen was approved for the indication of ALS with an *SOD1* gene mutation in April 2023 in the US, May 2024 in Europe, and September 2024 in China.

The applicant has submitted the application for marketing approval in Japan based on results from a global phase III study, which demonstrates the efficacy and safety of tofersen in treatment of ALS with an *SOD1* gene mutation.

Tofersen has been designated as an orphan drug for the intended indication of "Amyotrophic lateral sclerosis" (Orphan Drug Designation No. 489 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 1125-9 dated November 25, 2020).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

A solution of the drug substance is a colorless to pale-yellow clear solution, and the pH and dissociation constant are determined. The drug substance is a 20-mer oligonucleotide of which 10 have methoxyethyl at 2'-hydroxy group of ribose (2'-*O*-(2-methoxyethyl)-D-ribose) and internucleotide linkages are

replaced with phosphorothioate diester or phosphodiester internucleotide linkage. It is a mixture of 32768 (2^{15}) diastereomers attributable to the chirality of a phosphorus atom.

The chemical structure of the drug substance has been elucidated by nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR), electrospray ionization time-of-flight mass spectrometry (ESI TOF-MS), tandem mass spectrometry (MS/MS), and melting temperature.

2.1.2 Manufacturing process

The drug substance is manufactured through solid-phase synthesis using 4 types of [redacted] ([redacted], [redacted], [redacted], and [redacted])[1)] and 3 types of [redacted] ([redacted], [redacted], and [redacted])[2)] as starting materials.

Quality by design (QbD) approaches were utilized to identify critical quality attributes (CQAs). Then, the process parameters that have an impact on the CQAs have been identified by the quality risk assessment, design of experiments, and one-factor-at-a-time method, and thereby the drug substance control strategy is established (Table 1).

Table 1. Overview of drug substance control strategy

CQA	Control method
Content	Specifications
Description	Specifications
Identification	Specifications
[redacted]	Manufacturing process and specifications
pH	Manufacturing process and specifications
Purity	Manufacturing process and specifications
Bacterial endotoxins	Manufacturing process and specifications
Microbial limit	Manufacturing process and specifications
Osmolality	Manufacturing process
Residual solvent	Manufacturing process
[redacted] impurities	Manufacturing process

[redacted], [redacted] chromatography, [redacted] chromatography and [redacted] filtration/[redacted] filtration processes have been defined as critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (most abundant mass [high performance liquid chromatography with ultraviolet and mass spectrometry detection (HPLC-UV-MS)], retention time [high performance liquid chromatography with ultraviolet detection (HPLC-UV)], [redacted] [HPLC-UV-MS], [redacted]), pH, purity (purity [HPLC-UV-

1) [redacted]

2) [redacted]

MS] and related substances [HPLC-UV-MS]), bacterial endotoxins, microbial limit, and assay (HPLC-UV-MS).

2.1.4 Stability of drug substance

The major stability studies of the drug substance are shown in Table 2, and the study results showed that the drug substance is stable. Photostability testing results showed that the drug substance is sensitive to light.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	4 commercial production batches	5°C ± 3°C	Ambient humidity	Sterile low density polyethylene bag	36 months
Accelerated	4 commercial production batches	25°C ± 2°C	60% ± 5%RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored in the sterile low density polyethylene bag at 5°C ± 3°C and protected from light. Long-term testing will be continued up to 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection containing 100 mg of tofersen per vial (15 mL). The drug product contains sodium dihydrogen phosphate hydrate, anhydrous dibasic sodium phosphate, sodium chloride, potassium chloride, calcium chloride hydrate, magnesium chloride, and water for injection as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through the process consisting of preparation of bulk drug product, sterile filtration, aseptic filling, visual inspection, storage, and packaging/labeling/storage/testing. Preparation of bulk drug product, sterile filtration, and aseptic filling have been defined as critical steps, all of which have the process control items and process control values in place.

QbD approaches were utilized to identify CQAs. Then, the process parameters that have an impact on the CQAs have been identified by the quality risk assessment and design of experiments, and thereby the drug product control strategy is established (Table 3).

Table 3. Overview of drug product control strategy

CQA	Control method
Strength	Specifications
Description	Specifications
Identification	Specifications
Osmolality	Manufacturing process and specifications
pH	Manufacturing process and specifications
Purity	Manufacturing process and specifications
Bacterial endotoxins	Manufacturing process and specifications
Extractable volume	Manufacturing process and specifications
Foreign insoluble matter	Specifications
Insoluble particulate matter	Manufacturing process and specifications
Sterility	Manufacturing process and specifications
Excipients	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (retention time [HPLC-UV], [redacted] [UV]), osmolality, pH, purity (purity and impurities [HPLC-UV]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC-UV).

2.2.4 Stability of drug product

The major stability studies of the drug product are shown in Table 4, and the study results showed that the drug product is stable. Photostability testing results showed that the drug product is sensitive to light.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	4 commercial production batches	5°C ± 3°C	Ambient humidity	Glass vial + chlorobutyl rubber stopper and aluminum-seal with a flip-off cap	36 months
Accelerated	4 commercial production batches	25°C ± 2°C	60% ± 5%RH		12 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when filled in a glass vial with a chlorobutyl rubber stopper and an aluminum-seal with a flip-off cap, which is packaged in a carton to protect from light and stored at 2°C to 8°C. Long-term testing will be continued up to 60 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.R.1 Novel excipients

The novel excipients contained in the drug product are potassium chloride, calcium chloride hydrate, and magnesium chloride, which have not been used in existing intrathecal injections.

PMDA concluded that all the novel excipients conform to the compendial specifications in Japan, and there are therefore no particular problems with the specifications. Based on the submitted data, PMDA also concluded that the safety concerns are unlikely to be raised with the amounts used in the drug product.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical pharmacology data of tofersen in the form of results from primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology studies. Results from main studies are presented below.

3.1 Primary pharmacodynamics

3.1.1 *In silico* analysis

3.1.1.1 Analysis for binding site of tofersen (CTD 4.2.1.1-1, CTD 4.2.1.2-2, and CTD 4.2.1.2-3)

The target sequence of tofersen is in the 3'-untranslated region of human *SOD1* mRNA. An informatics analysis was performed to investigate a binding potential of tofersen to *SOD1* mRNA of non-human animal species. The analysis revealed that mouse and rat *SOD1* mRNA have more than 5 base pairs mismatched to the target sequence of tofersen, and cynomolgus monkey *SOD1* mRNA has only single base pair mismatched.

Mutation databases in the human general population and the patients with ALS were searched for polymorphisms of the target binding site of tofersen. The search revealed that the Single Nucleotide Polymorphisms Database (dbSNP) version 141 included 2 polymorphisms of rs11556622 and rs41391245. However, single nucleotide polymorphism (SNP) rs11556622 lacks information on frequency in the population because of the unvalidated status, and SNP rs41391245 occurred at a frequency of <0.1% in 1000 genomes and not included in the Exome Aggregation Consortium (ExAC) database (http://exac.broadinstitute.org).[3)] SNP is considered to occur rarely in the target binding site of the human *SOD1* gene. Furthermore, the Amyotrophic Lateral Sclerosis online Database (ALSoD) (*Amyotroph Lateral Scler.* 2008;9:249-50) was searched for *SOD1* gene sequences in patients with ALS. The search revealed that the sequences in these patients had no polymorphisms at the binding site of tofersen.

Based on the above, the applicant explained that tofersen binds to human *SOD1* mRNA, regardless of an *SOD1* gene mutation or its type.

3.1.2 *In vitro* study

3.1.2.1 Decrease in *SOD1* mRNA expression (CTD 4.2.1.1-2)

Tofersen (0.062-15 µmol/L) was added with 2 human cell lines (neuroblastoma cell lines SH-SY5Y and epithelial carcinoma-derived cell lines A431), and the effect on *SOD1* mRNA expression was investigated by reverse transcription polymerase chain reaction (RT-PCR). Tofersen decreased human *SOD1* mRNA expression in a concentration-dependent manner, and the half-maximal effective concentration (EC_{50}) was 1.1 µmol/L in SH-SY5Y cells and 0.65 µmol/L in A431 cells.

3) As of October 2024, The Genome Aggregation Database (gnomAD) https://gnomad.broadinstitute.org/

Tofersen (0.0273-14 μmol/L) was added with cynomolgus monkey hepatocyte culture, and the effect on *SOD1* mRNA expression was investigated by RT-PCR. Tofersen decreased monkey *SOD1* mRNA expression in a concentration-dependent manner, and the EC_{50} was 0.98 μmol/L.

3.1.3 *In vivo* study

In mice and rats expressing mutant SOD1 protein, ALS-like findings such as abnormal nerve conduction at neuromuscular junctions and motor neuronal deaths were observed (*Neuropathol Appl Neurobio*l. 1996;22:373-87, *Science.* 1994;264:1772-5, etc.). *In vivo* studies were conducted in not only monkeys but also mice and rats transfected with *SOD1* gene bearing G93A mutation (*SOD1*-G93A mice and rats).

3.1.3.1 Decrease in *SOD1* mRNA expression (CTD 4.2.1.1-3, CTD 4.2.1.1-9, and CTD 4.2.3.2-4)

Tofersen (10, 30, 100, 300, or 700 μg) or vehicle (phosphate-buffered saline [PBS]) was intraventricularly administered to *SOD1*-G93A mice, and *SOD1* mRNA expression in the lumbar cord and cerebral cortex at 2 weeks were measured by quantitative RT-PCR. Tofersen decreased *SOD1* mRNA expression in a dose-dependent manner, and the EC_{50} was 0.87 μg/g in the lumbar cord and 7.9 μg/g in the cerebral cortex.

Tofersen (10, 30, 100, 300, 1000, or 3000 μg) or vehicle (PBS) was intrathecally administered to *SOD1*-G93A rats, and *SOD1* mRNA expression in the lumbar cord and cervical cord were measured by quantitative RT-PCR. Tofersen decreased *SOD1* mRNA expression in a dose-dependent manner, and the EC_{50} was 1.4 μg/g in the lumbar cord and 2.3 μg/g in the cervical cord.

Tofersen (4, 12, or 35 mg) or vehicle (artificial cerebrospinal fluid [CSF]) was intrathecally administered to cynomolgus monkeys. Then, *SOD1* mRNA expression in the central nervous system (lumbar cord, thoracic cord, cervical cord, frontal cortex, motor cortex, hippocampus, pons, and cerebellum) was measured by quantitative RT-PCR. Tofersen decreased *SOD1* mRNA expression in a dose-dependent manner, and the EC_{50} was 20.7 μg/g.

3.1.3.2 Physiological and biochemical effects including that on SOD1 protein (CTD 4.2.1.1-8)

Tofersen (10, 30, or 100 μg) or negative control ASO was intraventricularly administered to *SOD1*-G93A mice. SOD1 protein concentrations in the central nervous system were measured, and compound muscle action potential (CMAP) in the tibialis anterior muscle in response to electrical stimulation on the sciatic nerve was measured. In addition, concentrations of serum phosphorylated-neurofilament heavy chain, a biomarker potentially representative of nerve degeneration, were determined. Tofersen decreased wild-type and mutant SOD1 protein concentrations in the cerebral cortex and lumbar cord in a dose-dependent manner. Furthermore, compared with negative control ASO, tofersen increased CMAP in the tibialis anterior muscle in a dose-dependent manner and decreased serum phosphorylated-neurofilament heavy chain concentrations in a dose-dependent manner.

3.1.3.3 Electrophysiological and histological study (CTD 4.2.1.1-6)

Tofersen 300 μg or negative control ASO was intraventricularly administered to *SOD1*-G93A mice. CMAP in the tibialis anterior muscle in response to electrical stimulation on the sciatic nerve was

measured, and the number of neuromuscular junctions in the tibialis anterior muscle was measured by immunostaining using anti-vesicular acetylcholine transporter antibody and α-bungarotoxin. Specimens stained by Gomori method and immunostained using anti-myosin antibody were subjected to an image analysis to measure the muscle fiber size in the tibialis anterior muscle and the number of clusters positive for slow muscle myosin in the soleus muscle.

Compared with the negative control ASO group, the tofersen group showed high CMAP in the tibialis anterior muscle, which was similar to that in wild-type mice. Compared with the negative control ASO group, the tofersen group showed a large number of neuromuscular junctions in the tibialis anterior muscle, which was similar to that in wild-type mice, and an increased muscle fiber size in the tibialis anterior muscle. Furthermore, the analysis on clusters by muscle fiber-type revealed a decrease in the number of clusters positive for slow muscle myosin in the tofersen group as observed in wild-type mice, compared with that in the negative control ASO group.

3.1.3.4 Histological investigation (CTD 4.2.1.1-7)

Tofersen 100 µg or negative control ASO was intraventricularly administered to *SOD1*-G93A mice at the age of 50 days and 94 days. The effect on muscle fiber composition in the tibialis anterior muscle was evaluated based on the number of fibers positive for slow muscle myosin, and expression levels of neurogenic inflammation markers (GFAP and IBA-1) in the spinal cord were evaluated by immunostaining. Compared with the negative control ASO group, the tofersen group showed the decreased ratio of the number of fibers positive for slow muscle myosin to that positive for fast muscle myosin and decreased expression levels of GFAP and IBA-1 in the spinal cord specimens.

3.1.3.5 Effects on survival period and coordinated movement (CTD 4.2.1.1-5)

Tofersen (100 or 300 µg) or negative control ASO was intraventricularly administered to *SOD1*-G93A mice at the age of 50 days and 94 days. The number of days to onset (when body weight was decreased by >10%), survival period, and coordinated movement measured by a rotarod method were evaluated. Time to onset (median) was 20, 25.3, and 26.1 weeks in the negative control, tofersen 100 µg, and tofersen 300 µg groups, respectively, and the survival period (median) was 24, 28.3, and 29.3 weeks, respectively. Time to fall off the rotarod in either tofersen group was longer than that in the negative control ASO group.

3.2 Secondary pharmacodynamics

3.2.1 Induction of human chemokines (CTD 4.2.1.2-1)

Tofersen, the other ASOs targeting *SOD1* gene sequence (ISIS 333611, ISIS 666859, ISIS 666870, and ISIS 666919), and TLR9-activating positive control ASO were added with HEK293XL cells overexpressing human TLR9 to investigate their induction of chemokines. No IL-8 production was detected with any ASO targeting *SOD1* gene at concentrations up to 200 µmol/L. On the other hand, an increase in IP-10 was observed with ISIS 333611, ISIS 666859, and tofersen, but its extent was smaller than that with positive control ASO.

3.2.2 Off-target gene analysis

The applicant explanation:

Based on the following investigations, tofersen is unlikely to raise safety problems caused by the hybridization-dependent off-target effect.

3.2.2.1 *In silico* analysis (CTD 4.2.1.2-2 and CTD 4.2.1.2-3)

Search for gene transcription products to which tofersen might bind was performed in the datasets of the human mRNA sequence set and pre-mRNA sequence set prepared from hg38/GRCh38[4)] and RefSeq[5)] using an algorithm program of Bowtie (*Genome Biol.* 2009;10:R25). The search identified 27 genes as potential off-target genes that included sequences with up to 2 mismatch, insertion, and/or deletion bases in total in comparison with the complementary sequence of tofersen (*ADIPOR1, BCAP29, CDC123, CDYL2, CLPTM1L, COL28A1, CREB1, CSNK2A2, DCLRE1A, KCNH8, KCTD16, KLF12, LINC01924, LMBR1, LOC101927066, LOC105370805, LOC107986330, MIR4435-2HG, LINC00669/MIR924HG, NDST4, POU6F2, RBFOX2, RPS6KA2, SGSM2, SLC30A9, SND1,* and *USP33*).

Of the above 27 genes, 6 genes (*LINC01924*, *LOC101927066*, *LOC105370805*, *LOC107986330*, *LINC00669/MIR924HG*, and *NDST4*) were found to have no reports indicating a relationship to diseases or physiological changes in the search of NCBI Gene and Online Mendelian Inheritance in Man (OMIM), while *MIR4435-2HG* was found that its decreased expression led to decreased myeloid cells (eosinophils, neutrophils, and monocytes) (*Nature.* 2016;537:239-43). The applicant explained that no adverse events related to decreased myeloid cells were observed in clinical studies of tofersen, and thus tofersen in clinical use is unlikely to have a substantial effect on mRNA expression of *MIR4435-2HG*.

3.2.2.2 *In vitro* analysis (CTD 4.2.1.2-2 and CTD 4.2.1.2-3)

Of the 27 potential off-target genes identified in the *in silico* analysis, the above 6 genes of unknown functions and *MIR4435-2HG* were excluded, and the remaining 20 genes (*ADIPOR1, BCAP29, CDC123, CDYL2, CLPTM1L, COL28A1, CREB1, CSNK2A2, DCLRE1A, KCNH8, KCTD16, KLF12, LMBR1, POU6F2, RBFOX2, RPS6KA2, SGSM2, SLC30A9, SND1,* and *USP33*) were analyzed for an effect of tofersen on their mRNA expression. In this analysis, tofersen was added with human cutaneous squamous cell carcinoma-derived cell lines (A431 cells) or human neuroblastoma cell lines (SH-SY5Y cells), and the effect on mRNA expression was measured by quantitative RT-PCR. For 6 genes (*SLC30A9, KCTD16, BCAP29, KCNH8, RPS6KA2,* and *CDYL2*), mRNA expression was decreased by >10% at the highest concentration in either cell line, but tofersen has selectivity to *SOD1* mRNA more than 90 times higher than that to these mRNA sequences. The applicant therefore explained that tofersen in clinical use is unlikely to have a substantial effect on mRNA expression of these genes.

3.3 Safety pharmacology

Safety pharmacology study results are summarized in Table 5.

4) Downloaded on [redacted], 20[redacted]. Used as human genome reference sequences.
5) Downloaded on [redacted], 20[redacted]. Used for genome annotation.

Table 5. Summary of safety pharmacology study results

Item	Test system	Endpoint, method, etc.	Dose or concentration	Route of administration	Findings	CTD
Central nervous system	Rat (n = 10/sex/group)	FOB method	0,[a] 0.1, 0.3, 1.0, 3.0 mg; single dose	Intrathecal	3 mg: Decreased arousal, gait, locomotor activity, and sensorimotor scores	4.2.3.1-1
	Cynomolgus monkey (n = 3-5/sex/group)	Modified Irwin method[b]	0,[a] 4, 12, 35 mg; 5 doses in total[c]	Intrathecal	35 mg: Transient decreased activity	4.2.3.2-4
	Cynomolgus monkey (n = 4/sex/group)	Modified Irwin method[d]	0,[a] 4, 12, 35 mg; 11 doses in total[e]		35 mg: Transient muscle cramp, intermittent tremor	4.2.3.2-5
Cardiovascular system	HEK293 cells	hERG current	1, 3, 10, 34 µmol/L	*In vitro*	IC_{50}: >34 µmol/L	4.2.1.3-1
	Cynomolgus monkey (n = 3-5/sex/group)	ECG and blood pressure	0,[a] 4, 12, 35 mg; 5 doses in total[c]	Intrathecal	No effect	4.2.3.2-4
	Cynomolgus monkey (n = 4/sex/group)		0,[a] 4, 12, 35 mg; 11 doses in total[e]			4.2.3.2-5
Respiratory system	Rat (n = 10/sex/group)	Clinical observations and FOB method	0,[a] 0.1, 0.3, 1.0, 3.0 mg; single dose	Intrathecal	3 mg: Decreased respiratory score	4.2.3.1-1
	Cynomolgus monkey (n = 3-5/sex/group)	Blood gas parameter	0,[a] 4, 12, 35 mg; 5 doses in total[c]	Intrathecal	No effect	4.2.3.2-4
	Cynomolgus monkey (n = 4/sex/group)		0,[a] 4, 12, 35 mg; 11 doses in total[e]			4.2.3.2-5

a) Vehicle: Artificial CSF
b) Assessed on Days 28 and 84
c) Administered on Days 1, 14, 28, 56, and 84
d) Assessed on Days 169 and 259
e) Administered on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics of tofersen

The applicant's explanation about the effect of tofersen on ALS associated with a mutation in the SOD1 gene (SOD1-ALS):

Although the mechanism of how *SOD1* gene mutations cause ALS remains unclear, these mutations render SOD1 protein toxic and thereby cause motor neuronal death, but do not deprive it of its function (*Science.* 1998;281:1851-4, *Nature.* 1993;362:59-62).

Tofersen is an oligonucleotide complementary to 20 nucleotide residues in the 3'-untranslated region of human *SOD1* mRNA [see Section 3.1.1.1] and binds to this region through hybridization, inducing RNase-H-mediated degradation of *SOD1* mRNA (*J Biol Chem.* 1981;256:11569-73, *Mol Pharmacol.* 2007;71:73-82).

Tofersen has been demonstrated to decrease *SOD1* mRNA expression or SOD1 protein production in human cell lines as well as in the central nervous system in animals transfected with mutant *SOD1* gene and cynomolgus monkeys in a concentration- or dose-dependent manner [see Sections 3.1.2.1, 3.1.3.1, and 3.1.3.2]. When tofersen was administered to *SOD1*-G93A mice, compared with the negative control

ASO group, the tofersen group showed a large number of neuromuscular junctions in the tibialis anterior muscle and did not show an increase in the number of clusters positive for slow muscle myosin, suggesting that tofersen could prevent nerve damage. The higher CMAP in the tibialis anterior muscle in the tofersen group than in the negative control ASO group suggested that tofersen could prevent nerve damage and atrophy of the innervated muscle [see Section 3.1.3.3]. Furthermore, compared with the negative control ASO, the tofersen group showed decreased expression levels of nerve degeneration and neurogenic inflammation markers [see Sections 3.1.3.2 and 3.1.3.4] as well as an increasing trend of the survival period and an improving trend of coordinated movement function [see Section 3.1.3.5].

Based on the above, tofersen is expected to be effective in treatment of SOD1-ALS by eliminating *SOD1* mRNA and thereby decreasing expression of mutant SOD1 protein, which causes SOD1-ALS.

Based on the submitted study results, PMDA concluded that tofersen can be expected to have efficacy in patients with SOD1-ALS.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical pharmacokinetic data of tofersen in the form of study results on absorption, distribution, metabolism, and excretion in mice, rats, rabbits, and monkeys. Results from main studies are presented below.

Tofersen concentrations in monkey CSF, plasma, and tissue were determined using hybridization enzyme-linked immunosorbent assay (ELISA) (lower limit of quantification; 0.500 ng/mL in CSF and plasma, 15.0 ng/g in tissue). Tofersen concentrations in mouse plasma and milk were determined by hybridization ELISA (lower limit of quantification; 0.500 ng/mL in plasma, 0.250 ng/mL in milk).

4.1 Absorption (CTD 4.2.3.2-5)

Tofersen 4, 12, or 35 mg was intrathecally administered to male and female monkeys for 39 weeks (administered on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253). Table 6 and Table 7 show tofersen concentrations in CSF and pharmacokinetic parameters in plasma.

Table 6. Pre-dose tofersen concentrations in CSF in monkeys during a period of intrathecal administration

	4 mg		12 mg		35 mg	
	Female (n = 4)	Male (n = 4)	Female (n = 4)	Male (n = 4)	Female (n = 10)	Male (n = 10)
Day 1	BLQ (4)	BLQ (4)	BLQ (4)	BLQ (4)	1.12 ± 1.95 (10)	1.06 ± 2.01 (10)
Day 15	5.23 ± 2.48 (4)	4.04 ± 2.36 (4)	6.38 ± 6.35 (4)	7.74 ± 2.63 (4)	19.2 ± 22.9 (10)	16.1 ± 15.3 (10)
Day 29	12.3 ± 8.88 (4)	15.0 ± 12.8 (4)	20.8 ± 9.19 (4)	16.6 ± 5.47 (4)	25.1 ± 10.0 (10)	44.8 ± 50.0 (10)
Day 57	16.2 ± 6.99 (4)	11.2 ± 8.31 (4)	21.2 ± 13.4 (4)	12.3 ± 2.64 (4)	32.1 ± 38.1 (10)	19.4 ± 10.6 (10)
Day 85	13.7 ± 5.27 (4)	14.6 ± 6.7 (4)	23.5 ± 19.7 (3)	15.1 ± 5.48 (4)	40.3 ± 43.4 (10)	49.4 ± 64.6 (10)
Day 113	11.7 ± 4.39 (4)	23.0 ± 16.5 (4)	15.4 ± 6.93 (3)	18.6 ± 6.62 (4)	45.0 ± 36.8 (9)	27.7 ± 20.0 (10)
Day 141	13.1 ± 0.82 (4)	14.8 ± 6.53 (4)	31.0 ± 22.7 (3)	21.0 ± 9.18 (4)	94.7 ± 90.2 (10)	45.5 ± 39.2 (10)
Day 169	11.8 ± 2.68 (4)	18.1 ± 5.98 (4)	40.1 ± 32.9 (3)	26.7 ± 7.41 (4)	123 ± 165 (8)	70.4 ± 79.9 (10)
Day 197	16.1 ± 10.4 (4)	20.1 ± 6.71 (4)	29.6 ± 12.6 (3)	24.1 ± 13.5 (4)	92.5 ± 110 (5)	79.7 ± 98.9 (6)
Day 225	14.3 ± 5.06 (4)	17.0 ± 6.67 (4)	26.5 ± 4.16 (3)	22.7 ± 9.43 (4)	224 ± 388 (5)	45.8 ± 42.3 (5)
Day 253	12.5 ± 3.21 (4)	16.2 ± 5.48 (4)	43.9 ± 27.3 (3)	25.5 ± 14.4 (4)	88.5 ± 72 (6)	64.3 ± 80.1 (6)
Day 267	31.3 ± 18.8 (4)	26.9 ± 12.4 (4)	52.4 ± 19.3 (3)	43.6 ± 21.8 (4)	190 ± 178 (6)	86.2 ± 72.7 (6)
Day 288					23.2 (1)	45.9, 64.0 (2)
Day 344					8.6, 52.4 (2)	23.8, 16.8 (2)
Day 400					4.9, 8.4 (2)	8.1, 10.2 (2)
Day 456					3.3, 12.1 (2)	1.9, 2.9 (2)

Mean ± standard deviation (SD) or individual values (number of animals evaluated); BLQ, Below the lower limit of quantification
The last dose was administered on Day 253, and tofersen concentrations in CSF on and after Day 288 were measured values during the recovery period without the administration.

Table 7. Plasma pharmacokinetic parameters of tofersen in monkeys after intrathecal administration

Dose	Day of measurement	Sex	n	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
4 mg	Day 1	Female	4	1320 ± 473	1.5 [1.0, 4.0]	6840 ± 1200
		Male	4	1180 ± 108	2.0 [1.0, 2.0]	5690 ± 908
	Day 253	Female	4	926 ± 383	3.0 [1.0, 4.0]	8010 ± 3440
		Male	4	1060 ± 138	2.0 [1.0, 4.0]	7460 ± 3850
12 mg	Day 1	Female	4	13100 ± 1820	2.0 [2.0, 2.0]	53800 ± 2300
		Male	4	10200 ± 5730	2.0 [2.0, 4.0]	36400 ± 15600
	Day 253	Female	3	5980 ± 2650	4.0 [4.0, 4.0]	39800 ± 2980
		Male	4	4000 ± 2090	2.0 [2.0, 10]	22600 ± 8430
35 mg	Day 1	Female	10	33500 ± 12400	2.0 [2.0, 4.0]	176000 ± 19200
		Male	10	24700 ± 6140	2.0 [2.0, 4.0]	143000 ± 31300
	Day 253	Female	4	48000 ± 20500	4.0 [1.0, 4.0]	223000 ± 54200
		Male	4	25500 ± 12900	2.0 [2.0, 4.0]	134000 ± 49100

Mean ± SD, t_{max} is presented as median [range].

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.3.2-5)

Tofersen 4, 12, or 35 mg was intrathecally administered to male and female monkeys for 39 weeks (administered on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253). Table 8 shows tofersen concentrations on Day 267 and terminal phase elimination half-life in each tissue.

Table 8. Tofersen concentrations on Day 267 and terminal phase elimination half-life in each tissue in male and female monkeys after repeated intrathecal administration of tofersen

Tissue	Concentration (μg/g)			Terminal phase elimination half-life (days)[a)]
	4 mg	12 mg	35 mg	
Cerebellum	6.6 ± 4.4 (8)	20.5 ± 12.8 (7)	33.5 ± 22.1 (8)	55.2
Brain cortex	7.4 ± 4.6 (8)	27.8 ± 16.4 (7)	39.1 ± 27.4 (8)	61.5
Hippocampus	4.6 ± 2.9 (8)	13.2 ± 9.4 (7)	24.3 ± 15.5 (8)	66.9
Brain medulla	4.6 ± 2.5 (8)	11.7 ± 5.6 (7)	21.0 ± 15.7 (8)	48.8
Cervical cord	7.9 ± 3.9 (8)	17.0 ± 8.9 (7)	32.8 ± 20.6 (8)	65.8
Lumbar cord	23.1 ± 8.2 (8)	44.4 ± 15.3 (7)	110.0 ± 63.1 (8)	51.2
Thoracic cord	13.6 ± 7.8 (8)	28.8 ± 14.9 (7)	53.0 ± 33.3 (8)	49.8
Kidney	57.1 ± 19.6 (8)	67.6 ± 14.6 (7)	219.0 ± 91.5 (8)	23.7
Liver	4.7 ± 2.8 (8)	29.8 ± 21.0 (7)	92.7 ± 54.8 (8)	20.3

Mean ± SD (number of animals evaluated)

a) Calculated from 2 concentrations on Days 267 and 456 in the 35 mg group

4.2.2 Plasma protein binding (CTD 4.2.2.3-1)

Tofersen (0.1 or 30 μg/mL) was added to mouse and monkey plasma followed by ultrafiltration to determine the protein binding. The protein binding in plasma was consistent across concentrations investigated, and it was approximately 96% in mouse plasma and approximately 98% in monkey plasma.

4.2.3 Placental transfer

Placental transfer of tofersen has not been investigated. The applicant explained that placental transfer of tofersen was limited as with the other oligonucleotides because (1) nusinersen, which is an ASO modified with 2'-O-(2-methoxyethyl) (2'-MOE) (2'-MOE-modified ASO) like tofersen and comprised of 18 bases, was subcutaneously administered at a dose of 25 mg/kg every other day from 2 weeks before mating to Gestation Day 15, and concentrations in the fetal liver on Gestation Day 18 were not more than the lower limit of quantification ("Spinraza Intrathecal Injection 12 mg" data submitted for application on December 7, 2016, CTD 4.2.3.5.1-1) and (2) placental transfer of oligonucleotides is limited (*Birth Defects Res B Dev Reprod Toxicol.* 2004;71:368-73, *Birth Defects Res B Dev Reprod Toxicol.* 2006;77:22-8).

4.3 Metabolism (CTD 4.2.2.4-1)

Metabolism of tofersen intrathecally administered was investigated using the liver and renal cortex in monkeys which intrathecally received a total of 5 doses of tofersen 10 mg on Days 1, 15, 29, 57, and 85.

In the pooled liver specimen on Day 92 (n = 4/sex), 6 metabolites in males and 12 metabolites in females were identified and, including N-2, N-15, and N-16 (via 5'-exonuclease) as well as N-6, N-7, N-8, N-9, N-10, N-11, N-12, N-13, and N-14 (via 3'-exonuclease). Any of the identified short oligonucleotides accounted for <6% of the total area of peaks derived from tofersen determined by LC-MS. The most abundant molecular species was unchanged tofersen, accounting for 80% and 75% of the total area of peaks derived from tofersen in males and females, respectively.

In the pooled renal cortex specimen on Day 92 (n = 4/sex), 3 metabolites in males and 2 metabolites in females were identified and, including N-2 (via 5'-exonuclease) as well as N-6 and N-7 (via 3'-exonuclease). These short oligonucleotides accounted for <2% of the total area of peaks derived from tofersen. The most abundant molecular species was unchanged tofersen, accounting for 92% of the total area of peaks derived from tofersen in both males and females.

4.4 Excretion

4.4.1 Urinary and fecal excretion

Urinary and fecal excretion of tofersen has not been investigated. The applicant explained that tofersen is considered to be mainly excreted into urine as its metabolites and unchanged tofersen, like gapmer ASOs with 5'- and 3'-terminals modified with 2'-MOE, which are metabolized in tissues and mainly excreted into urine as its metabolites and unchanged tofersen (*Drug Metab Dispos.* 2003;31:1419-28, *Drug Metab Dispos.* 2007;35:460-8).

4.4.2 Excretion in milk (CTD 4.2.3.5.3-1)

To pregnant mice, tofersen was subcutaneously administered at 3, 10, or 30 mg/kg every other day during a period of Gestation Days 6 to 22 and Post-partum (Lactation) Days 1 to 21, and tofersen was detected in milk in all dose groups on Post-partum Day 13. The mean tofersen concentrations in milk in the tofersen 3, 10, and 30 mg/kg groups were 22.2, 96.9, and 88.3 ng/mL, which were 0.00046, 0.00076, and 0.00025 times, respectively, the tofersen concentrations in the maternal liver in the corresponding group on Post-partum Day 21.

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic study results, PMDA concluded that tofersen has no particular problems.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted the toxicity data of tofersen in the form of results from single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and other toxicity (related to impurities) studies. Because tofersen was considered to potentially act as a drug only in monkeys among normal animals owing to varied mRNA sequences from animal species to animal species [see Sections 3.1.1.1 and 3.1.3.1], monkeys were used to evaluate on-target and off-target toxicity, and the other animal species were used to evaluate off-target toxicity.

5.1 Single-dose toxicity

A single intrathecal dose toxicity study in rats was conducted, and an approximate lethal dose of tofersen was determined to be 3 mg/dose (11 mg/kg) (Table 9).

Table 9. Summary of single-dose toxicity study

Test system	Route of administration	Dose (mg/dose)	Main findings	Approximate lethal dose	CTD
Male and female rats (SD)	Intrathecal	0,[a] 0.1, 0.3, 1, 3	Death: 3 (1 of 10 males) ≥0.1: Increased mononuclear cells in CSF 3: Transient acute tactile hypersensitivity reaction; decreased arousal, gait, mobility, respiration, and sensorimotor scores in FOB; perivascular mononuclear cell infiltration in the brain and spinal cord; and vacuolated and granulated macrophages in the cerebral meninges and thoracic spinal cord	3 mg/dose (11 mg/kg)	4.2.3.1-1

a) Artificial CSF

5.2 Repeated-dose toxicity

Repeated subcutaneous dose toxicity studies in mice (12 and 26 weeks) and repeated intrathecal dose toxicity studies in monkeys (13 and 39 weeks) were conducted (Table 10).

The major findings in monkeys intrathecally treated with tofersen were neurologic signs (intermittent tremor and transient hyporeflexia), vacuolated neurons in the brain and spinal cord, and mononuclear cell infiltration in the meninges in the brain and spinal cord.

In the 39-week repeated intrathecal dose toxicity study in monkeys, exposure to tofersen[6)] at the lowest dose (4 mg/dose) and no-observed-adverse-effect level (NOAEL) (12 mg/dose) (concentrations in CSF, 29.1 ng/mL and 47.4 ng/mL; $AUC_{0\text{-}24h}$, 7.73 µg·h/mL and 30 µg·h/mL) was 1.1 and 1.8 times the exposure[7)] in CSF (concentration in CSF, 25.67 ng/mL; $AUC_{0–24h}$, 13.57 µg·h/mL) and 0.57 and 2.2 times the exposure in plasma at the human recommended clinical dose (100 mg), respectively.

6) The exposure in monkeys represents the concentrations in CSF on Day 267 and $AUC_{0\text{-}24h}$ in plasma on Day 253 in the respective groups.
7) The exposure in humans represents the mean concentration in CSF on Day 29 (the maximum concentration in CSF across sampling points) and $AUC_{0\text{-}24h}$ in plasma on Day 85 in the tofersen group in a global phase III study (part C of Study 233AS101 [Study 101]).

Table 10. Summary of repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose	Main findings	NOAEL	CTD
Male and female mice (CD-1)	Subcutaneous	12 weeks (every 2 weeks)	0,[a] 25, 150 mg/kg	≥25: Low eosinophil count, low TG and BUN, basophil granules in the tubular epithelium, hypertrophic hepatic Kupffer cells, hypertrophic macrophages throughout the body 150: Low white blood cell, neutrophil, and lymphocyte counts	150 mg/kg[b]	4.2.3.2-1
Male and female mice (CD-1)	Subcutaneous	26 weeks (every 2 weeks) + 8 weeks of recovery	0,[c] 6, 30, 150 mg/kg	≥6: Low body weight, vacuolated macrophages throughout the body, vacuolated bladder urothelial cells, high blood phosphorus value ≥30: High reticulocyte count; low blood glucose, basophil granules in tubular epithelial cells, vacuolated urothelial cells in the renal pelvis, subcutaneous hemorrhage 150: Low red blood cell count, Hb, Ht, and platelet count; low mean cell volume and mean cell hemoglobin; high red cell distribution width; high ALT and AST; low A/G ratio; decreased T-lymphocytes; skin erosion, ulcer, and mixed-cell inflammation at the injection site Reversible (except for red cell distribution width, change in platelet count, and high AST)	150 mg/kg[b]	4.2.3.2-2
Male and female cynomolgus monkey	Intrathecal	13 weeks (administered on Days 1, 14, 28, 56, and 84) + 13 weeks of recovery	0,[d] 4, 12, 35 mg/dose	≥4: Vacuolated neurons in the hippocampus and cerebral cortex, inflammatory mononuclear cell infiltration in the dura mater and meninges at the injection site (lumbar spinal cord) ≥12: High total protein and albumin in CSF 35: Transient decreased activity,[e] tremor, limping, high AST, vacuolated and hypertrophic macrophages in lymph nodes Reversible (a new finding of vacuolated neurons in the lumbar spinal cord was obtained after the recovery period)	35 mg/dose	4.2.3.2-4
Male and female cynomolgus monkey	Intrathecal	39 weeks (administered on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253) + 26 weeks of recovery	0,[d] 4, 12, 35 mg/dose	≥4: High microalbumin, total protein concentration, white blood cell count, and red blood cell count in CSF; meningeal and perivascular mononuclear cell infiltration in the brain and spinal cord; mononuclear cell infiltration in the spinal nerve root; vacuolated neurons and macrophages in the hippocampus ≥12: Vacuolated neurons in the spinal cord 35[f]: Transient muscle cramp,[e] delayed recovery from anesthesia,[e] intermittent tremor,[e] transiently decreased patellar reflex and foot grasp reflex,[e] vacuolated neurons in the cerebral cortex and medulla Reversible (except for vacuolated neurons in the brain and spinal cord and mononuclear cell infiltration in the meninges)	12 mg/dose	4.2.3.2-5

a) Physiological saline
b) The applicant does not deem the hematological findings as adverse changes, because no relevant histopathological changes were observed, and the histopathological changes are consistent with changes associated with administration of ASO in the previous reports (*Nucleic Acid Ther.* 2016;26:199-209, *Toxicol Pathol.* 2015;43:78-89, etc.)
c) PBS
d) Artificial CSF
e) The applicant considers it as a finding related to blood concentrations of tofersen.
f) The hippocampus and lumbar cord in the 35 mg group were subjected to an ultrastructure analysis under a transmission electron microscope. Vacuolated neurons were covered with a monolayer limiting membrane suggestive of endosome/lysosome origin and contained granular substances. The applicant considers the granular substances as a change suggestive of accumulation of tofersen.

5.3 Genotoxicity

Genotoxicity studies included *in vitro* studies of a bacterial reverse mutation assay and a chromosomal aberration assay in Chinese hamster lung cells and an *in vivo* study of micronucleus assay in mouse bone marrow (Table 11). All the studies showed negative results, the applicant considers that tofersen is not genotoxic.

Table 11. Summary of genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentrations or doses	Study result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9-/+	0,[a] 15, 50, 150, 500, 1500, 5000 (μg/plate)	Negative	4.2.3.3.1.-1
	Chromosomal aberration assay in cultured mammalian cells	Chinese hamster lung cells	S9+ (6 hours)	0,[a] 125, 250, 500 (μg/mL)	Negative	4.2.3.3.1-2
			S9- (6 and 22 hours)			
In vivo	Micronucleus assay in rodents	Male mouse (CD-1) bone marrow		0,[b] 500, 1000, 2000 (mg/kg/day) (subcutaneous, twice daily)	Negative	4.2.3.3.2-1

a) Distilled water
b) PBS

5.4 Carcinogenicity

No results from carcinogenicity studies of tofersen were submitted. A 2-year carcinogenicity study in mice treated subcutaneously is currently ongoing, and the final report is scheduled to be obtained in May 2027. The applicant explained that results from the carcinogenicity study in mice will be submitted after the market launch of tofersen so that tofersen will be provided to clinical settings at the earliest possible time because SOD1-ALS is a serious life-threatening disease. Risk evaluation of tofersen for carcinogenicity based on information available to date and the necessity of a carcinogenicity study in rats are discussed in Section 5.R.2.

5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity risk attributable to the off-target toxicity of tofersen was evaluated in reproductive and developmental toxicity studies in mice and rabbits (Table 12).

Although fertility in male mice was not affected, male reproductive organs were affected by tofersen. The estimated exposure to tofersen at NOAEL (10 mg/kg) for general toxicity ($AUC_{0\text{-}24h}$, 17.2 μg·h/mL) was approximately 1.3 times the exposure in humans at the recommended clinical dose (100 mg) ($AUC_{0\text{-}24h}$, 13.57 μg·h/mL). No findings related to tofersen were obtained for any of fertility and embryo-fetal development in female mice, development of F1 offspring, and embryo-fetal development in rabbits.

The exposure to tofersen in female mice subcutaneously treated with tofersen at NOAEL (30 mg/kg) for fertility and embryo-fetal development as well as development of F1 offspring ($AUC_{0\text{-}24h}$, 51 μg·h /mL) was approximately 3.8 times the exposure[7)] in humans at the recommended clinical dose (100 mg) ($AUC_{0\text{-}24h}$, 13.57 μg·h/mL).

The exposure to tofersen in rabbits subcutaneously treated with tofersen at NOAEL (30 mg/kg) for embryo-fetal development ($AUC_{0\text{-}24h}$, 283 μg·h /mL) was approximately 20.9 times the exposure[7)] in humans at the recommended clinical dose (100 mg) ($AUC_{0\text{-}24h}$, 13.57 μg·h/mL).

Table 12. Summary of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	CTD
Fertility, early embryonic development to implantation, and embryo-fetal development	Male mouse (ICR)	Subcutaneous	From 4 weeks before mating through mating period (every other day)	0,[a] 3, 10, 30	≥10: Vacuolated amphophil macrophages in interstitial tissues in the testis and epididymis 30: Increased prostate weight; degeneration, dilation, and sperm cell retention in the seminiferous tubules; and epithelial cell apoptosis, increased cellular debris, and hypospermia in the epididymis	Parent animal Male fertility: 30 Male general toxicity: 10	4.2.3.5.1-1
	Female mouse (ICR)		From 2 weeks before mating to Gestation Day 14 (every other day)		Parent animal (fertility) None Embryo-fetal development None	Parent animal (female fertility): 30 Embryo-fetal development: 30	
Embryo-fetal development	Pregnant rabbit (NZW)	Subcutaneous	Gestation Days 7 to 19 (every other day)	0,[a] 3, 10, 30	Parent animal (general toxicity) None Embryo-fetal development None	Parent animal: 30 Embryo-fetal development: 30	4.2.3.5.2-3
Effects on pre- and postnatal development, including maternal function	Pregnant mouse (ICR)	Subcutaneous	From Gestation Day 6 to Lactation Day 21 (every other day)	0,[a] 3, 10, 30	Parent animal (general toxicity) None F1 offspring None	Parent animal (general toxicity): 30 Development of F1 offspring: 30	4.2.3.5.3-1

a) PBS

5.6 Local tolerance

In the 13-week and 39-week intrathecal dose toxicity studies in monkeys (CTD 4.2.3.2-4 and 4.2.3.2-5), a local irritant effect of tofersen was evaluated, and inflammatory cell infiltration was observed at the injection site of the lumbar cord meninges.

5.7 Other studies

5.7.1 Photosafety

No photosafety testing of tofersen has been conducted. The applicant explained that tofersen does not raise any particular concern about its photosafety because a 2'-MOE-modified ASO, when intravenously administered to rats, was scarcely distributed in the skin and eyes (*Drug Metab Dispos.* 2007;35:460-8).

5.7.2 Safety of impurities

For oligonucleotide related substances potentially contained in the drug substance, the safety of these impurities at up to the upper acceptance limit has been evaluated in toxicity studies with tofersen batches that contained the oligonucleotides related substances.

5.R Outline of the review conducted by PMDA

5.R.1 Findings in the central nervous system

The applicant's explanation about mechanisms of development, reversibility, and toxicological meaning of findings in the central nervous system in monkeys (inflammation in the meninges and spinal nerve root as well as vacuolated neurons):

- Inflammation in the meninges and spinal nerve root, as well as vacuolated neurons, is considered attributable to a proinflammatory effect of ASO (*Int Immunopharmacol.* 2002;2:1657-66) and accumulation of ASO in endosomes or lysosomes [see Section 5.2], respectively.
- In the 39-week intrathecal dose toxicity study in monkeys, the exposure to tofersen in CSF continued even during the recovery period [see Section 4.1], and thus the findings in the central nervous system are considered to have been found non-reversible. However, the findings in the central nervous system are considered to be found reversible after the concentration of tofersen in CSF is decreased, in view of non-worsening of the findings during recovery period and the mechanisms of development of these histopathological changes.
- No abnormalities were observed by the modified Irwin method or in the neurological examination [see Sections 3.3 and 5.2], and neither degeneration of neurons nor intraparenchymal inflammatory cell infiltration or glial cell reactions in the central nervous system were observed [see Section 5.2]. These findings are also considered little toxicologically meaningful.

PMDA's view:

For the findings in the central nervous system, the toxicological relevance should be carefully interpreted, for the following reasons: (1) These findings may occur in humans as well in view of the mechanisms of development; (2) the exposure to tofersen in CSF and plasma at 4 mg/dose, which led to the findings in the central nervous system, was equivalent to or smaller than that in CSF and plasma at the human recommended clinical dose [see Section 5.2]; and (3) inflammatory diseases involving the central nervous system, which seem to be potentially related to these findings, were observed in clinical studies. The safety in the central nervous system in humans is continuously discussed in Section 7.R.3. The findings in the central nervous system obtained in monkeys should be included in the package insert for information provision.

5.R.2 Carcinogenicity evaluation

The applicant's explanation:

The information available to date, presented below, does not suggest a carcinogenic risk of tofersen.

- In view of the following points, a carcinogenic risk related to the pharmacologic effect of tofersen is considered low:
  - Spontaneous neoplastic changes in the liver occur in *SOD1*-deficient mice more frequently (*Oncogene.* 2005;24:367-80). In humans treated with tofersen, SOD1 protein concentrations were decreased but its expression was maintained [see Section 6.2.2.2].
  - In the 39-week intrathecal dose toxicity study in monkeys, in which tofersen has a pharmacologic effect, none of hyperplasia, preneoplastic lesions, neoplastic lesions, hormonal variations, and immunosuppression was observed.

- Based on the following findings, a carcinogenic risk attributable to the hybridization-independent off-target effect of tofersen is considered low:
  - Genotoxicity and carcinogenicity studies of ASOs (nusinersen, mipomersen,[8)] inotersen,[9)] and volanesorsen[10)]) which have phosphorothioate backbone and 2'-MOE chemical modification as with tofersen were conducted and have raised no concerns about genotoxicity or carcinogenicity.
  - In the 26-week subcutaneous dose toxicity study in mice and 39-week intrathecal dose toxicity study in monkeys, none of hyperplasia, preneoplastic lesions, neoplastic lesions, hormonal variations, and immunosuppression was observed.
  - Tofersen tested negative for genotoxicity [see Section 5.3].
- Based on the off-target gene analysis results [see Section 3.2.2], tofersen is considered unlikely to present a hybridization-dependent off-target effect which leads to carcinogenesis.

The applicant's additional explanation:
Distribution and metabolism of an ASO chemically modified with 2'-MOE do not differ between mice and rats (*Drug Metab Dispos.* 2003;31:1419-28, *Drug Metab Dispos.* 2007;35:460-8). Based on the above finding, conduct of the carcinogenicity study in rats is scarcely required since distribution and metabolism of tofersen in rats are expected to be similar to those in mice.

PMDA's view:
Although data from the carcinogenicity study of tofersen have not been submitted, the information available to date does not suggest a carcinogenic risk of tofersen, according to the applicant's explanation.

The applicant's decision not to conduct the carcinogenicity study in rats is acceptable in view of the applicant's explanation and the following reasons: (1) The carcinogenicity study in rodents, in which tofersen has no pharmacologic effect, is only intended to evaluate the hybridization-independent off-target toxicity, and (2) carcinogenicity of 2'-MOE-modified ASOs has been evaluated to a certain extent.

SOD1-ALS is a serious disease that can rapidly progress depending on the genotype, and options currently available for treatment of ALS are extremely limited. In view of this status, clinical use of tofersen is considered acceptable even in a situation where the carcinogenicity evaluation in mice has not been completed. However, if any findings suggestive of a carcinogenic potential of tofersen from the carcinogenicity study in mice are obtained in the future, the applicant should promptly provide the information to healthcare professionals and consider the necessity of additional safety measures, etc.

5.R.3 Risk evaluation of reproductive and developmental toxicity

The applicant's explanation about hazards and risks of reproductive and developmental toxicity assumed from the mechanism of action of tofersen:
In females, SOD1 is involved in secretion of progesterone, which acts for ovulation, luteal activity, and pregnancy maintenance (*Oxid Med Cell Longev.* 2017;2017:4371714), and *SOD1* knockout mice exhibit

8) FDA Pharmacology Review, Application number: 203568Orig1s000
9) FDA Pharmacology Review, Application number: 211172Orig1s000
10) EMA Assessment Report, EMA/180717/2019

decreased fertility and embryonic deaths in females and decreased sperm count, motility, and fertility in males (*Biol Reprod.* 2012;87:121). Tofersen is thus assumed to pose hazards of decreased male and female fertility and embryonic death owing to the pharmacologic effect.

The hazards of reproductive and developmental toxicity associated with the pharmacologic effect have been already known, and no reproductive and developmental toxicity studies were conducted in monkeys, in which tofersen has a pharmacologic effect, but a risk for reproduction and development was evaluated as follows:

- In the 39-week intrathecal dose toxicity study in monkeys, in which tofersen has a pharmacologic effect, a histopathological examination on the male and female reproductive organs showed no effects of tofersen. Tofersen is therefore considered unlikely to pose a risk affecting male and female fertility.
- Based on the following findings, tofersen is considered unlikely to affect embryo-fetal development:
  - An ASO is assumed to hardly cross the placenta [see Section 4.2.3].
  - Regarding the on-target toxicity of tofersen, the frequency of embryonic deaths in *SOD1* heterozygous mice is approximately one tenth that in *SOD1* knockout mice (*J Biol Chem.* 1998;273:7765-9).
  - Regarding the off-target toxicity of tofersen, the embryo-fetal development studies in mice and rabbits (CTD 4.2.3.5.1-1 and 4.2.3.5.2-3) raise no concerns [see Section 5.5].
- Based on the following findings, tofersen is considered unlikely to affect offspring through milk:
  - Regarding the on-target toxicity of tofersen, in the study for effects on pre- and postnatal development, including maternal function in mice (CTD 4.2.3.5.3-1), tofersen was detected in milk, and the tofersen concentration in milk in maternal animals in the maximum dose group was 88.3 ng/mL [see Section 4.4.2]. Tofersen is considered unlikely to exert a pharmacologic effect in offspring through milk, for the following reasons: (1) There is a substantial difference between the tofersen concentration in milk and EC_{50} of tofersen in reducing *SOD1* mRNA in *SOD1*-G93A mice (0.87 μg/g, 870 ng/mL based on the assumed density of 1 g/mL) [see Section 3.1.3.1], and (2) ASOs have low membrane permeability owing to its physical properties (hydrophilic and macromolecular properties) and is thus poorly absorbed when orally taken (*J Pharm Sci.* 2008:97:225-36).
  - Regarding the off-target toxicity of tofersen, the study for effects on pre- and postnatal development, including maternal function in mice (CTD 4.2.3.5.3-1) raise no concerns [see Section 5.5].

In view of the above evaluation, the applicant will include information about findings of the reproductive and developmental toxicity in *SOD1* knockout mice and cautionary statement that tofersen should be used in pregnant women or women of childbearing potential only if the expected therapeutic benefits outweigh the possible risks associated with treatment in the package insert.

PMDA's view:

Based on the study results discussed, no particular problems are found in the applicant's determination that tofersen is unlikely to affect fertility and offspring through milk. Regarding the effect on embryo-fetal development and pregnancy maintenance, tofersen is unlikely to act directly on embryos and

fetuses based on the discussion about the placental transfer of ASOs, but in view of the information about embryo-fetal development in *SOD1*-gene modified mice, tofersen may adversely affect embryo-fetal development or pregnancy maintenance by acting on the maternal body. However, in view of the seriousness of SOD1-ALS, the intended indication, tofersen may be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment, on the condition that women of child bearing potential use contraception and findings of the reproductive and developmental toxicity in *SOD1* knockout mice be included in the package insert to raise caution.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Tofersen concentrations in human plasma and CSF were determined by hybridization ELISA (lower limit of quantification, 1.00 ng/mL), and total SOD1 protein concentrations in CSF were determined by ELISA (lower limit of quantification, 0.078 ng/mL). Anti-drug antibody (ADA) concentrations in plasma were determined by immunoassay.

In Parts A and B of Study 233AS101 (Study 101), the 2-vial formulation consisted of 1 vial filled with a solution of tofersen at 20 mg/mL and the other one filled with artificial CSF for dilution was used to allow preparation and use of different doses. In Part C of Study 101, the 1-vial formulation filled with a solution of tofersen at 6.7 mg/mL was used. In Study 233AS102 (Study 102), an extension study, the 1-vial formulation used in Part C was used, but to subjects who entered the extension study from Parts A and B of Study 101, the 2-vial formulation was supplied until the 1-vial formulation became substitutable. The to-be marketed formulation has the same formulation as that of the 1-vial formulation used in Part C of Study 101 and Study 102.

6.2 Clinical pharmacology

6.2.1 Studies using human biological samples

(a) Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-1)

Tofersen (0.1 or 30 μg/mL) was added to human plasma followed by ultrafiltration to determine the protein binding rate. The plasma protein binding rate was 98.1% for tofersen 0.1 μg/mL and 97.9% for 30 μg/mL.

(b) Investigation of metabolites

The metabolism was not investigated using human samples.

The applicant's explanation:

Based on the information about metabolites of tofersen identified in monkeys and mice treated with tofersen and published literature (*Expert Opin Drug Metab Toxicol.* 2013;9:169-82, *Drug Metab Dispos.* 2007;35:460-8), tofersen is presumed not to undergo metabolism by cytochrome P450 (CYP) but to be hydrolyzed into shorter oligonucleotides by nuclease present throughout the body.

(c) Enzyme inhibition and enzyme induction (CTD 4.2.2.6-3 and 4.2.2.6-4)

Using substrates[11] of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, the inhibitory effect of tofersen (0.1-100 µmol/L) against these CYP isoforms was investigated, and tofersen did not inhibit any metabolic enzyme.

Tofersen (100 µg/mL) was added to human hepatocytes, and the inducing effect of tofersen on CYP1A2, CYP2B6, and CYP3A4 was investigated based on their mRNA expression. Tofersen did not induce any of these metabolic enzymes.

(d) Assessment of tofersen as a substrate for drug transporters or its inhibitory effect (CTD 4.2.2.6-1 and 4.2.2.6-2)

To examine if tofersen (1 and 10 µmol/L) is transported by BCRP, MDR1, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2, cells expressing each transporter or monolayer membrane was used. Tofersen was not a substrate for any of these transporters.

Tofersen (10 and 100 µmol/L) did not inhibit transport of the representative substrates[12] of BCRP, BSEP, MDR1, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

6.2.2 Investigations in patients

6.2.2.1 Foreign phase I/II study (CTD 5.3.3.2.1, Parts A and B of Study 101, January 2016 to January 2019)

In Part A, a single dose of tofersen was administered to non-Japanese patients with SOD1-ALS (15 patients included in the pharmacokinetic evaluation) to investigate the pharmacokinetics. A single dose of placebo or tofersen 10, 20, 40, or 60 mg was intrathecally administered. Pharmacokinetic parameters of tofersen are shown in Table 13. The tofersen concentration (mean ± standard deviation [SD]) in CSF on Day 29 was 1.47 ± 0.17, 2.37 ± 0.30, and 1.91 ± 1.02 ng/mL in the tofersen 20, 40, and 60 mg groups, respectively. In the tofersen 10 mg group, measured concentrations in all patients were below the lower limit of quantification.

Table 13. Pharmacokinetic parameters in plasma after single-dose administration of tofersen

Dose	No. of patients evaluated	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
10 mg	3	80.7 ± 67.8	4.00 [4.0, 6.0]	1054 ± 811
20 mg	3	85.1 ± 52.6	6.00 [2.0, 6.0]	1039 ± 200
40 mg	3	203.7 ± 31.1	6.00 [6.0, 6.0]	2915 ± 600
60 mg	6	686.8 ± 487.6	2.00 [2.0, 6.0]	5729 ± 2847

Mean ± SD, t_{max} is presented as median [range].

In Part B, a total of 5 doses of tofersen (the first 3 doses every 2 weeks and the subsequent 2 doses every 4 weeks) were administered to non-Japanese patients with SOD1-ALS (38 patients included in the pharmacokinetic evaluation) to investigate the pharmacokinetics. Multiple doses of placebo or tofersen 20, 40, 60, or 100 mg were intrathecally administered. Table 14 shows pharmacokinetic parameters of

[11] CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, diclofenac; CYP2C19, S-mephenytoin; CYP2D6, dextromethorphan; CYP2E1, chlorzoxazone; CYP3A4, midazolam and testosterone.

[12] BCRP, estrone-3-sulfate; BSEP, taurocholic acid; MDR1, N-methylquinidine; MATE1, metformin; MATE2-K, metformin; OAT1, tenofovir; OAT3, estrone-3-sulfate; OATP1B1, estradiol-17-β-glucuronide; OATP1B3, cholecystokinin octapeptide; OCT1, sumatriptan; OCT2, metformin

tofersen in plasma on Days 1 and 85. Table 15 shows tofersen concentrations in CSF at each sampling point.

Table 14. Pharmacokinetic parameters in plasma after single and multiple administrations of tofersen

Dose	Day of measurement	No. of patients evaluated	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
20 mg	Day 1	10	121.9 ± 118.8	6.00 [2.0, 24.0]	1192.8 ± 630.5
	Day 85	9	131.2 ± 64.6	4.00 [2.0, 6.0]	
40 mg	Day 1	9	350.9 ± 315.5	6.00 [1.0, 6.0]	3501.0 ± 2005.4
	Day 85	8	245.1 ± 170.6	6.00 [1.0, 6.0]	
60 mg	Day 1	9	603.6 ± 569.4	2.00 [1.0, 6.0]	4970.6 ± 2732.7
	Day 85	9	546.7 ± 395.6	4.00 [1.0, 6.0]	
100 mg	Day 1	10	1414.4 ± 1124.2	3.00 [1.0, 24.0]	13662.7 ± 7932.2
	Day 85	10	1490.8 ± 1009.1	4.00 [1.0, 6.0]	

Mean ± SD, t_{max} is presented as median [range].

Table 15. Tofersen concentrations in CSF after multiple administrations of tofersen

Dose	Day 15	Day 29	Day 57	Day 85 (last dose)	Day 106	Day 169
20 mg	3.17 ± 2.40 (10)	4.14 ± 2.64 (9)	2.58 ± 1.82 (9)	2.58 ± 1.45 (9)	3.03 ± 1.58 (9)	0.58 ± 0.22 (8)
40 mg	4.26 ± 2.27 (9)	6.90 ± 2.95 (9)	3.45 ± 1.27 (9)	3.40 ± 1.90 (9)	5.28 ± 2.68 (9)	1.20 ± 0.75 (6)
60 mg	5.00 ± 2.48 (8)	7.94 ± 4.18 (9)	3.80 ± 1.42 (9)	3.81 ± 1.98 (9)	4.97 ± 2.33 (8)	0.80 ± 0.39 (7)
100 mg	6.49 ± 2.68 (10)	10.44 ± 4.40 (10)	5.71 ± 3.05 (10)	5.70 ± 2.72 (10)	8.72 ± 4.95 (10)	1.12 ± 0.76 (8)

Unit, ng/mL; Mean ± SD (number of patients evaluated)

Total SOD1 protein concentrations in CSF were measured after multiple administrations of tofersen, and based on the mixed-effects models for repeated measures (MMRM), the geometric mean ratio of the total SOD1 protein concentration in CSF on Day 85 to the baseline value was 0.99, 0.73, 0.79, and 0.64 in the tofersen 20, 40, 60, and 100 mg groups, respectively, and 0.97 in the placebo group.

6.2.2.2 Global phase III study (CTD 5.3.5.1.1.1, Part C of Study 101, March 2019 to July 2021)

A total of 8 doses of placebo or tofersen 100 mg (the first 3 doses every 2 weeks and the subsequent 5 doses every 4 weeks) were intrathecally administered to Japanese and non-Japanese patients with SOD1-ALS (72 patients included in the pharmacokinetic evaluation). Table 16 shows tofersen concentrations in plasma and CSF in the tofersen group. Table 17 shows total SOD1 protein concentrations in CSF.

Table 16. Trough tofersen concentrations in plasma and CSF after multiple administrations of tofersen

Evaluation point	Concentration in CSF	Concentration in plasma
Day 15	19.12 ± 24.59 (71)	0.79 ± 0.64 (72)
Day 29	25.67 ± 35.04 (71)	18.47 ± 146.05 (71)
Day 57	17.95 ± 20.18 (66)	0.76 ± 0.40 (67)
Day 85	17.58 ± 18.88 (62)	0.74 ± 0.51 (64)
Day 113	20.39 ± 22.21 (66)	0.86 ± 1.18 (65)
Day 141	23.62 ± 24.57 (63)	1.18 ± 2.30 (62)
Day 169	27.04 ± 23.90 (61)	2.00 ± 5.43 (64)
Day 197	24.18 ± 24.38 (58)	2.84 ± 7.33 (49)

Unit, ng/mL; Mean ± SD (number of patients evaluated)
Measured concentrations in CSF ≥300 ng/mL are not included in calculation of statistics.

Table 17. Change in total SOD1 protein concentration in CSF from baseline and the geometric mean ratio to baseline value

Evaluation point	Placebo (n = 36)		Tofersen (n = 72)	
	Change (ng/mL)	Geometric mean ratio	Change (ng/mL)	Geometric mean ratio
Day 15	−8.9 ± 38.8 (36)	0.91	−5.5 ± 50.4 (71)	0.93
Day 29	−5.0 ± 32.2 (35)	0.96	−15.7 ± 31.2 (70)	0.87
Day 57	−16.2 ± 31.2 (33)	0.89	−30.2 ± 33.9 (65)	0.75
Day 85	−14.5 ± 43.4 (36)	0.91	−34.7 ± 34.5 (63)	0.71
Day 113	−14.7 ± 54.1 (33)	0.88	−30.6 ± 87.9 (65)	0.69
Day 141	−7.3 ± 65.7 (34)	0.93	−38.1 ± 47.8 (63)	0.67
Day 169	−5.0 ± 56.6 (33)	0.93	−30.5 ± 61.1 (61)	0.72
Day 197	4.3 ± 49.6 (28)	1.03	−43.1 ± 51.5 (54)	0.66

Change from baseline, Mean ± SD (number of patients)
The baseline value was 125.5 ± 70.0 in the placebo group and 118.7 ± 56.3 ng/mL in the tofersen group.

6.R Outline of the review conducted by PMDA

6.R.1 Difference in pharmacokinetics between Japanese and non-Japanese patients

PMDA asked the applicant to explain differences in pharmacokinetics of tofersen between Japanese and non-Japanese patients.

The applicant's explanation:

Table 18 and Table 19 show trough tofersen concentrations in CSF and pharmacokinetic parameters in plasma in Japanese and non-Japanese patients enrolled in the tofersen group in Part C of Study 101, conducted as a global phase III study. Trough tofersen concentrations in CSF and pharmacokinetic parameters of tofersen in plasma in Japanese patients were within the corresponding range in non-Japanese patients, and the applicant considers that the pharmacokinetics of tofersen does not greatly differ between Japanese and non-Japanese patients.

Table 18. Trough tofersen concentrations in CSF in Japanese and non-Japanese patients with SOD1-ALS intrathecally treated with tofersen 100 mg

Evaluation point	Japanese	Non-Japanese
Day 15	18.29 [10.7, 85.4] (3)	9.27 [1.3, 103.8] (68)
Day 29	40.87 [14.2, 256.5] (3)	15.71 [1.8, 96.5] (68)
Day 57	31.79 [23.9, 46.4] (3)	7.13 [1.5, 90.8] (63)
Day 85	19.96 [3.3, 53.7] (3)	9.00 [1.1, 83.3] (59)
Day 113	25.56 [3.2, 47.4] (3)	10.01 [0.5, 91.2] (63)
Day 141	30.53 [6.1, 77.2] (3)	10.54 [1.5, 87.5] (60)
Day 169	33.8, 47.8[a)] (2)	19.39 [1.3, 89.4] (59)
Day 197	3.71 [3.5, 6.1] (3)	15.01 [1.6, 87.9] (55)

Unit, ng/mL; Median [range] (number of patients evaluated)
Values ≥300 ng/mL are not included in calculation of statistics.
a) Individual values in 2 patients

Table 19. Tofersen concentrations and pharmacokinetic parameters in plasma on Day 1 in Japanese and non-Japanese patients with SOD1-ALS intrathecally treated with tofersen 100 mg

	No. of patients evaluated	Concentration in plasma (ng/mL)					Pharmacokinetic parameter		
		1 hour post-dose	2 hours post-dose	4 hours post-dose	6 hours post-dose	24 hours post-dose	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)
Japanese	3	19.3 [5.0, 419.2]	97.5 [59.5, 1180.7]	272.9 [179.1, 1435.4]	226.6 [192.8, 959.5]	167.6 [42.7, 303.7]	303.7 [227, 1435]	6.0 [4, 24]	5358.6 [4242, 15040]
Non-Japanese	19	115.4 [4.1, 4240.5]	426.4 [24.6, 3481.4]	686.4 [36.7, 2919.2]	633.1 [36.0, 2491.3]	-	940.6 [57, 4240]	4.0 [1, 6]	13984.5 [836, 53918]

Median [range]; -, Not measured

PMDA's view:
Trough tofersen concentrations in CSF and pharmacokinetic parameters of tofersen in plasma in Japanese subjects were confirmed to be within the corresponding range in non-Japanese subjects. However, the data in Japanese subjects are very limited, and thus discussion about differences in pharmacokinetics of tofersen between Japanese and non-Japanese subjects has limitations. Differences in efficacy and safety between Japanese and non-Japanese patients are continuously discussed in Sections 7.R.2 and 7.R.3.

6.R.2 Pharmacokinetics in patients with renal impairment

PMDA asked the applicant to explain pharmacokinetics of tofersen and the necessity of dose adjustment in patients with renal impairment.

The applicant's explanation:
Metabolism and elimination of tofersen have not been investigated in humans. However, as with the other 2'-MOE-modified ASOs, tofersen is supposed to be metabolized by nuclease, the plasma protein binding rate of tofersen is as high as ≥95%, and the protein-bound form is not allowed to undergo glomerular filtration. Thus, unchanged tofersen is not basically supposed to be excreted into urine. Furthermore, a human mass balance study of volanesorsen, which has phosphorothioate backbone and 2'-MOE chemical modification as with tofersen, demonstrated that the renal excretion of metabolites shortened by nuclease played the main role in excretion. When volanesorsen was systemically administered, radioactivity of the urine excreted within 24 hours after the last dose accounted for approximately 16.5% of the dose, and unchanged volanesorsen excreted in the urine accounted for only 3.2% of the total dose (*Drug Metab Dispos.* 2019;47:1164-73).

Based on the above, tofersen is supposed to be mainly metabolized into short oligonucleotides, and these metabolites are then expected to be excreted into urine. Renal impairment is thus unlikely to affect pharmacokinetics of tofersen in a clinically meaningful manner, and dose adjustment of tofersen is considered unnecessary for patients with renal impairment.

PMDA's view:
Although detailed investigation of metabolism and excretion of tofersen in humans such as a mass balance study has not been conducted, the applicant explained that contribution of renal function to elimination of unchanged tofersen is limited based on the information in published literature on the ASOs in similar structure. The applicant's explanation is understandable to a certain extent. Based on the information available to date, existing renal impairment is considered unlikely to affect pharmacokinetics of tofersen to a clinically relevant extent. Therefore, adjustment of the dosage regimen of tofersen is unnecessary for patients with renal impairment.

6.R.3 QT/QTc interval prolongation

Any thorough QT study of tofersen has not been conducted. PMDA asked the applicant to explain a potential of tofersen to prolong the QT/QTc interval.

The applicant's explanation:
In a non-clinical study, tofersen did not inhibit hERG current at up to the maximum concentration investigated (34 μmol/L), and the concerned concentration was ≥170 times the C_{max} at the human recommended clinical dose (100 mg). Intrathecal administration of tofersen at up to 35 mg in monkeys did not affect electrocardiogram (ECG) parameters, and the C_{max} in monkeys was approximately 20 to 30 times that in humans [see Section 3.3].

Tofersen is intended to be administered by intrathecal injection, a highly invasive procedure, and the thorough QT study in healthy adults is not feasible. ECG during tofersen treatment was evaluated in clinical studies in patients with SOD1-ALS.

Table 20 shows categorical analysis results on QTcF interval obtained from ECG data in Part C of Study 101. None of the subjects in the tofersen group were found to have absolute QTcF interval >480 ms or a change in QTcF interval from baseline >60 ms. The number of subjects who had a change in QTcF interval from baseline >30 ms and ≤60 ms was 8 in the tofersen group, which was greater than 2 in the placebo group. However, tofersen concentrations in plasma in these 8 subjects were within the concentration range in subjects who had a change in QTcF interval ≤30 ms, and no adverse events coded to the system organ class (SOC) "Cardiac disorders," events related to arrhythmia, or events potentially attributable to QTcF prolongation were observed.

Table 20. Categorical analysis results on QTcF interval in Part C of Study 101

		Placebo (n = 36)	Tofersen (n = 72)
Maximum QTcF interval	>450 ms and ≤480 ms	2 (5.6)	2 (2.8)
	>480 ms and ≤500 ms	0	0
	>500 ms	0	0
Change in QTcF interval from baseline	>30 ms and ≤60 ms	2 (5.6)	8 (11.3)
	>60 ms	0	0

Number of patients in the category (incidence [%])

In Part C of Study 101, adverse events[13)] related to QT/QTc interval prolongation and a proarrhythmic effect occurred in 2 of 36 patients in the placebo group (syncope and loss of consciousness) and 1 of 72 patients in the tofersen group (loss of consciousness and electrocardiogram QT prolonged), and a causal relationship to the study drug was ruled out for all of the events.

In the thorough QT studies in healthy adults[14)] using mipomersen and volanesorsen, ASOs which have phosphorothioate backbone and 2'-MOE chemical modification and is comprised of 20 bases as with tofersen, results indicated that these drugs are unlikely to affect QT interval in a clinically meaningful manner (*Eur J Clin Pharmacol.* 2016;72:267-75, *Nucleic Acid Ther.* 2020;30:198-206).

Based on the above, tofersen when used according to the proposed dosage and administration is considered unlikely to pose a risk of QT interval prolongation.

13) Events coded to Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Queries (SMQ) (broad) "Torsade de pointes/QT prolongation" and high level term (HLT) "ECG investigations"
14) The maximum dose and administration route investigated in the thorough QT study was 200 mg for mipomersen and 300 mg for volanesorsen, both administered intravenously. The proposed dosage and administration for tofersen is 100 mg per dose administered intrathecally.

PMDA's view:

Based on information available to date, including ECG data obtained in Part C of Study 101, incidences of adverse events, non-clinical study results, and published literature, tofersen when used according to the proposed dosage and administration is considered unlikely to pose a risk of QT interval prolongation. Caution in the package insert is unnecessary.

6.R.4 Effects of anti-drug antibody on efficacy and safety of tofersen

The applicant's explanation about development of ADA[15)] against tofersen during the tofersen treatment and effects of ADA on pharmacokinetics, efficacy, and safety:

Table 21 shows development of ADA in Studies 101 and 102.

Table 21. Development of ADA in clinical studies (data cutoff in July 2022)

	Part C of Study 101		Studies 101 and 102	
	Placebo (n = 36)	Tofersen 100 mg (n = 72)	Subjects treated with tofersen 100 mg in Study 101 or Study 102 (n = 147)	Subjects treated with tofersen in Study 101 or Study 102 (n = 166)
ADA negative	34 (94.4)	50 (69.4)	54 (36.7)	69 (41.6)
ADA positive	2 (5.6)	22 (30.6)	93 (63.3)	97 (58.4)
Persistent ADA response	2 (5.6)	19 (26.4)	76 (51.7)	83 (50.0)
Transient ADA response	0	3 (4.2)	17 (11.6)	14 (8.4)

Number of patients with/without development (incidence [%])

Regarding an effect of ADA on pharmacokinetics of tofersen, Table 22 shows trough tofersen concentrations in plasma and CSF in ADA-positive and ADA-negative patients in the tofersen group in Part C of Study 101. Although tofersen concentrations in plasma were higher in ADA-positive subjects than in ADA-negative subjects, pharmacokinetic parameters in plasma at Week 12 in Part C of Study 101 include $AUC_{0\text{-}24h}$ (median [range]) of 13590.3 ng·h/mL [3473, 29604] and C_{max} of 769.0 ng/mL [162, 1750] in ADA-negative subjects (n = 11), and $AUC_{0\text{-}24h}$ of 9988.2 ng·h/mL [5009, 27181] and C_{max} of 474.1 ng/mL [287, 1231] in ADA-positive subjects (n = 8). The exposure in ADA-positive subjects was within the range of exposure in ADA-negative subjects. Tofersen concentrations in CSF are not considered to clearly differ between ADA-negative and ADA-positive subjects in view of the intra-subject variability. Generally, macromolecules such as ADA hardly cross the blood-brain barrier and seldom enter CSF; therefore, the effect of ADA on tofersen in CSF is considered negligible.

15) Subjects meeting either condition were assessed as ADA positive.
- Subjects who were negative for ADA just before the first dose of tofersen and received a positive result at least once after baseline
- Subjects who were positive for ADA just before the first dose of tofersen and showed the antibody titer increased ≥2 times at least once after baseline

Persistent ADA response was defined as the condition where evaluable data after the first positive result include at least 2 positive results on and after Day 112 or at least 1 positive result after baseline before Day 112.
Transient ADA response was defined as the condition where at least 1 positive result was available but no persistent ADA response was documented.

Table 22. Trough tofersen concentrations in CSF and plasma in ADA-negative and ADA-positive subjects in the tofersen group in Part C of Study 101 (Part C of Study 101 and Study 102)

	Trough concentration in CSF		Trough concentration in plasma	
	ADA-negative	ADA-positive	ADA-negative	ADA-positive
Pre-dose at Week 4	26.9 ± 22.7 (29) 20.8 [1.8, 93.7]	24.8 ± 41.7 (42) 10.8 [3.3, 256.5]	1.13 ± 0.60 (29) 1.08 [0.5, 2.3]	30.45 ± 189.89 (42) 0.50 [0.5, 1231.7]
Pre-dose at Week 12	18.1 ± 18.8 (23) 10.3 [1.6, 67.7]	17.3 ± 19.2 (39) 9.0 [1.1, 83.3]	0.65 ± 0.36 (24) 0.50 [0.5, 1.7]	0.79 ± 0.58 (40) 0.50 [0.5, 3.3]
Pre-dose at Week 24	26.8 ± 24.4 (22) 20.3 [1.3, 77.8]	27.2 ± 24.0 (39) 20.0 [1.8, 89.4]	0.94 ± 1.25 (24) 0.50 [0.5, 6.6]	2.64 ± 6.76 (40) 0.50 [0.5, 41.3]
Pre-dose at Week 48	7.5 ± 3.4 (21) 7.5 [3.0, 14.0]	13.6 ± 12.4 (33) 10.5 [2.7, 64.2]	0.68 ± 0.38 (18) 0.50 [0.5, 1.8]	7.54 ± 14.6 (31) 2.32 [0.5, 62.2]

Unit, ng/mL; Measured concentrations in CSF ≥300 ng/mL are not included in calculation of statistics.
Top, :Mean ± SD (number of subjects), Bottom, Median [range]

For the efficacy, a change in ALS Functional Rating Scale-Revised (ALSFRS-R) total score[16] from baseline to Week 28 in subjects in Part C of Study 101 (based on analysis of covariance [ANCOVA] model) was −8.2 in ADA-negative subjects and −2.1 in ADA-positive subjects in the tofersen group, and an extent of score worsening tended to be smaller in ADA-positive subjects than in ADA-negative subjects. The ratio of total SOD1 protein concentration in CSF at Week 28 to the baseline value (mean [range]) was 0.73 [0.5, 1.5] in ADA-negative subjects and 0.73 [0.2, 3.0] in ADA-positive subjects in the tofersen group, showing no clear difference between ADA-negative and ADA-positive subjects. However, definite discussion about the efficacy by presence or absence of ADA is difficult because the number of subjects in each group is limited and SOD1-ALS symptoms are highly heterogeneous.

For the safety, Table 23 shows adverse events in ADA-negative subjects and ADA-positive subjects in the population of subjects treated with tofersen 100 mg in Studies 101 and 102. No clear difference was observed between ADA-negative subjects and ADA-positive subjects.

Table 23. Adverse events in ADA-positive subjects and ADA-negative subjects in the population of 147 subjects treated with tofersen 100 mg (data cutoff in July 2022)

	ADA negative (n = 54)	ADA positive (n = 93)
All adverse events	53 (98.1)	92 (98.9)
Serious adverse events	26 (48.1)	33 (35.5)
Adverse events leading to treatment discontinuation	14 (25.9)	12 (12.9)

Number of patients with the event (incidence [%])

Furthermore, events related to hypersensitivity[17] were evaluated as adverse events in a specific class likely related to immunoreaction for their occurrence. The events related to hypersensitivity occurred in 57.4% (31 of 54) of ADA-negative subjects and 64.5% (60 of 93) of ADA-positive subjects in the population of subjects treated with tofersen 100 mg in Studies 101 and 102 (data cutoff in July 2022), showing no clear difference between ADA-negative and ADA-positive subjects.

PMDA's view:
Results in Studies 101 and 102 showed that tofersen concentrations in plasma at each sampling point tended to be higher in ADA-positive subjects than in ADA-negative subjects. However, the efficacy did

16) Rating scale of functional impairment developed to assess to what extent the functions of daily living are impaired in patients with ALS. A total of 12 items, i.e., speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency, are rated on a 5-point scale (0-4, 4 representing normal function) (48 points, in total).
17) Events coded to MedDRA SMQ "Hypersensitivity," "Anaphylactic reaction," and "Angioedema"

not tend to be lower in ADA-positive subjects than in ADA-negative subjects, and the adverse events did not tend to greatly differ between ADA-negative and ADA-positive subjects in terms of the incidence or type. During use of tofersen, development of ADA is unlikely to raise clinically relevant problems.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from clinical studies listed in Table 24.

Table 24. List of main clinical studies for efficacy and safety

Category	Region	Study CTD	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoint
Evaluation	Foreign	Parts A and B of Study 233AS101 5.3.3.2.1	I/II	Patients with genetically diagnosed SOD1-ALS	Part A: 20 Part B: 40	Part A: Single-dose administration of placebo or tofersen 10, 20, 40, or 60 mg Part B: Administration of 3 loading doses of placebo or tofersen 20, 40, 60, or 100 mg (every 2 weeks), followed by 2 maintenance doses (every 4 weeks)	Safety Pharmacokinetics
Evaluation	Global	Part C of Study 233AS101 5.3.5.1.1	III	Patients with genetically diagnosed SOD1-ALS	108	Administration of 3 loading doses of placebo or tofersen 100 mg (every 2 weeks), followed by 5 maintenance doses (every 4 weeks)	Efficacy Safety
Evaluation	Global	Study 233AS102 5.3.5.2.1	III	Patients with SOD1-ALS who completed Study 101	139	Maintenance doses of tofersen 100 mg (every 4 weeks)	Safety

7.1 Foreign phase I/II study (CTD 5.3.3.2.1, Parts A and B of Study 101, January 2016 to January 2019)

7.1.1 Part A (single-dose part)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 4 countries[18)] to evaluate the safety and pharmacokinetics of tofersen intrathecally administered as a single dose in non-Japanese patients with genetically diagnosed SOD1-ALS aged ≥18 years[19),20)] (target sample size, 20 to up to 36 patients[21)]) [for pharmacokinetics, see Section 6.2.2.1].

A single dose of placebo or tofersen 10, 20, 40, or 60 mg was intrathecally administered. To each of tofersen 10, 20, and 40 mg cohorts, 4 patients (1 in the placebo group and 3 in the tofersen group) were

18) US, Canada, Belgium, and Germany

19) Patients meeting the following criteria were eligible:
- Patients with muscular weakness attributable to ALS observed at 2 screening visits and a genetically confirmed *SOD1* gene mutation
- Patients with forced vital capacity (FVC) (measured in sitting position) ≥50% of predicted value as adjusted for sex, age, and height. Patients with %FVC stably ≥45% and <50% and a ≤5% decrease in the past 6 months were considered potentially eligible by an investigator.

20) Initially, 12 patients were enrolled in Part A, regardless of an *SOD1* gene mutation, but upon issuance of the revised version 2 protocol, which additionally required patients with a genetically confirmed *SOD1 gene* mutation for enrollment, 8 patients additionally meeting this criterion were enrolled. Six subjects were not confirmed to have a *SOD1* gene mutation.

21) The final sample size in Part A was determined based on the number of subjects with dose-limiting toxicity (DLT). If no DLT has occurred, the minimum 20 patients will be randomized; or if DLT has occurred, based on the number of patients with DLT, a total of up to 16 patients (12 in the tofersen group and 4 in the placebo group) may be additionally allocated to the selected dose in Part A.

randomized, and to the tofersen 60 mg cohort, 8 patients (2 in the placebo group and 6 in the tofersen group) were randomized.

The 20 randomized patients (5 in the placebo group, 3 each in the tofersen 10, 20, and 40 mg groups, 6 in the 60 mg group) were included in the ITT population and safety analysis population. Because of consent withdrawal, 1 patient (tofersen 10 mg group) discontinued the study. Of 19 patients who completed Part A, 2 patients were enrolled again in Part B.

For the safety, adverse events occurred in 2 patients (40.0%) in the placebo group, 2 patients (66.7%) in the tofersen 10 mg group, 3 patients (100%) in the 20 mg group, 3 patients (100%) in the 40 mg group, and 6 patients (100%) in the 60 mg group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Adverse events reported by ≥2 patients across the groups were procedural pain (1 patient in the placebo group, 0 patients in the tofersen 10 mg group, 1 patient in the 20 mg group, 0 patients in the 40 mg group, 3 patients in the 60 mg group, the same order applies hereinafter), headache (0 patients, 0 patients, 2 patients, 1 patient, 1 patient), back pain (0 patients, 0 patients, 0 patients, 0 patients, 2 patients), muscle spasms (0 patients, 0 patients, 0 patients, 0 patients, 2 patients), pain in extremity (0 patients, 0 patients, 0 patients, 1 patient, 1 patient), and post procedural contusion (0 patients, 0 patients, 1 patient, 0 patients, 1 patient).

7.1.2 Part B (multiple-dose part)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 6 countries[22] to evaluate the efficacy, safety, and pharmacokinetics of tofersen intrathecally administered multiple times in non-Japanese patients with genetically diagnosed SOD1-ALS aged ≥18 years[19] (target sample size, 48 patients; 12 per cohort [3 in the placebo group and 9 in the tofersen group]) [for pharmacokinetics, see Section 6.2.2.1].

Placebo or tofersen 20, 40, 60, or 100 mg was intrathecally administered 3 times every 2 weeks and then 2 times every 4 weeks over a period of 12 weeks.

All of the 50 randomized patients (12 in the placebo group, 10 in the tofersen 20 mg group, 9 in the 40 mg group, 9 in the 60 mg group, 10 in the 100 mg group) were included in the ITT population, safety analysis population, and clinical function analysis population.[23] A total of 5 patients (2 in the placebo group, 2 in the tofersen 20 mg group, 1 in the 60 mg group) discontinued the study, mainly because of deaths (1 patient in the placebo group, 1 patient in the tofersen 20 mg group, 1 patient in the 60 mg group).

Table 25 shows data on a change in ALSFRS-R total score from baseline, the efficacy endpoint.

[22] US, Canada, Belgium, France, Germany, and UK
[23] Subjects who were included in the ITT population and underwent evaluation for clinical function endpoints at least once

Table 25. Change in ALSFRS-R total score from baseline to Day 85 (clinical function analysis population[23])

	Placebo (n = 12)	Tofersen			
		20 mg (n = 10)	40 mg (n = 9)	60 mg (n = 9)	100 mg (n = 10)
Baseline value[a)]	36.0 ± 4.81	34.4 ± 7.41	36.7 ± 9.53	38.3 ± 6.54	38.2 ± 2.39
Change from baseline[b)]	−5.63 [−8.90, −2.36]	−0.76 [−4.49, −2.97]	−0.82 [−4.50, −2.85]	−2.13 [−5.82, 1.56]	−1.19 [−4.67, −2.29]
Difference from placebo[b)]	-	4.88 [−0.04, 9.79]	4.81 [−0.09, 9.70]	3.50 [−1.42, 8.42]	4.44 [−0.34, 9.22]

a) Mean ± SD; The baseline value was defined as the score before administration of the study drug on Day 1. When the score on Day 1 was missing, the last score before the first dose was used as the baseline value.
b) Least squares mean [95% confidence interval (CI)]

For the safety, adverse events occurred in all patients (50 of 50 patients). Deaths occurred in 3 patients (1 in the placebo group [respiratory failure], 1 in the tofersen 20 mg group [pulmonary embolism], 1 in the 60 mg group [respiratory failure]), but a causal relationship to the study drug was ruled out for all the events. Serious adverse events other than deaths occurred in 4 patients (1 of 12 patients in the placebo group [acute respiratory failure], 1 in the tofersen 20 mg group [dyspnoea], 1 in the tofersen 40 mg group [respiratory failure], 1 in the tofersen 60 mg group [CSF protein increased and CSF white blood cell count increased]), and a causal relationship to the study drug was ruled out for all the events, except for CSF protein increased and CSF white blood cell count increased (1 patient) in the tofersen 60 mg group. There were no adverse events leading to treatment discontinuation except for deaths. Table 26 shows main adverse events in Part B of Study 101.

Table 26. Incidences of adverse events in Part B of Study 101 (safety analysis population)

	Placebo (n = 12)	Tofersen			
		20 mg (n = 10)	40 mg (n = 9)	60 mg (n = 9)	100 mg (n = 10)
Adverse events reported by ≥4 subjects in any group					
Procedural pain	5 (41.7)	4 (40.0)	1 (11.1)	4 (44.4)	7 (70.0)
Headache	7 (58.3)	4 (40.0)	2 (22.2)	4 (44.4)	6 (60.0)
Back pain	0	1 (10.0)	1 (11.1)	1 (11.1)	5 (50.0)
Fall	3 (25.0)	3 (30.0)	3 (33.3)	2 (22.2)	5 (50.0)
Pain in extremity	2 (16.7)	0	1 (11.1)	0	3 (30.0)
Post lumbar puncture syndrome	3 (25.0)	4 (40.0)	3 (33.3)	3 (33.3)	3 (30.0)
CSF protein increased	0	0	1 (11.1)	4 (44.4)	1 (10.0)
Upper respiratory tract infection	0	4 (40.0)	0	2 (22.2)	0

Number of patients with the event (incidence [%])

7.2 Global phase III study (CTD 5.3.5.1.1.1, Part C of Study 101, March 2019 to July 2021)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 9 countries[24] to evaluate the efficacy and safety of tofersen in patients with genetically diagnosed SOD1-ALS aged ≥18 years (target sample size; 99 patients [33 in the placebo group, 66 in the tofersen group], 60 patients meeting the prognostic enrichment criteria[25] [20 in the placebo group, 40 in the tofersen group[26]]) [for pharmacokinetics, see Section 6.2.2.2].

Enrolled patients with SOD1-ALS were divided into a subgroup of subjects who met the prognostic enrichment criteria for rapid disease progression based on their gene mutation type and an extent of disease progression[25] and a subgroup of the other subjects,[27] stratified according to 3 factors of whether the patient met the prognostic enrichment criteria for rapid disease progression, use of edaravone at baseline, and use of riluzole at baseline,[28] and randomized to the placebo group and tofersen group in a ratio of 1:2.

Placebo or tofersen 100 mg was intrathecally administered 3 times every 2 weeks and then 5 times every 4 weeks over a period of 24 weeks. Each dose should be administered over 1 to 3 minutes. The subjects who completed Part C were allowed to enter an open-label extension study (Study 102).

A total of 108 patients (36 in the placebo group, 72 in the tofersen group, the same order applies hereinafter) who were randomized and received the study drug at least once were included in the ITT population, of which 60 patients (21, 39) who met the prognostic enrichment criteria for rapid disease progression were included in the mITT population. The ITT and mITT populations were used as the safety and efficacy primary analysis populations, respectively. A total of 12 patients (3, 9) in the ITT population and 8 patients (2, 6) in the mITT population discontinued the study mainly because of disease progression (5 patients [2, 3] in the ITT population, 5 patients [2, 3] in the mITT population) and adverse events (3 patients [0, 3] in the ITT population, 2 patients [0, 2] in the mITT population).

Table 27 shows *SOD1* gene mutations observed in each population.

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[24] US, Canada, Belgium, France, Germany, Italy, UK, Denmark, and Japan

[25] Defined as subjects meeting either criterion a) or b) below, and for participation in this study, the slow vital capacity (SVC) (measured in sitting position) was required to be ≥65% of predicted value as adjusted for sex, age, and height.
a) One of the following *SOD1* gene mutations and an ALSFRS-R decline slope ≥0.2 per month (calculated as [full ALSFRS-R total score of 48 − baseline score]/time since symptom onset): p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val or p.Val149 Gly
b) An ALSFRS-R decline slope ≥0.9 per month (calculated as [full ALSFRS-R total score of 48 − baseline score]/time since symptom onset)

[26] The number of subjects was calculated using the slopes per month that were estimated from decreases in ALSFRS-R score over 6 months in the placebo group and the tofersen group (3.83 in the placebo group and −0.74 in the tofersen group; SD of pooled data, 3.166), based on results in 12 patients in the placebo group and 4 in the tofersen 100 mg group who met the criteria for the mITT population in Part C of Study 101 and were included in results in Part B of Study 101 and a controlled randomized study of arimoclomol in patients with SOD1-ALS (*Neurology.* 2018;90:e565-74). The survival rates (82% in the placebo group and 90% in the tofersen group) used in calculation of the sample size were based on the estimated survival rate in subjects with p.Ala5Val mutation, the most common variant among enrolled subjects and associated with rapid disease progression (median survival period from the Kaplan-Meier analysis is consistently ≤1.2 years) (*J Neurol Neurosurg Psychiatry.* 2017;88:99–105, *Nature Communications.* 2022;13:6901). Based on the above hypothesis, a two-sided test was calculated to have a power of 84% at a significance level of 0.05 when performed by the Joint-Rank methodology with a change in ALSFRS-R total score from baseline and survival period taken into account.

[27] For participation in this study, the SVC (measured in sitting position) was required to be ≥50% of predicted value as adjusted for sex, age, and height in addition to presence of an *SOD1* gene mutation other than those listed in the footnote 25) a).

[28] Use of both edaravone and riluzole was classified as use of edaravone.

Table 27. List of *SOD1* gene mutations in subjects enrolled in Part C of Study 101

	mITT		non-mITT		ITT		
Mutation	Placebo (n = 21)	Tofersen (n = 39)	Placebo (n = 15)	Tofersen (n = 33)	Placebo (n = 36)	Tofersen (n = 72)	Total (n = 108)
Intron[a)]	1 (4.8)	0	0	0	1 (2.8)	0	1 (0.9)
p.Ala5Ser	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Ala5Thr[b)]	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Ala5Val[b)]	6 (28.6)	11 (28.2)	0	0	6 (16.7)	11 (15.3)	17 (15.7)
p.Gly13Arg	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Phe21Ile	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Gln23Leu	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Gly38Arg	0	1 (2.6)	1 (6.7)	2 (6.1)	1 (2.8)	3 (4.2)	4 (3.7)
p.Leu39Val[b)]	1 (4.8)	1 (2.6)	0	0	1 (2.8)	1 (1.4)	2 (1.9)
p.Gly42Asp	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Gly42Ser[b)]	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.His44Arg[b)]	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.His47Arg[c)]	0	0	4 (26.7)	1 (3.0)	4 (11.1)	1 (1.4)	5 (4.6)
p.Glu50Lys	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Phe65Leu	0	0	1 (6.7)	1 (3.0)	1 (2.8)	1 (1.4)	2 (1.9)
p.Leu85Phe	0	3 (7.7)	0	0	0	3 (4.2)	3 (2.8)
p.Asn87Ser	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Ala90Thr	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Ala90Val	0	2 (5.1)	1 (6.7)	1 (3.0)	1 (2.8)	3 (4.2)	4 (3.7)
p.Asp91Ala	1 (4.8)	0	1 (6.7)	0	2 (5.6)	0	2 (1.9)
p.Gly94Ala[b)]	1 (4.8)	0	0	0	1 (2.8)	0	1 (0.9)
p.Gly94Arg	1 (4.8)	0	0	0	1 (2.8)	0	1 (0.9)
p.Gly94Asp	0	0	1 (6.7)	0	1 (2.8)	0	1 (0.9)
p.Gly94Cys	1 (4.8)	1 (2.6)	1 (6.7)	3 (9.1)	2 (5.6)	4 (5.6)	6 (5.6)
p.Gly94Ser[c)]	1 (4.8)	0	0	2 (6.1)	1 (2.8)	2 (2.8)	3 (2.8)
p.Glu101Gly	0	1 (2.6)	0	2 (6.1)	0	3 (4.2)	3 (2.8)
p.Glu101Lys	0	0	1 (6.7)	1 (3.0)	1 (2.8)	1 (1.4)	2 (1.9)
p.Asp102Gly	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Ile113Thr	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Ile114Thr	6 (28.6)	5 (12.8)	4 (26.7)	5 (15.2)	10 (27.8)	10 (13.9)	20 (18.5)
p.Arg116Gly	0	1 (2.6)	0	1 (3.0)	0	2 (2.8)	2 (1.9)
p.His121Gln	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Asp125Val	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Leu127Ser[c)]	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Thr138Ile	2 (9.5)	0	0	0	2 (5.6)	0	2 (1.9)
p.Ala141Gly	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Leu145Phe	0	0	0	4 (12.1)	0	4 (5.6)	4 (3.7)
p.Leu145Ser	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Ala146Thr	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)
p.Gly148Ser	0	0	0	1 (3.0)	0	1 (1.4)	1 (0.9)
p.Val149Gly[b)]	0	2 (5.1)	0	0	0	2 (2.8)	2 (1.9)
p.Ile150Thr	0	1 (2.6)	0	0	0	1 (1.4)	1 (0.9)

a) c.358-10T>G is a mutation that causes insertion of 9 nucleotides between Exons 4 and 5, resulting in production of SOD1 protein with 3 amino acid residues inserted (*Transl Neurodegener.* 2024;13:28)
b) Mutation included in the prognostic enrichment criteria
c) Mutation also found in Japanese subjects

Table 28 shows data on a change in ALSFRS-R total score from baseline to Week 28, the primary endpoint in the primary analysis in the mITT population. Comparison of point estimates showed that a decrease in ALSFRS-R total score from baseline tended to be smaller in the tofersen group than in the placebo group but no statistically significant difference was observed between the tofersen group and the placebo group.

Table 28. Change in ALSFRS-R total score from baseline to Week 28 (mITT population)

Group	No. of patients evaluated	Baseline value	Change from baseline[a)]	Difference between groups [95% CI][b)]	*P* value[c)]
Placebo	21	35.4 ± 5.66	−8.1 ± 1.79	1.2 [−3.19, 5.53]	0.9689
Tofersen	39	36.0 ± 6.40	−7.0 ± 1.42		

Mean ± SD

a) Least squares mean ± standard error (SE) calculated in an ANCOVA model using duration of disease up to baseline, ALSFRS-R score at baseline, and use of riluzole or edaravone as covariates and applying multiple imputation (MI) to missing data

b) Differences between groups and CI were calculated in the above ANCOVA model.

c) Calculated by the Joint-Rank methodology (see Footnote 29). Two-sided significance level of 5%

Table 29 shows data on a change in ALSFRS-R total score from baseline to Week 28 in the non-mITT population and ITT population.

Table 29. Change in ALSFRS-R total score from baseline to Week 28 (non-mITT population, ITT population)

Analysis population	Group	No. of patients evaluated	Baseline value	Change from baseline[a)]	Difference between groups [95% CI][b)]
Non-mITT	Placebo	15	39.9 ± 5.09	−2.73 ± 1.10	1.4 [−1.1, 3.9]
	Tofersen	33	38.1 ± 5.13	−1.33 ± 0.80	
ITT	Placebo	36	37.3 ± 5.81	−5.8 ± 1.27	1.4 [−1.3, 4.1]
	Tofersen	72	36.9 ± 5.91	−4.5 ± 1.01	

Mean ± SD

a) Least squares mean ± SE calculated in an ANCOVA model using duration of disease up to baseline, ALSFRS-R total score at baseline, and use of riluzole or edaravone as covariates and applying MI to missing data

b) Differences between groups and CI were calculated in the above ANCOVA model.

Table 30 shows data on a change in total SOD1 protein concentration in CSF from baseline to Week 28 in the mITT population, non-mITT population, and ITT population.

Table 30. Change in total SOD1 protein concentration in CSF from baseline to Week 28

Analysis population	Group	No. of patients evaluated	Baseline value	Geometric mean change from baseline	Difference between groups [95% CI][a)]
mITT population	Placebo	21	118.1 ± 63.1	1.16	0.62 [0.49, 0.78]
	Tofersen	39	117.2 ± 62.0	0.71	
Non-mITT population	Placebo	15	135.8 ± 79.8	0.81	0.74 [0.63, 0.88]
	Tofersen	33	120.4 ± 49.7	0.60	
ITT population	Placebo	36	125.5 ± 70.0	1.02	0.66 [0.52, 0.86]
	Tofersen	72	118.7 ± 56.3	0.68	

Mean ± SD

a) Calculated in an ANCOVA model using treatment as a fixed effect and duration of disease up to baseline, total SOD1 protein concentration at baseline, and use of riluzole or edaravone as adjustment factors

For the safety, adverse events occurred in 94.4% (34 of 36) of patients in the placebo group and 95.8% (69 of 72) of patients in the tofersen group. Table 31 shows the main adverse events.

[29)] The Joint-Rank test was performed according to the following procedure:

1. Missing data are imputed by the multiple imputation method.
2. In all combinations, the score to be evaluated in a subject is compared with that in every other subject, and the following process was performed: +1 is given if the score in a surviving subject is greater than the comparator subject, −1 is given if the score is smaller, and ±0 is given if the score is the same; and −1 is given if the death in a subject resulting in death occurred earlier than in the comparator subject and ±0 is given if the death occurred on the same day. The value obtained from this process was used as a rank score.
3. The rank scores were analyzed and tested by ANCOVA using duration of disease up to baseline, ALSFRS-R score at baseline, and use of riluzole or edaravone as covariates.

Table 31. Incidences of adverse events in Part C of Study 101 (ITT population)

	Placebo (n = 36)	Tofersen (n = 72)
All adverse events	34 (94.4)	69 (95.8)
Events reported by ≥7% of subjects in either group		
Procedural pain	21 (58.3)	41 (56.9)
Headache	16 (44.4)	33 (45.8)
Pain in extremity	6 (16.7)	19 (26.4)
Fall	15 (41.7)	17 (23.6)
Back pain	2 (5.6)	15 (20.8)
Post lumbar puncture syndrome	11 (30.6)	13 (18.1)
Fatigue	2 (5.6)	12 (16.7)
Arthralgia	2 (5.6)	10 (13.9)
Myalgia	2 (5.6)	10 (13.9)
Nausea	6 (16.7)	9 (12.5)
Pain	0	7 (9.7)
CSF white blood cell count increased	0	7 (9.7)
Paraesthesia	6 (16.7)	6 (8.3)
Constipation	4 (11.1)	6 (8.3)
CSF protein increased	1 (2.8)	6 (8.3)
Nasopharyngitis	7 (19.4)	2 (2.8)
Dyspnoea	5 (13.9)	4 (5.6)
Diarrhoea	5 (13.9)	1 (1.4)
Muscular weakness	4 (11.1)	4 (5.6)
Neck pain	4 (11.1)	4 (5.6)
Post procedural complication	4 (11.1)	3 (4.2)
Musculoskeletal procedural complication	3 (8.3)	3 (4.2)
Skin abrasion	3 (8.3)	3 (4.2)
Skin laceration	3 (8.3)	0
Dizziness	3 (8.3)	4 (5.6)
Depression	3 (8.3)	1 (1.4)
Anxiety	3 (8.3)	4 (5.6)
Insomnia	3 (8.3)	3 (4.2)

Number of patients with the event (incidence [%])

Death occurred in 1 patient in the tofersen group (cardiac failure congestive), and a causal relationship to the study drug was ruled out. Serious adverse events other than deaths occurred in 13.9% (5 of 36) of patients in the placebo group and 18.1% (13 of 72) of patients in the tofersen group. The details are shown in Table 32. The events leading to treatment discontinuation other than deaths occurred in 3 patients in the tofersen group (myelitis, meningitis chemical, and pulmonary embolism in 1 patient each), and a causal relationship to the study drug could not be ruled out for myelitis and meningitis chemical.

Table 32. Serious adverse events other than deaths (ITT population)

Placebo	Dyspnoea in 2 patients; Pulmonary embolism, atelectasis, and dehydration in 1 patient each (5 patients in total)
Tofersen	Pulmonary embolism in 2 patients; respiratory complication associated with device, pneumonia aspiration, acute respiratory failure; pulmonary embolism, aspiration, pneumonia aspiration; hypothermia, loss of consciousness; faecaloma, impaired self-care; meningitis chemical*; fibula fracture; lumbar radiculopathy*; myelitis transverse*; respiratory failure; deep vein thrombosis; and myelitis* in 1 patient each (13 patients in total)

* Event for which a causal relationship to the study drug could not be ruled out

7.3 Global phase III study (CTD 5.3.5.2.1.1 and 5.3.5.2.1.2, Study 102, March 2017 to data cutoff in January 2022)

An open-label study was conducted to evaluate the long-term safety and efficacy of tofersen in patients with SOD1-ALS who had completed Part A, B, or C of Study 101.

Subjects who had completed Part A or B of Study 101 underwent a wash-out period of approximately 16 weeks from the last dose of the study drug in Study 101 to the first dose in Study 102 and then received tofersen at the same dose as that in the completed part (20, 40, 60, or 100 mg) 3 times every 2 weeks and then up to 90 times every 4 weeks (until the last enrolled subject reached Week 152).[30)] Subjects who had completed Part C of Study 101 directly entered the blinded study treatment period without undergoing the wash-out period and intrathecally received tofersen 100 mg or placebo 3 times every 2 weeks and then up to 90 times every 4 weeks.[31)]

Of a total of 159 subjects who had completed Study 101 (19 subjects completing Part A [including 2 also enrolled in Part B], 45 subjects completing Part B, 97 subjects completing Part C), 139 subjects were enrolled in Study 102. All of the 139 subjects enrolled were included in the ITT population and safety analysis population.

As of data cutoff, 43 patients discontinued the study mainly because of deaths in 17 patients and disease progression in 15 patients.

Table 33 shows data on a change in ALSFRS-R total score to each measurement timepoint, the efficacy endpoint.[32)]

Table 33. Change in ALSFRS-R total score from baseline of Study 102 (population transferred from Part C of Study 101)

	Tofersen (n = 63)	Placebo/delayed-start tofersen (n = 32)
Baseline value of Study 102	34.1 ± 7.71	30.9 ± 9.23
Change from baseline		
Week 12[a)]	−1.2 ± 0.39	−1.9 ± 0.52
Week 24[a)]	−1.4 ± 0.60	−2.3 ± 0.82

Mean ± SD

a) Least squares mean ± SE. Calculated in an ANCOVA model using treatment in Part C of Study 101 as a fixed effect and duration of disease at baseline and ALSFRS-R total score as adjustment factors. Missing data are imputed by the MI method.

For the safety, adverse events occurred in 96.4% (134 of 139) of patients. Table 34 shows the main adverse events.

30) The number of maintenance doses had been initially specified as [redacted], but revision of the protocol made during the study changed provisions on the loading and maintenance doses as follows:
- The revised protocol, version [redacted], specified that 3 loading doses of tofersen 20 mg (Cohort 1), 40 mg (Cohort 2), 60 mg (Cohort 3), or 100 mg (Cohort 4) should be administered at intervals of approximately 2 weeks followed by administration of [redacted] maintenance doses at intervals of approximately 4 weeks.
- The revised protocol, version [redacted], specified that 3 loading doses of tofersen 100 mg should be administered at intervals of approximately 2 weeks over the first 4 weeks followed by administration of up to [redacted] maintenance doses at intervals of approximately 4 weeks.
- The revised protocol, version [redacted], specified that as a maintenance dose, tofersen may be administered up to 90 times at intervals of approximately 4 weeks.

31) During the blinded loading treatment period, subjects from the placebo group in Part C of Study 101 received tofersen 100 mg 3 times every 2 weeks, and subjects from the tofersen group in Part C of Study 101 received tofersen 100 mg 2 times (Days 1 and 29) and placebo once (Day 15). After the blinded loading treatment period, the subjects entered the maintenance treatment period.

32) Hereinafter, in descriptions about the efficacy results in Study 102, subjects who had been allocated to the placebo group in Part C of Study 101 and started tofersen in Study 102 were referred to as the “placebo/delayed-start tofersen group,” and subjects who had been allocated to the tofersen group in Part C of Study 101 and continued tofersen in Study 102 were referred to as the “tofersen group.”

Table 34. Incidences of adverse events in Study 102 (safety analysis population)

	Tofersen (n = 139)
All adverse events	134 (96.4)
Adverse events reported by ≥7% of patients	
Headache	73 (52.5)
Procedural pain	62 (44.6)
Fall	56 (40.3)
Back pain	49 (35.3)
Pain in extremity	39 (28.1)
Arthralgia	35 (25.2)
CSF protein increased	33 (23.7)
Post lumbar puncture syndrome	29 (20.9)
Fatigue	27 (19.4)
Nausea	25 (18.0)
Contusion	23 (16.5)
Dizziness	23 (16.5)
Pyrexia	22 (15.8)
Myalgia	22 (15.8)
CSF white blood cell count increased	22 (15.8)
Constipation	20 (14.4)
Nasopharyngitis	19 (13.7)
Muscle spasms	19 (13.7)
Muscular weakness	15 (10.8)
Respiratory failure	14 (10.1)
Diarrhoea	13 (9.4)
Urinary tract infection	13 (9.4)
Dyspnoea	13 (9.4)
Dysphagia	12 (8.6)
Pneumonia aspiration	12 (8.6)
Salivary hypersecretion	11 (7.9)
COVID-19	11 (7.9)
Pleocytosis	11 (7.9)
Pain	10 (7.2)

Number of patients with the event (incidence [%])

Deaths occurred in 17 patients (respiratory failure in 9 patients; respiratory arrest in 2 patients; respiratory failure and ALS, ALS, sudden death, cardiac arrest, pneumonia aspiration, and euthanasia in 1 patient each). A causal relationship to the study drug was ruled out for all the events. Serious adverse events other than deaths occurred in 25.2% (35 of 139) of patients. The details are shown in Table 35. The events leading to treatment discontinuation other than deaths occurred in 4 patients (pneumonia aspiration, pancreatitis, gastritis, and vocal cord paralysis; dyspnoea; neurosarcoidosis; and muscular weakness and salivary hypersecretion in 1 patient each). A causal relationship to the study drug could not be ruled out for pancreatitis and gastritis.

Table 35. Serious adverse events other than deaths (safety analysis population)

Pneumonia aspiration in 4 patients; dysphagia in 3 patients; fall/neurosarcoidosis/back pain/staphylococcus test positive/muscular weakness/headache/head injury, respiratory distress/fall/skull fracture/dysphagia/respiratory failure, gastritis*/pneumonia aspiration/vocal cord paralysis/pancreatitis,* meningitis aseptic*/optic disc oedema*/back pain,* pneumonia bacterial/COVID-19/pneumonia, pneumonia aspiration/acute respiratory failure/cardio-respiratory arrest/pneumothorax/sepsis, constipation/chronic respiratory failure/pneumonia aspiration, stoma site pain/acute respiratory failure/pneumonia aspiration, pulmonary embolism/pneumonia, pneumonia pseudomonal/COVID-19, dysphagia/pneumonia aspiration, pulmonary embolism/myocarditis, ankle fracture/fall, intracranial pressure increased*/myelitis,* respiratory failure, respiratory failure/dysphagia, intracranial pressure increased,* acute respiratory failure, gastric ulcer perforation, cholecystitis, gastrostomy, streptococcal bacteraemia, nervous system disorder,* dyspnoea, radiculopathy,* migraine, gastric perforation, nephrolithiasis, and faecaloma in 1 patient each (35 patients in total)

* Event for which a causal relationship to the study drug could not be ruled out

7.R Outline of the review conducted by PMDA

7.R.1 Evaluation strategy for efficacy of tofersen

For conduct of global phase III studies (Part C of Study 101, Study 102), PMDA asked the applicant to explain differences in intrinsic and extrinsic factors among ethnic groups potentially affecting the efficacy and safety of tofersen and plan for Part C of Study 101.

The applicant's explanation:

Disease progression of SOD1-ALS differs depending on type of mutation, and gene mutations in SOD1-ALS are known to differ between Japanese and non-Japanese patients. In Japan, *SOD1* gene mutations mainly found in patients with ALS are p.His47Arg, p.Leu127Ser, p.Ala5Val, p.Gly94Ser, and p.Lys4Glu (*Transl Neurodegener.* 2024;13:28), and the mean durations of disease are approximately 17, 7, 1, 8, and 7 years, respectively. The mean age of onset is approximately 46 to 58 years old (*J Neurol Neurosurg Psychiatry.* 2017;88:99-105, *Ann Neurol.* 1997;41:210-21). In North America, mutations mainly found are p.Ala5Val, p.Glu101Gly, p.Ile114Thr, p.Gly94Ala, and p.Gly86Arg, and the mean durations of disease are approximately 1, 9, 5, 2, and 2 years, respectively. The mean age of onset is approximately 43 to 57 years old. In Europe, mutations mainly found are p.Asp91Ala (homozygote), p.Asp91Ala (heterozygote), p.Arg116Gly, p.Leu145Phe, and p.Glu101Lys, and the mean durations of disease are approximately 11, 10, 2, 11, and 9 years, respectively. The mean age of onset is approximately 40 to 55 years old (*Transl Neurodegener.* 2024;13:28). As shown above, although gene mutations differ from region to region, pathological characteristics of SOD1-ALS such as the duration of disease and age of onset do not clearly differ. The mechanism of onset of SOD1-ALS remains to be fully elucidated, but the presumed pathogenesis of accumulation of toxic SOD1 protein mediated by the gain-of-abnormal-function mechanism is shared, regardless of the type of *SOD1* gene mutation.

Both in and outside Japan, a confirmed diagnosis of SOD1-ALS requires documented dysfunction of both upper and lower motor neurons, documented progression, exclusion of similar diseases, and positive test result for *SOD1* gene mutation. For SOD1-ALS, similar treatment is applied both in and outside Japan, regardless of *SOD1* gene mutation. Approval and recommendation statuses of some therapeutic drugs for ALS differ between Japan and the other countries, but therapeutic effects of these drugs are limited, and the difference between Japan and the other countries is thus not considered large enough to affect the efficacy evaluation of tofersen.

Tofersen binds to the 3'-untranslated region of the *SOD1* gene, and an allele frequency of single nucleotide polymorphism in the tofersen's binding site is as quite low as less than 1 person per 5000 persons, regardless of Japanese or non-Japanese (*Nature.* 2024;625:92-100, *Nucleic Acids Research.* 2024;52:D622-32). No ethnic difference in target sequence likely to affect tofersen's binding has been observed.

Furthermore, data on pharmacokinetics of tofersen in CSF and plasma in Part C of Study 101 and Study 102 showed that tofersen concentrations in measurement samples from the Japanese subgroup were all within the range of those from the non-Japanese subgroup, and thus the pharmacokinetics of tofersen is not considered to differ substantially between Japanese and non-Japanese patients.

Based on the above, considering that the intrinsic and extrinsic ethnic factors would not affect evaluation of the efficacy and safety of tofersen substantially, the applicant decided to conduct confirmatory Part C of Study 101 as a global study including Japan and evaluate the efficacy and safety in Japanese patients mainly based on results from the concerned Part C.

In view of varied disease progression rates of SOD1-ALS, the applicant established the prognostic enrichment criteria in terms of gene mutations and a pre-randomization slope of the change in ALSFRS-R total score to control disease heterogeneity and defined a population of subjects with a rapid disease progression potential as the mITT population to be used as the primary efficacy analysis population in the study plan of Part C of Study 101. The primary endpoint was specified as a change in ALSFRS-R total score from baseline, which has been used as an evaluation indicator in many clinical studies in patients with ALS and correlate with quality of life (QOL) and survival period (*Neurodegener Dis.* 2013;12:81-90, *Amyotroph Lateral Scler.* 2010;11:116-21). In addition, time of evaluation for the primary endpoint in Part C of Study 101 was specified at Week 28 based on the finding in a randomized controlled study to evaluate the efficacy of arimoclomol in patients with SOD1-ALS (*Neurology.* 2018;90:e565-74) where all patients in the placebo group experienced a decrease in ALSFRS-R total score within 6 months. The sample size (60 patients in the primary analysis population) was determined by estimating changes in ALSFRS-R total score over time based on the data set in Part B of Study 101 and results from the randomized controlled study of arimoclomol.[26)]

PMDA's view:
The applicant explained that the differences in intrinsic and extrinsic ethnic factors would not affect evaluation of the efficacy or safety of tofersen substantially. The applicant's explanation is understandable to a certain extent. In view of the above explanation, no particular problems are noted in the applicant's selected development strategy, by which Japanese patients participated in Part C of Study 101 and Study 102, and the efficacy and safety of tofersen were evaluated.

As described in Section 7.R.2, however, data on a change in ALSFRS-R total score from baseline to Week 28, the primary endpoint, in confirmatory Part C of Study 101 did not demonstrate superiority of tofersen over placebo. In response to the above result of Part C of Study 101, conduct of additional clinical studies should be considered in regular clinical development, but SOD1-ALS is an extremely rare and serious disease and tofersen has been already approved in the US and Europe, and the European Academy of Neurology Guideline on the Management of Amyotrophic Lateral Sclerosis (*Eur J Neurol.* 2024;00:e16264) recommends tofersen for patients with progressive ALS caused by *SOD1* gene mutation. Based on the above, feasibility of an additional confirmatory study in patients with SOD1-ALS in or outside Japan is very low. In addition, therapeutic options for SOD1-ALS are limited.

In comprehensive consideration of the above situations, PMDA decided to evaluate the efficacy and safety in Japanese patients based on results from Part C of Study 101 and Study 102. The efficacy and safety of tofersen are reviewed in the following sections.

7.R.2 Efficacy of tofersen

7.R.2.1 Efficacy evaluation based on data on biomarker

The applicant's explanation about a sensitivity analysis of ALSFRS-R total score using the neurofilament light chain (NfL) concentration in plasma at baseline as a covariate in Part C of Study 101:

NfL is a subunit of the neurofilament, an intermediate filament specific to neurons. Axonal damage or degeneration triggers neurofilament to enter interstitial fluid and then CSF and circulating blood, and neurological diseases characterized by axonal damage are accompanied by increased NfL concentrations in CSF or blood (*J Neurol Neurosurg Psychiatry.* 2019;90:870-81, *Nat Rev Neurol.* 2018;14:577-89). When Part C of Study 101 was planned, usefulness of the concerned parameter was not fully recognized as a tool to control disease heterogeneity. However, from reports that an increase in NfL concentration occurred before onset of ALS (*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration.* 2019;20:303-9, *Ann ClinTransl Neurol.* 2019;6:1971-9) and increases in NfL concentration in serum and CSF were observed in subjects harboring the *SOD1* gene mutation related to rapid disease progression and some of the subjects with definite clinical symptoms (*Ann Neurol.* 2018;84:130-9), findings suggesting that NfL is a potential biomarker reflecting disease progression of ALS have accumulated. In view of these findings, the applicant considered that the treatment effect of tofersen in patients with SOD1-ALS could be more precisely estimated by adjusting the baseline NfL concentration in plasma as a continuous covariate and thus performed a sensitivity analysis on ALSFRS-R total score in the mITT population and non-mITT population using the baseline NfL concentration in plasma as a covariate in the ANCOVA model. The sensitivity analysis was included in the statistical analysis plan before the final database lock in Part C of Study 101.

PMDA asked the applicant to explain relationships of clinical outcome measures to various biomarkers including the NfL concentration in plasma.

The applicant's explanation:

Total SOD1 protein concentrations in CSF in patients with SOD1-ALS remained generally stable over time and did not correlate to disease progression (*JAMA Neurol.* 2013;70:201-7). Figure 1 shows a scatter plot of changes in ALSFRS-R total score against changes in SOD1 protein concentration in CSF in the ITT population in Part C of Study 101. No definite correlation was observed between decreases in SOD1 protein concentration in CSF and changes in disease progression measure.

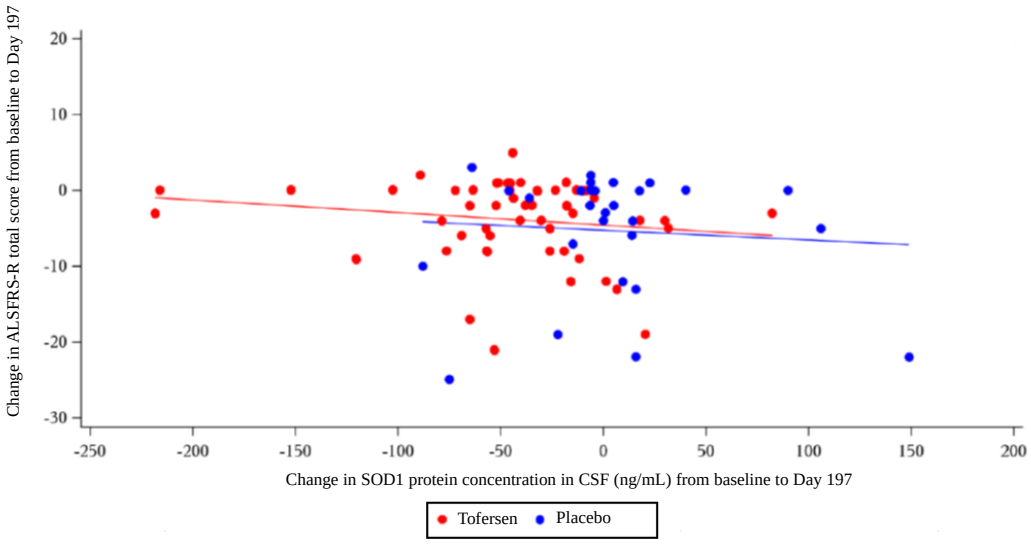

Figure 1. Relationship between changes in SOD1 protein concentration in CSF and changes in ALSFRS-R total score at Week 28 (Part C of Study 101, ITT population)

Recently, multiple researches showed that NfL concentrations in plasma correlate to disease progression rate (measured as a worsening rate of ALSFRS-R total score) (*J Neurol.* 2020;267:1699-708, *Neurology.* 2020;95:e59-69, etc.). Table 36 shows changes in NfL concentration in plasma in Part C of Study 101. NfL concentrations in plasma in the tofersen group tended to decrease more than those in the placebo group.

Table 36. Changes in NfL concentration in plasma from baseline to Week 28 (Part C of Study 101)

	mITT		Non-mITT		ITT	
	Placebo	Tofersen	Placebo	Tofersen	Placebo	Tofersen
No. of patients evaluated	21	39	15	33	36	72
Baseline value[a)]	127.3 ± 94.4	146.2 ± 82.6	37 ± 29.5	47.6 ± 41.8	89.7 ± 86.5	100.4 ± 82.8
Change from baseline to Week 28[b)]	1.20 [0.94, 1.52]	0.40 [0.33, 0.48]	0.95 [0.81, 1.12]	0.50 [0.44, 0.56]	1.12 [0.94, 1.32]	0.45 [0.39, 0.52]

Unit, pg/mL

a) Mean ± SD; b) Geometric mean ratio [95% CI], Missing data were imputed by the MI method.

Figure 2 shows a scatter plot of changes in ALSFRS-R total score against changes in NfL concentration in plasma in Part C of Study 101. Spearman's correlation coefficient between changes in NfL concentration in plasma and changes in ALSFRS-R total score was 0.44 in the tofersen group and −0.40 in the placebo group, and the correlation coefficient in the overall population was 0.07. Spearman's correlation coefficient between changes from baseline in NfL concentration in plasma and changes from baseline in total SOD1 protein concentration in CSF was −0.02 in the tofersen group and 0.06 in the placebo group, indicating no correlation.

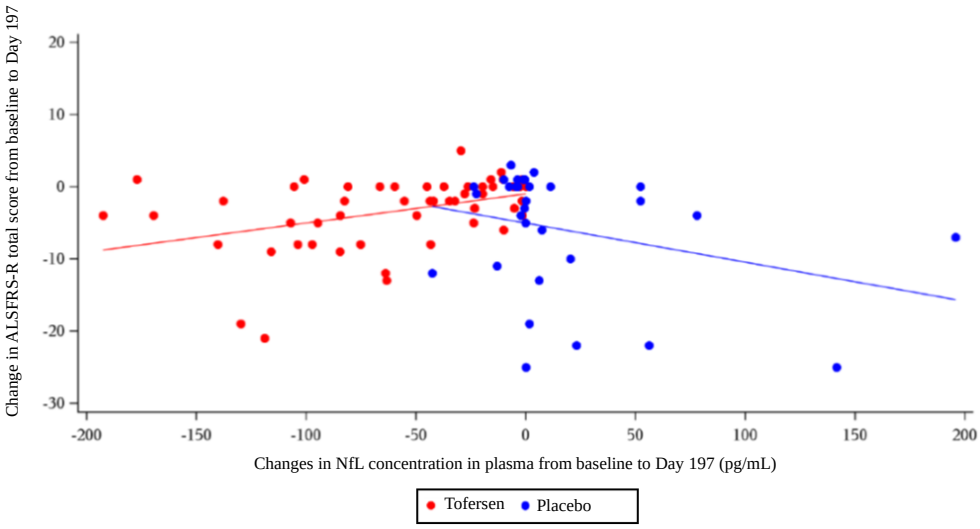

Figure 2. Relationship between changes in NfL concentration in plasma and changes in ALSFRS-R total score at Week 28 (Part C of Study 101, ITT population)

PMDA's view:

The changes in total SOD1 protein concentration in CSF observed in Part C of Study 101 [see Section 6.2.2.2] can be deemed to demonstrate the effect in humans expected from the mechanism of action of tofersen. However, as explained by the applicant, the results in Part C of Study 101 did not indicate a correlation between changes in total SOD1 protein concentration in CSF and changes in ALSFRS-R total score. Tofersen tended to decrease the NfL concentration in plasma from baseline, but no definite correlation was observed between changes in NfL concentrations in plasma and changes in ALSFRS-R total score in the overall population. PMDA therefore cannot conclude that the treatment effect of tofersen in clinical settings is demonstrated by the decreases in NfL concentrations in plasma and total SOD1 protein concentration in CSF observed during tofersen treatment.

The applicant changed the statistical analysis plan after the start of the study and made adjustments using the baseline NfL concentration in plasma as a covariate in an ANCOVA model [see Section 7.R.2.2]. The applicant's explanation that findings on a relationship between the natural course of SOD1-ALS and NfL in plasma did not adequately accumulate at the time of study planning is understandable. However, (a) at present, the NfL concentration in plasma has not been established as a prognostic factor of ALS, and its correlation to ALSFRS-R total score is not definite; and (b) the concerned analysis was performed as a sensitivity analysis, thus results of the analysis performed by adjusting the baseline NfL concentration in plasma as a continuous covariate should be positioned as results of an exploratory analysis. The efficacy of tofersen should not be discussed mainly based on results of the concerned analysis. PMDA thus decided to review results of the analysis without adjustment using the baseline NfL concentration in plasma. Unless otherwise specified, the study results presented below are obtained without adjustment using the baseline NfL concentration in plasma as a covariate.

7.R.2.2 Efficacy of tofersen in a global phase III study

PMDA asked the applicant to explain the efficacy of tofersen in global phase III studies (Part C of Study 101 and Study 102).

The applicant's explanation:

Table 28 shows data on a change in ALSFRS-R total score from baseline to Week 28 in the mITT population, the primary endpoint in the primary analysis population in Part C of Study 101. Comparison of point estimates showed that a decrease in score tended to be smaller in the tofersen group than in the placebo group but no statistically significant difference was observed between the tofersen group and placebo group. Reasons for the failure to show a statistically significant difference are as follows:

When Part C of Study 101 was started, the target sample size was established by assuming that a change in ALSFRS-R total score from baseline to Week 28, the primary endpoint, was −24.7 in the placebo group and −4.8 in the tofersen group based on results from Part B of Study 101 (*N Engl J Med.* 2020;383:109-19) and a randomized controlled study which evaluated the efficacy of arimoclomol in patients with SOD1-ALS (*Neurology.* 2018;90:e565-74). However, the actual change in ALSFRS-R total score from baseline to Week 28 in Part C was −8.1 in the placebo group and −7.0 in the tofersen group, and the disease progression in subjects enrolled in Part C of Study 101 was slower than assumed before the start of the study. A reason why the actual changes were different from the previously assumed ones was considered as follows: To control heterogeneity of disease progression, the prognostic enrichment criteria[33)] for a pre-randomization slope of the decline in ALSFRS-R total score were adopted in Part C of Study 101, but changes in ALSFRS-R total score were non-linear, posing limitations in using the pre-randomization slope of ALSFRS-R total score as a marker of disease progression. Disease progression of SOD1-ALS greatly varies from individual to individual even harboring the same mutation, and thus prediction of neurological prognosis based on limited clinical study results in patients with SOD1-ALS was difficult. Furthermore, in view of the following findings, more subjects showing rapid disease progression at baseline might be allocated to the tofersen group than to the placebo group: (1) The rate of a decline in ALSFRS-R total score from screening for Part C of Study 101 to Day 15 was greater in the tofersen group than in the placebo group; and (2) the baseline NfL concentration in plasma, a potential marker of nerve degeneration, tended to be higher in the tofersen group than in the placebo group.

In Part C of Study 101, a decline in ALSFRS-R total score at Week 28 tended to be smaller in the tofersen group than in the placebo group, and the point estimate of a difference between the groups was 1.2 (see Table 28). Although the minimal clinically important difference threshold of ALSFRS-R total score has not been established, even a slight decline in ALSFRS-R total score is known to be potentially associated with remarkable impairment of functional ability, and a decline in ALSFRS-R total score by 1 point increases a risk of death or tracheostomy by 7% (*Neurology.* 2005;64;38-43). Therefore, the difference in change in ALSFRS-R total score from baseline between the groups observed in Part C may be clinically meaningful to a certain extent

33) Adapted as the prognostic enrichment criteria in Part C of Study 101 based on results from the EMPOWER study, which evaluated the efficacy of dexpramipexole in patients with ALS and showed that subjects with a pre-randomization slope of a decline in ALSFRS-R being 0.9 points/month maintained the mean slopes of declines at Months 6, 9, and 12 at ≥0.9 points/month (*Lancet Neurol.* 2013;12:1059-67).

Results other than those on the primary endpoint in Part C of Study 101 and Study 102 are shown below.

Table 37 shows results on predicted slow vital capacity (SVC)%, handheld dynamometry (HHD) megascore,[34] and ALS Assessment Questionnaire (ALSAQ-5)[35] at Week 28 in Part C of Study 101. The results suggested that tofersen would have efficacy greater than placebo. Occurrences of events (death or permanent ventilation) in Part C (mITT population) were very limited (death occurred in 1 patient in the tofersen group [cardiac failure congestive] and 0 in the placebo group; permanent ventilation occurred in 3 patients in the tofersen group and 2 in the placebo group), the median time to event was not estimated. In the non-mITT population, no events occurred.

Table 37. Changes in each efficacy endpoint from baseline to Week 28 in Part C of Study 101 (ITT population)

Endpoint	Placebo[a]	Tofersen[a]	Difference between groups [95% CI][b]
Predicted SVC%	−13.0 ± 3.36 (25)	−6.5 ± 2.61 (52)	3.0 [−0.8, 13.7]
HHD megascore	−0.25 ± 0.064 (27)	−0.20 ± 0.050 (58)	0.04 [−0.097, 0.181]
ALSAQ-5	11.0 ± 3.15 (31)	6.7 ± 2.45 (61)	−4.3 [−11.15, 2.46]

a) Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline value on the measure assessed and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
b) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

For the long-term efficacy of tofersen, Table 38 and Figure 3 show results on a change in ALSFRS-R total score from baseline in subjects from Part C of Study 101 in the ITT population in Studies 101 and 102, and Table 39 shows results in the mITT population and non-mITT population. At any evaluation timepoint in any analysis population, a change in ALSFRS-R total score from baseline (point estimate) tended to be smaller in the tofersen group than in the placebo/delayed-start tofersen group.

Table 38. Baseline ALSFRS-R total score and change in ALSFRS-R total score from baseline (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102,[a] data cutoff in February 2023)

	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d]
Baseline value[b]	37.3 ± 5.81 (36)	36.9 ± 5.91 (72)	-
Change from baseline[c]			
Week 12	−1.7 ± 0.68 (36)	−1.3 ± 0.54 (66)	0.4 [−1.1, 1.8]
Week 28	−5.5 ± 1.34 (33)	−4.0 ± 1.06 (63)	1.5 [−1.4, 4.4]
Week 40	−7.7 ± 1.60 (29)	−5.4 ± 1.27 (58)	2.3 [−1.2, 5.7]
Week 52	−7.9 ± 1.77 (28)	−5.4 ± 1.41 (57)	2.4 [−1.4, 6.3]
Week 64	−9.0 ± 1.93 (22)	−6.5 ± 1.52 (55)	2.5 [−1.6, 6.6]
Week 76	−9.1 ± 2.01 (20)	−6.9 ± 1.58 (54)	2.2 [−2.1, 6.5]
Week 88	−9.8 ± 2.25 (21)	−7.7 ± 1.75 (51)	2.1 [−2.7, 6.9]
Week 104	−11.0 ± 2.46 (20)	−8.6 ± 1.95 (49)	2.3 [−2.9, 7.6]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline ALSFRS-R total score and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

[34] Determined by calculating mean Z scores for 16 muscle groups on the upper and lower limbs (right and left shoulder flexions, elbow flexions, wrist extensions, index finger abductions, thumb abductions, little finger abductions, knee extensions, and ankle dorsiflexion).
[35] ALSAQ-5 is a patient self-report questionnaire for health condition specific to the disease and intended for use in patients with ALS or the other diseases involving motor neurons. ALSAQ-5 is comprised of 5 questions to assess physical mobility, activities of daily living (ADL) and independence, eating and drinking, communication, and emotional reactions (*Neurologio i Neurochirurgio Polsko.* 2010;44:560-6). Each question should be responded on a 5-point scale (0 representing "Never" to 4 representing "Always" or "Cannot do at all"). The lower score indicates the better health condition. The obtained total score was multiplied by 5 to perform assessment on a 100-point scale.

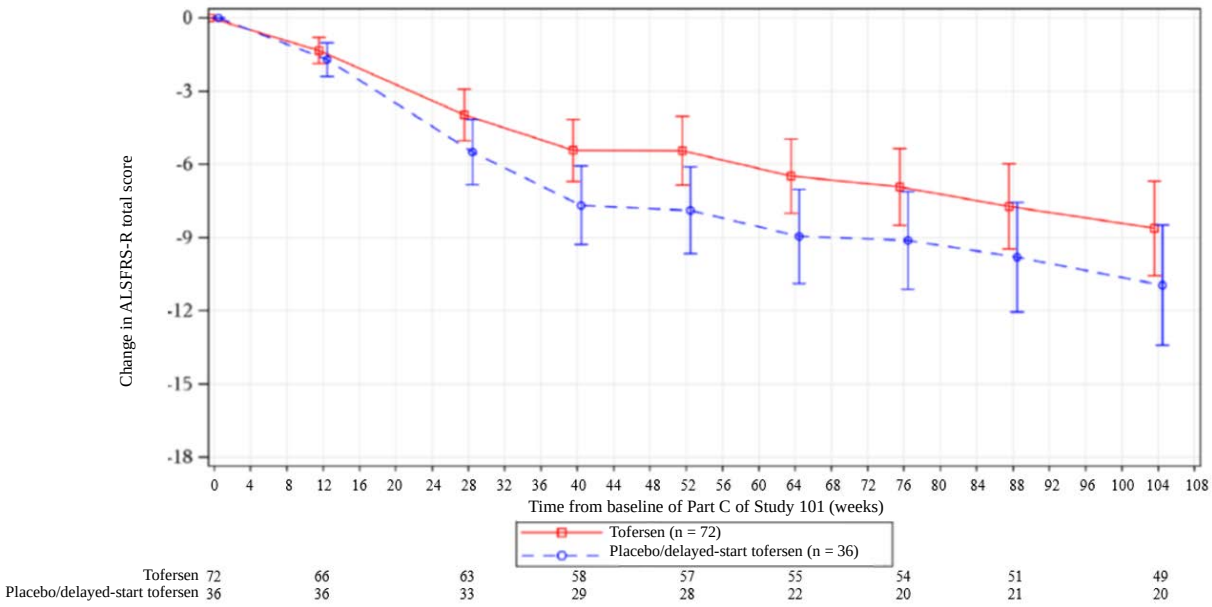

Figure 3. Change in ALSFRS-R total score from baseline (least squares mean ± SE) (ITT population) (pooled analysis data from Studies 101 and 102, data cutoff in February 2023)

Table 39. Baseline ALSFRS-R total score and change in ALSFRS-R total score from baseline (Part C of Study 101, mITT population and non-mITT population) (pooled analysis data from Studies 101 and 102,[a] data cutoff in February 2023)

	mITT population			Non-mITT population		
	Placebo/ delayed-start tofersen	Tofersen	Difference between groups[d]	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d]
Baseline value[b]	35.4 ± 5.66 (21)	36.0 ± 6.40 (39)	-	39.9 ± 5.09 (15)	38.1 ± 5.13 (33)	-
Change from baseline[c]						
Week 12	−2.9 ± 0.94 (21)	−2.6 ± 0.77 (35)	0.3 [−2.0, 2.6]	−0.5 ± 0.65 (15)	−0.3 ± 0.48 (31)	0.2 [−1.3, 1.7]
Week 28	−8.1 ± 1.80 (19)	−6.6 ± 1.44 (33)	1.5 [−2.9, 5.9]	−2.5 ± 1.20 (14)	−1.3 ± 0.88 (30)	1.2 [−1.6, 3.9]
Week 40	−10.5 ± 2.14 (17)	−8.5 ± 1.81 (29)	2.0 [−3.3, 7.2]	−4.0 ± 1.47 (12)	−1.5 ± 1.04 (29)	2.5 [−0.8, 5.8]
Week 52	−11.7 ± 2.37 (15)	−8.9 ± 2.01 (27)	2.8 [−3.0, 8.5]	−3.6 ± 1.59 (13)	−1.3 ± 1.15 (30)	2.3 [−1.3, 5.9]
Week 64	−12.0 ± 2.63 (11)	−9.7 ± 2.08 (26)	2.3 [−3.7, 8.4]	−4.0 ± 1.81 (11)	−2.0 ± 1.29 (29)	2.0 [−2.1, 6.1]
Week 76	−12.0 ± 2.92 (10)	−10.6 ± 2.21 (24)	1.3 [−5.4, 8.1]	−4.5 ± 1.76 (10)	−2.0 ± 1.24 (30)	2.5 [−1.5, 6.4]
Week 88	−13.6 ± 3.19 (11)	−11.8 ± 2.65 (22)	1.9 [−5.7, 9.4]	−4.5 ± 1.89 (10)	−2.6 ± 1.31 (29)	1.9 [−2.3, 6.2]
Week 104	−14.4 ± 3.35 (10)	−12.9 ± 2.81 (19)	1.5 [−6.5, 9.6]	−5.7 ± 2.27 (10)	−2.9 ± 1.55 (30)	2.8 [−2.3, 7.9]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline ALSFRS-R total score and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

As of data cut-off in February 2023, the follow-up period (median [range]) in the ITT population in Part C of Study 101 was 3.4 [2.2, 3.9] years. Table 40, Figure 4, and Figure 5 show events (death or permanent mechanical ventilation) in the subjects included in the pooled data from Part C of Study 101 and Study 102. The proportion of subjects resulting in death, or death or permanent mechanical ventilation tended to be smaller in the tofersen group than in the placebo/delayed-start tofersen group. The median time either to “death or permanent mechanical ventilation” or to “death” could not be estimated because of the limited number of events.

To compare the survival period of subjects with the natural history reported for patients with SOD1-ALS (duration of disease, 2.3 years [*Nat Commun.* 2022;13:6901]), a period from onset of ALS, identified for the enrolled patients in advance, to death or censoring (discontinuation of the study or data

cutoff [February 2023]) was calculated. As of data cut-off in February 2023, the median period from onset of SOD1-ALS to death or censoring was 3.3 years (range, 0.7-12.2 years) in the placebo/delayed-start tofersen group and 3.9 years (range, 0.7-15.7 years) in the tofersen group. Time to death or censoring in subjects treated with tofersen exceeded the duration of disease reported as natural history.

Table 40. Incidences of events (death or permanent mechanical ventilation)
(Part C of Study 101, ITT population)
(pooled analysis data from Studies 101 and 102, data cutoff in February 2023)

	Placebo/delayed-start tofersen (n = 36)	Tofersen (n = 72)
Death or permanent mechanical ventilation[a)]	9 (25.0)	16 (22.2)
Death	5 (13.9)	7 (9.7)
Permanent mechanical ventilation	4 (11.1)	9 (12.5)

Number of patients (incidence)

a) Death or use of ventilator (invasive or non-invasive) for ≥22 hours per day for ≥21 consecutive days. Subjects not meeting the definition were censored on the day of last survival confirmation.

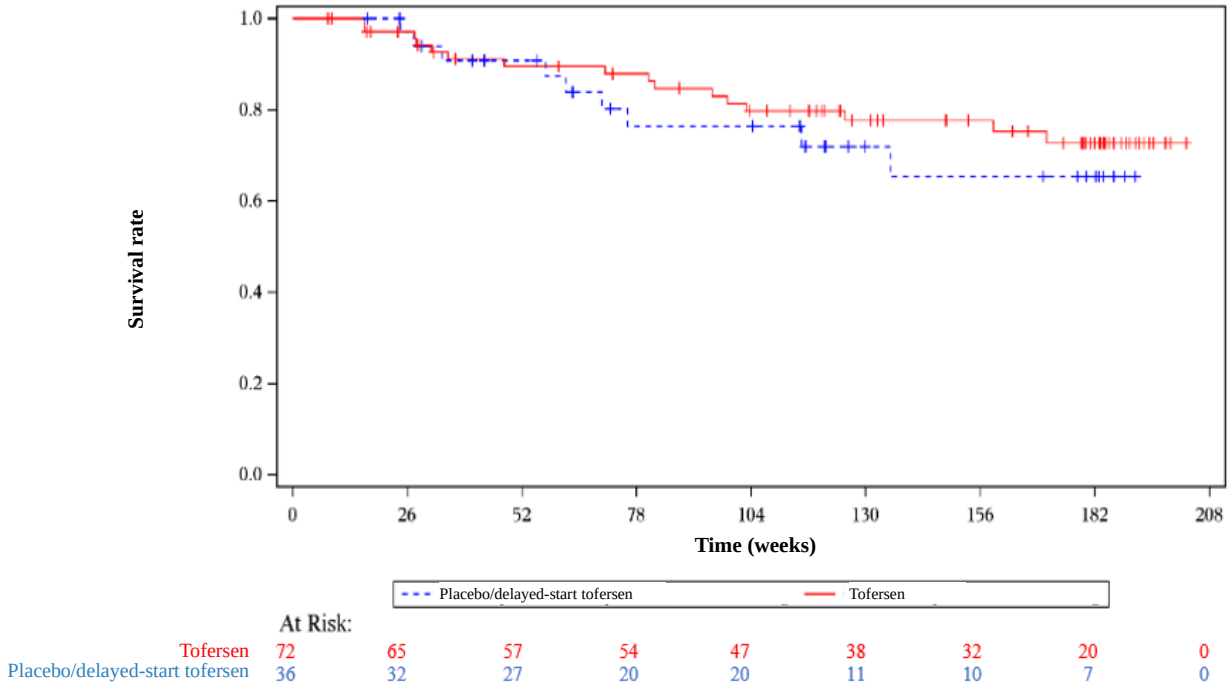

Figure 4. Kaplan-Meier curve for time to death or permanent ventilation
(Part C of Study 101, ITT population)
(pooled analysis data from Studies 101 and 102, data cutoff in February 2023)

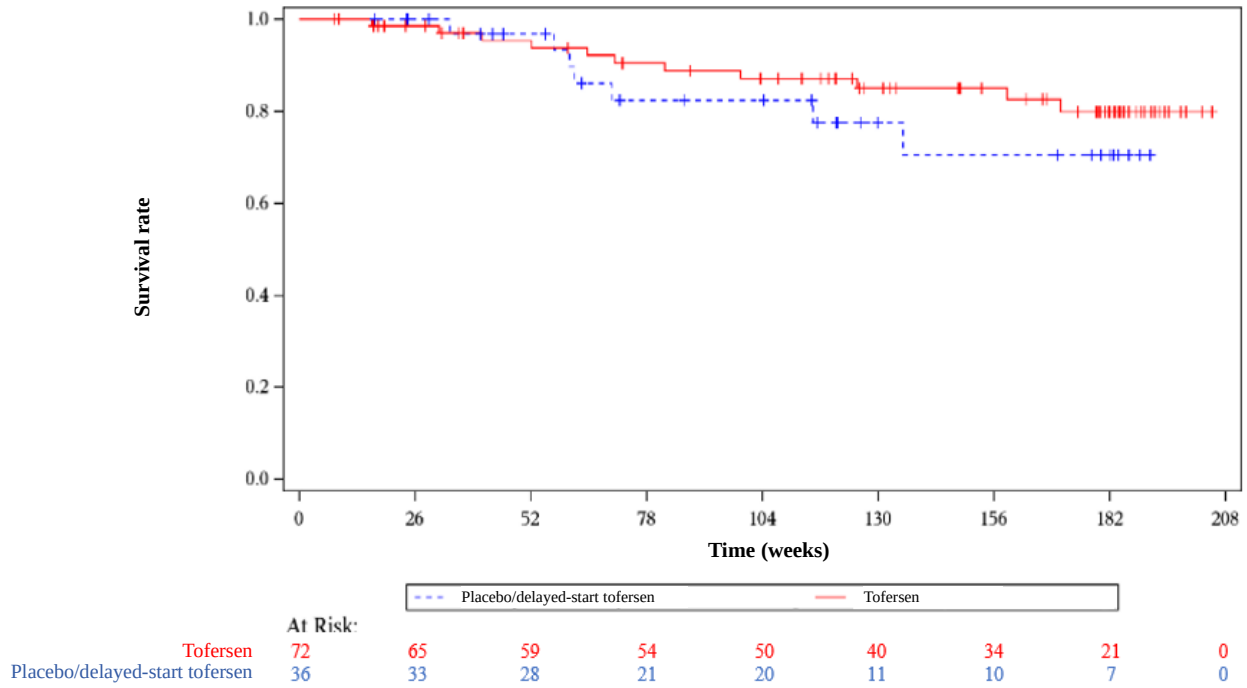

Figure 5. Kaplan-Meier curve for time to death (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102, data cutoff in February 2023)

Table 41 shows data on a change in predicted SVC% from baseline in Studies 101 and 102 in subjects who participated in Part C of Study 101. The decline in predicted SVC% from baseline tended to be smaller in the tofersen group than in the placebo/delayed-start tofersen group throughout the treatment period. Taking into account that slowing the decline of predicted SVC% by 1.5% per month reduced risks of the first onset of respiratory failure or death, first occurrence of tracheostomy or death, and death by 22%, 23%, and 23%, respectively, after 6 months (*JAMA Neurol.* 2018;75:58-64), the smaller decline in predicted SVC% in the tofersen group than in the placebo/delayed-start tofersen group was considered clinically meaningful.

Table 41. Baseline predicted SVC% and change in predicted SVC% from baseline (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102,[a)] data cutoff in February 2023)

	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d)]
Baseline value[b)]	85.1 ± 16.5 (36)	82.1 ± 16.6 (72)	-
Change from baseline[c)]			
Week 12	−6.2 ± 1.94 (34)	−3.1 ± 1.52 (59)	3.0 [−1.2, 7.2]
Week 28	−13.0 ± 3.36 (25)	−6.5 ± 2.61 (52)	6.5 [−0.8, 13.7]
Week 40	−17.7 ± 3.96 (20)	−9.0 ± 3.10 (39)	8.7 [0.2, 17.2]
Week 52	−15.2 ± 4.01 (20)	−9.7 ± 3.15 (38)	5.6 [−3.0, 14.1]
Week 64	−17.8 ± 4.42 (17)	−11.0 ± 3.47 (41)	6.8 [−2.7, 16.3]
Week 76	−16.9 ± 4.76 (17)	−11.8 ± 3.74 (39)	2.2 [−5.0, 15.3]
Week 88	−17.6 ± 5.68 (15)	−12.6 ± 4.39 (40)	4.9 [−7.1, 16.9]
Week 104	−19.5 ± 6.03 (10)	−12.2 ± 4.34 (31)	7.3 [−4.3, 18.9]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline predicted SVC% and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

Table 42 shows data on a change in HHD megascore[34)] from baseline in Studies 101 and 102 in subjects who participated in Part C of Study 101. The decline in score tended to be generally suppressed in the tofersen group than in the placebo/delayed-start tofersen group throughout the treatment period.

Table 42. Baseline HHD megascore and change in HHD megascore from baseline (z score) (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102,[a)] data cutoff in February 2023)

	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d)]
Baseline value[b)]	0.04 ± 0.571 (36)	−0.02 ± 0.802 (72)	-
Change from baseline[c)]			
Week 12	−0.13 ± 0.053 (35)	−0.10 ± 0.042 (64)	0.02 [−0.091, 0.135]
Week 28	−0.25 ± 0.064 (27)	−0.20 ± 0.050 (58)	0.04 [−0.097, 0.181]
Week 40	−0.37 ± 0.086 (24)	−0.17 ± 0.067 (47)	0.20 [0.013, 0.389]
Week 52	−0.37 ± 0.098 (25)	−0.14 ± 0.080 (42)	0.23 [0.005, 0.447]
Week 64	−0.32 ± 0.099 (19)	−0.17 ± 0.076 (50)	0.15 [−0.060, 0.369]
Week 76	−0.31 ± 0.119 (17)	−0.23 ± 0.087 (45)	0.08 [−0.166, 0.331]
Week 88	−0.36 ± 0.127 (19)	−0.29 ± 0.093 (46)	0.07 [−0.190, 0.339]
Week 104	−0.43 ± 0.149 (10)	−0.32 ± 0.100 (32)	0.11 [−0.206, 0.418]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline HHD megascore and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

Table 43 shows data on a change in ALSAQ-5 core[35)] from baseline in Studies 101 and 102 in subjects who participated in Part C of Study 101. The placebo/delayed-start tofersen group showed better results compared to the tofersen group throughout the treatment period.

Table 43. Baseline ALSAQ-5 and change in ALSAQ-5 from baseline (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102,[a)] data cutoff in February 2023)

	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d)]
Baseline value[b)]	24.17 ± 15.74 (36)	27.92 ± 15.38 (72)	-
Change from baseline[c)]			
Week 12	5.5 ± 2.09 (36)	2.0 ± 1.65 (66)	−3.5 [−8.00, 0.97]
Week 28	11.0 ± 3.15 (31)	6.7 ± 2.45 (61)	−4.3 [−11.15, 2.46]
Week 40	13.7 ± 3.77 (28)	7.7 ± 3.00 (50)	−6.0 [−14.13, 2.18]
Week 52	16.3 ± 3.90 (26)	8.4 ± 3.14 (49)	−7.8 [−16.29, −0.62]
Week 64	14.1 ± 3.97 (23)	9.0 ± 3.15 (48)	−5.1 [−13.66, 3.40]
Week 76	19.9 ± 4.82 (20)	12.6 ± 3.92 (46)	−7.3 [−17.75, 3.23]
Week 88	18.5 ± 5.08 (19)	14.4 ± 4.10 (44)	−4.1 [−15.16, 7.01]
Week 100[e)]	17.7 ± 5.15 (16)	14.5 ± 4.17 (43)	−3.2 [−14.33, 7.97]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline ALSAQ-5 total score and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].
e) Because ALSAQ-5 at Week 104 has not been assessed, the value at Week 100 is presented.

As described above, results on the primary endpoint did not present a statistically significant difference between the groups, but in view of results on the other endpoints than the primary endpoint in addition to the obtained difference between the groups, tofersen is expected to have efficacy in patients with SOD1-ALS.

Table 44 shows results on a change in ALSFRS-R total score from baseline in the ITT population in an ANCOVA model additionally including the NfL concentration in plasma as a covariate. As with results

on a change in ALSFRS-R total score based on the initial analysis plan, a decline in ALSFRS-R total score tended to be smaller in the tofersen group than in the placebo/delayed-start tofersen group at each timepoint.

Table 44. Baseline ALSFRS-R total score and change in ALSFRS-R total score from baseline in an ANCOVA model additionally including the baseline NfL concentration in plasma as a covariate (Part C of Study 101, ITT population) (pooled analysis data from Studies 101 and 102,[a] data cutoff in February 2023)

	Placebo/delayed-start tofersen	Tofersen	Difference between groups[d]
Baseline[b]	37.3 ± 5.81 (36)	36.9 ± 5.91 (72)	-
Change from baseline[c]			
Week 12	−1.9 ± 0.64 (36)	−1.4 ± 0.51 (66)	0.5 [−0.8, 1.9]
Week 28	−6.3 ± 1.13 (33)	−4.2 ± 0.89 (63)	2.1 [−0.3, 4.5]
Week 40	−8.8 ± 1.4 (29)	−5.7 ± 1.1 (58)	3.0 [0.1, 6.0]
Week 52	−9.6 ± 1.5 (28)	−6.0 ± 1.3 (57)	3.6 [0.4, 6.7]
Week 64	−10.7 ± 1.6 (22)	−7.1 ± 1.3 (55)	3.6 [0.2, 7.0]
Week 76	−11.0 ± 1.8 (20)	−7.6 ± 1.4 (54)	3.4 [−0.3, 7.1]
Week 88	−11.9 ± 1.9 (21)	−8.5 ± 1.5 (51)	3.3 [−0.7, 7.4]
Week 104	−13.2 ± 2.2 (20)	−9.5 ± 1.7 (49)	3.7 [−0.7, 8.2]

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Mean ± SD (number of patients evaluated). Value before administration of the study drug on Day 1 in Part C of Study 101.
c) Least squares mean ± SE (number of patients evaluated). Calculated in an ANCOVA model adjusted using treatment as a fixed effect and baseline NfL level in plasma, baseline ALSFRS-R total score, and use of riluzole or edaravone as covariates. Missing data were imputed by the MI method.
d) Difference in change between groups in an ANCOVA model. Least squares mean difference [95% CI].

PMDA's view:

In confirmatory Part C of Study 101, results on changes in ALSFRS-R total score from baseline to Week 28, the primary endpoint, do not demonstrate superiority of tofersen over placebo. In a comparison of point estimates though, the efficacy based on changes in ALSFRS-R total score from baseline tended to be higher in the tofersen group than in the placebo group. In a pooled analysis of Part C of Study 101 and Study 102, the change in ALSFRS-R total score from baseline (point estimate) tended to be smaller in the tofersen group than in the placebo/delayed-start tofersen group at any timepoint in any analysis population. In addition, the incidence of events (death or permanent mechanical ventilation) in the pooled analysis in Part C of Study 101 and Study 102 tended to be lower in the tofersen group than in the placebo/delayed-start tofersen group, although this evaluation has limitations because of the limited number of patients with the event in Part C of Study 101. Results on the other endpoints such as predicted SVC% obtained to date do not rule out the efficacy of tofersen.

The applicant explained that varied clinical courses of SOD1-ALS made it difficult to predict how symptoms would change over time in a clinical study from the mutation types and pre-randomization course of clinical symptoms. The applicant's explanation is understandable to a certain extent. PMDA reviewed results on the efficacy obtained from Part C of Study 101 and Study 102 comprehensively and concluded that the efficacy of tofersen can be expected in patients with SOD1-ALS.

7.R.2.3 Efficacy in Japanese patients

PMDA asked the applicant to explain the efficacy of tofersen in Japanese patients with SOD1-ALS enrolled in global phase III studies (Part C of Study 101 and Study 102).

The applicant's explanation:
In Part C of Study 101, 7 Japanese subjects (4 in the placebo group, 3 in the tofersen group) were randomized, and of them 1 subject (in the placebo group) was included in the mITT population and 6 subjects (3 each in the placebo group and tofersen group) was included in non-mITT population. In the Japanese subjects, 3 *SOD1* gene mutations were detected, including p.His47Arg, p.Leu127Ser, and p.Gly94Ser, and the mean duration of disease caused by each mutation was approximately 17, 7, and 8 years, respectively (*Transl Neurodegener.* 2024;13:28). All of the mutations were considered to be accompanied by slow progression.

All of the 7 Japanese subjects enrolled in Part C of Study 101 completed this part and then entered Study 102 (4 subjects in the placebo/delayed-start tofersen group, 3 in the tofersen group). In Study 102, 1 subject in the tofersen group discontinued the study because of disease progression. As of the data cutoff in January 2022, 6 subjects were participating in Study 102 (4 subjects in the placebo/delayed-start tofersen group, 2 in the tofersen group).

Table 45 shows changes in ALSFRS-R total score over time in each Japanese subject. The changes in ALSFRS-R total score in either group were within a range of those in the overall population and did not show any different trend from that in the overall population. In 1 subject in the tofersen group, a massive decline in ALSFRS-R total score from baseline was observed (p.Gly94Ser mutation positive, male in his 50s), but his disease progression was considered to have been possibly affected by his low baseline ALSFRS-R total score and patient characteristics different from those in the other Japanese subjects such as use of ventilatory support before screening.

Table 46 shows changes in predicted SVC% from baseline in the Japanese population over time. The changes in predicted SVC% in either group were within a range of those in the overall population and did not show any different trend from that in the overall population. In the Japanese population, no events related to death or permanent mechanical ventilation occurred.

Although the number of Japanese patients enrolled in Part C of Study 101 is very limited, changes in ALSFRS-R total score over time and results on the other efficacy endpoints did not show any trend clearly different from that in the overall population. The exposure in Japanese patients was within a range of that in the non-Japanese population [see Section 6.R.1]. In view of these findings, the efficacy of tofersen in Japanese patients with SOD1-ALS is evaluable based on the submitted clinical study results in the overall population, and as done in the overall population, the efficacy in Japanese patients can be expected.

Table 45. Baseline ALSFRS-R total score and scores at each timepoint in individual Japanese subjects (pooled analysis data from Studies 101 and 102,[a] data cutoff in February 2023)

	Placebo/delayed-start tofersen				Tofersen		
	Subject 1[b]	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7
Baseline value[c]	24	43	40	39	40	27	33
Week 12	24	45	37	40	39	30	33
Week 28	24	44	36	36	41	25	33
Week 40	24	43	38	36	37	22	33
Week 52	24	43	38	36	37	22	33
Week 64	24	44	38	36	36	20	33
Week 76	24	43	37	36	38	20	33
Week 88	24	41	38	35	37	18	33
Week 100	25	40	38	37	38	18	33
Week 104	25	39	38	36	37	18	33
Week 112	26	41	38	35	39	-	33
Week 124	26	41	38	36	39	-	34

a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Subject meeting the prognostic enrichment criteria
c) Value before administration of the study drug on Day 1 in Part C of Study 101

Table 46. Baseline predicted SVC% and change in predicted SVC% from baseline in Japanese subjects (pooled analysis data from Studies 101 and 102,[a] data cutoff in January 2022)

	Placebo/delayed-start tofersen	Tofersen
Baseline value[b]	98.7 ± 14.94 (4)	103.4 ± 6.97 (3)
Change from baseline[b]		
Week 12	3.2 ± 2.71 (4)	2.0 ± 3.23 (3)
Week 28	3.1 ± 3.25 (4)	2.9 ± 4.76 (3)
Week 40	0.1 ± 3.84 (4)	3.9 (1)
Week 52	1.2 ± 2.36 (4)	4.1 ± 6.30 (3)
Week 64	0.1 ± 4.70 (4)	5.8 ± 1.90 (3)
Week 76	0.5 ± 4.79 (3)	3, 8 (2)
Week 88	1.6 ± 4.26 (3)	5, 8 (2)
Week 100	1.5 ± 8.20 (3)	−1, 10 (2)
Week 104	−1.1 ± 6.48 (3)	0, 26 (2)
Week 112	−0.8 ± 2.95 (3)	4, 13 (2)
Week 124	-	−0.7 (1)

Mean ± SD (number of patients evaluated). Individual values in the case of ≤2 patients.
a) For subjects in whom the start of Study 102 was separated from the end of Study 101 by a certain period, the period without follow-up was excluded.
b) Value before administration of the study drug on Day 1 in Part C of Study 101

PMDA's view:

The number of Japanese patients enrolled in Part C of Study 101 is very limited, and especially rapid progression (mITT population) was limited to 1 patient in the placebo group. Thus, the obtained study results have limitations in evaluating the efficacy of tofersen in Japanese patients including those with rapid progression. Taking into account that (a) the progression rate of SOD1-ALS is greatly affected by type of gene mutation, but mechanism of action of tofersen is independent of type of gene mutation; and (b) changes in ALSFRS-R total score and other efficacy endpoints over time do not tend to greatly differ between the overall and Japanese populations, the efficacy of tofersen in Japanese patients with SOD1-ALS is evaluable based on the submitted clinical study results in the overall population, and as done in the overall population, the efficacy in Japanese patients can be expected.

7.R.2.4 Factors affecting the efficacy of tofersen

PMDA asked the applicant to explain factors affecting the efficacy of tofersen.

The applicant's explanation:

Table 47 shows subgroup analysis results on a change in ALSFRS-R total score from baseline in Part C of Study 101 by patient characteristic factor. Although the evaluation had limitations because of the very limited number of patients in some subgroups and greatly varied disease progression rate of SOD1-ALS from patient to patient, the result in each subgroup was generally consistent with that in the overall population, indicating no patient characteristic factors definitely affecting the efficacy of tofersen.

Table 47. Change in ALSFRS-R total score from baseline to Week 28 in Part C of Study 101 by patient characteristic factor (ITT population)

Patient characteristic factor		Placebo[a)]	Tofersen[a)]	Difference between groups [95% CI]
Sex	Female	−4.3 ± 1.94 (n = 17)	−4.8 ± 1.55 (n = 29)	−0.5 [−5.00, 4.06]
	Male	−5.7 ± 1.98 (n = 19)	−2.7 ± 1.59 (n = 43)	3.0 [−0.80, 6.84]
Age at baseline	<65 years	−5.7 ± 1.49 (n = 31)	−4.1 ± 1.14 (n = 63)	1.6 [−1.65, 4.88]
	≥65 years	−5.1 ± 1.69 (n = 5)	−3.7 ± 1.70 (n = 9)	1.4 [−3.79, 6.52]
Age at onset	<65 years	−5.6 ± 1.43 (n = 33)	−4.0 ± 1.11 (n = 66)	1.6 [−1.54, 4.68]
	≥65 years	−3.9 ± 3.36 (n = 3)	−4.9 ± 2.44 (n = 6)	−0.9 [−10.93, 9.09]
Baseline BMI	<25.4	−5.1 ± 1.68 (n = 17)	−4.7 ± 1.27 (n = 37)	0.4 [−3.51, 4.25]
	≥25.4	−5.3 ± 2.54 (n = 19)	−3.1 ± 2.03 (n = 35)	2.3 [−2.09, 6.61]
Duration of disease from onset to baseline	<11.79 months	−8.1 ± 2.34 (n = 15)	−7.2 ± 1.79 (n = 38)	0.9 [−3.79, 5.61]
	≥11.79 months	−4.6 ± 1.48 (n = 21)	−1.5 ± 1.22 (n = 34)	3.0 [−0.40, 6.42]
Site of onset	Bulbar paralysis	−12.6 ± 7.39 (n = 3)	−8.0 ± 10.54 (n = 3)	4.6 [−23.15, 32.41]
	Others	−5.0 ± 1.23 (n = 33)	−3.6 ± 0.95 (n = 69)	1.4 [−1.26, 4.06]
Population	mITT	−8.8 ± 2.21 (n = 21)	−7.3 ± 1.88 (n = 39)	1.5 [−2.82, 5.85]
	Non-mITT	−2.4 ± 1.22 (n = 15)	−1.4 ± 0.90 (n = 33)	1.0 [−1.78, 3.80]
SOD1 gene mutation	Rapid progression type	−12.9 ± 4.16 (n = 8)	−11.2 ± 2.73 (n = 17)	1.8 [−6.56, 10.11]
	Others	−3.6 ± 1.15 (n = 28)	−1.7 ± 0.95 (n = 55)	1.8 [−0.72, 4.36]
Baseline ALSFRS-R total score	<38 points	−2.6 ± 1.88 (n = 17)	−3.4 ± 1.54 (n = 35)	−0.8 [−4.67, 2.97]
	≥38 points	−7.6 ± 1.92 (n = 19)	−3.9 ± 1.49 (n = 37)	3.7 [−0.62, 7.95]
Pre-randomization slope of ALSFRS-R total score	≥0.9	−7.9 ± 2.10 (n = 18)	−7.0 ± 1.78 (n = 33)	0.9 [−3.41, 5.23]
	<0.9	−3.7 ± 1.72 (n = 18)	−2.4 ± 1.29 (n = 39)	1.4 [−2.47, 5.19]
Baseline predicted SVC%	<81.35%	−7.6 ± 2.17 (n = 15)	−3.9 ± 1.62 (n = 39)	3.7 [−1.00, 8.48]
	≥81.35%	−4.6 ± 1.54 (n = 21)	−4.1 ± 1.25 (n = 33)	0.5 [−2.72, 3.73]
Riluzole	Concomitant use	−4.7 ± 1.31 (n = 22)	−3.5 ± 0.93 (n = 45)	1.2 [−1.90, 4.39]
	Not concomitant use	−7.2 ± 2.30 (n = 14)	−5.5 ± 1.70 (n = 27)	1.8 [−3.85, 7.35]
Edaravone	Concomitant use	0.1 ± 4.50 (n = 3)	−5.4 ± 3.15 (n = 6)	−5.4 [−19.03, 8.20]
	Not concomitant use	−6.1 ± 1.25 (n = 33)	−4.1 ± 0.90 (n = 66)	2.0 [−1.00, 5.03]

a) Mean ± SD (number of patients evaluated)

PMDA confirmed that the limited number of patients in some subgroups precluded strict evaluation, but data in subgroups formed according to a particular patient characteristic factor do not show any trend generally ruling out the efficacy of tofersen.

7.R.3 Safety of tofersen

7.R.3.1 Safety profile of tofersen

PMDA asked the applicant to explain the safety profile of tofersen based on results from foreign clinical studies (Parts A and B of Study 101) and global phase III studies (Part C of Study 101 and Study 102) of tofersen.

The applicant's explanation:

Table 48 shows incidences of adverse events in Studies 101 and 102 as of the last data cutoff (February 2023). Most of the adverse events allowed tofersen treatment to be continued, not leading to discontinuation of tofersen, and many were related to the primary disease or treatment for the primary disease or related to procedures for the study drug administration. In Part C of Study 101, incidences of serious adverse events, Grade ≥3 adverse events rated according to CTCAE version 4, and adverse events leading to treatment discontinuation tended to be higher in the tofersen group than in the placebo group. Incidences of adverse events did not clearly differ between the Japanese and overall populations, although the comparison had limitations because of the limited number of Japanese patients.

Table 48. Incidences of adverse events in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled data from Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
All adverse events	69 (95.8)	34 (94.4)	103 (99.0)	146 (99.3)	7 (100)
Adverse events leading to death	1 (1.4)	0	18 (17.3)	22 (15.0)	0
Serious adverse events	13 (18.1)	5 (13.9)	48 (46.2)	65 (44.2)	2 (28.5)
Adverse events leading to treatment discontinuation	4 (5.6)	0	23 (22.1)	30 (20.4)	1 (14.3)
CTCAE Grade ≥3 adverse events	12 (16.7)	4 (11.1)	48 (46.2)	65 (44.2)	1 (14.3)
Main adverse events (events reported by ≥7% of patients in any population or group other than the Japanese population and events reported by ≥3 patients in the Japanese population)					
Headache	33 (45.8)	16 (44.4)	62 (59.6)	90 (61.2)	5 (71.4)
Procedural pain	41 (56.9)	21 (58.3)	60 (57.7)	86 (58.5)	1 (14.3)
Fall	17 (23.6)	15 (41.7)	45 (43.3)	71 (48.3)	2 (28.5)
Back pain	14 (19.4)	2 (5.6)	45 (43.3)	67 (45.6)	5 (71.4)
Pain in extremity	19 (26.4)	6 (16.7)	41 (39.4)	61 (41.5)	1 (14.3)
Arthralgia	10 (13.9)	2 (5.6)	35 (33.7)	50 (34.0)	0
COVID-19	1 (1.4)	1 (2.8)	33 (31.7)	44 (29.9)	1 (14.3)
Fatigue	12 (16.7)	2 (5.6)	30 (28.8)	42 (28.6)	2 (28.5)
CSF protein increased	6 (8.3)	1 (2.8)	28 (26.9)	39 (26.5)	3 (42.9)
Nausea	9 (12.5)	6 (16.7)	23 (22.1)	38 (25.9)	3 (42.9)
Post lumbar puncture syndrome	13 (18.1)	11 (30.6)	24 (23.1)	36 (24.5)	1 (14.3)
Muscle spasms	5 (6.9)	2 (5.6)	21 (20.2)	30 (20.4)	0
Nasopharyngitis	2 (2.8)	7 (19.4)	13 (12.5)	29 (19.7)	3 (42.9)
Myalgia	10 (13.9)	2 (5.6)	21 (20.2)	28 (19.0)	0
Dizziness	4 (5.6)	3 (8.3)	18 (17.3)	28 (19.0)	2 (28.5)
Constipation	6 (8.3)	4 (11.1)	22 (21.2)	28 (19.0)	1 (14.3)
CSF white blood cell count increased	7 (9.7)	0	22 (21.2)	27 (18.4)	1 (14.3)
Pyrexia	3 (4.2)	1 (2.8)	19 (18.3)	27 (18.4)	7 (100)
Contusion	3 (4.2)	1 (2.8)	15 (14.4)	25 (17.0)	1 (14.3)
Respiratory failure	3 (4.2)	0	16 (15.4)	22 (15.0)	0
Urinary tract infection	2 (2.8)	2 (5.6)	12 (11.5)	22 (15.0)	0
Diarrhoea	1 (1.4)	5 (13.9)	15 (14.4)	21 (14.3)	1 (14.3)
Muscular weakness	4 (5.6)	4 (11.1)	17 (16.3)	21 (14.3)	0
Dyspnoea	4 (5.6)	5 (13.9)	17 (16.3)	20 (13.6)	0
Upper respiratory tract infection	5 (6.9)	2 (5.6)	10 (9.6)	18 (12.2)	0
Salivary hypersecretion	4 (5.6)	1 (2.8)	15 (14.4)	17 (11.6)	0
Paraesthesia	6 (8.3)	6 (16.7)	13 (12.5)	16 10.9)	0
Cough	5 (6.9)	1 (2.8)	11 (10.6)	15 (10.2)	0
Neck pain	4 (5.6)	4 (11.1)	10 (9.6)	14 (9.5)	2 (28.5)
Rash	2 (2.8)	0	8 (7.7)	14 (9.5)	0
Pneumonia aspiration	1 (1.4)	0	13 (12.5)	14 (9.5)	0
Dysphagia	1 (1.4)	0	9 (8.7)	14 (9.5)	0
Pain	7 (9.7)	0	12 (11.5)	14 (9.5)	0
Pleocytosis	3 (4.2)	0	11 (10.6)	13 (8.8)	2 (28.5)
Anxiety	4 (5.6)	3 (8.3)	9 (8.7)	12 (8.2)	0
Insomnia	3 (4.2)	3 (8.3)	9 (8.7)	12 (8.2)	0
Musculoskeletal pain	4 (5.6)	2 (5.6)	8 (7.7)	12 (8.2)	1 (14.3)
Hypoaesthesia	3 (4.2)	1 (2.8)	7 (6.7)	12 (8.2)	1 (14.3)
Peripheral swelling	1 (1.4)	1 (2.8)	6 (5.8)	11 (7.5)	0
Skin abrasion	3 (4.2)	3 (8.3)	6 (5.8)	10 (6.8)	0
Pneumonia	0	0	8 (7.7)	10 (6.8)	0
Joint swelling	1 (1.4)	2 (5.6)	8 (7.7)	10 (6.8)	0
Sinusitis	1 (1.4)	1 (2.8)	8 (7.7)	10 (6.8)	0
Muscle contractions involuntary	4 (5.6)	1 (2.8)	8 (7.7)	10 (6.8)	0
Ligament sprain	4 (5.6)	2 (5.6)	8 (7.7)	9 (6.1)	1 (14.3)
Depression	1 (1.4)	3 (8.3)	4 (3.8)	9 (6.1)	0
Abdominal pain upper	0	0	5 (4.8)	9 (6.1)	3 (42.9)
Post procedural complication	3 (4.2)	4 (11.1)	3 (2.9)	6 (4.1)	0
Skin laceration	0	3 (8.3)	2 (1.9)	6 (4.1)	0

Number of patients with the event (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

Table 49 shows incidences of serious adverse events in Studies 101 and 102. Many of the serious events were related to the primary disease or treatment for the primary disease or related to procedures for the study drug administration. In Part C of Study 101, pulmonary embolism occurred more commonly in the tofersen group than in the placebo group, but a causal relationship to tofersen was ruled out for any event of pulmonary embolism in the tofersen group. Pulmonary embolism is a common event in patients with ALS (*Neurol: Clin Pract.* 2023;13:e200110) and considered attributable to the primary disease.

Table 49. Incidences of serious adverse events in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled analysis of Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
Serious adverse events	13 (18.1)	5 (13.9)	48 (46.2)	65 (44.2)	2 (28.5)
List of adverse events (events reported by ≥2 patients in any group or population)					
Respiratory failure	1 (1.4)	0	13 (12.5)	18 (12.2)	0
Pneumonia aspiration	1 (1.4)	0	11 (10.6)	12 (8.2)	0
Dysphagia	0	0	4 (3.8)	7 (4.8)	0
Pulmonary embolism	3 (4.2)	1 (2.8)	6 (5.8)	6 (4.1)	0
Acute respiratory failure	1 (1.4)	0	6 (5.8)	6 (4.1)	0
Pneumonitis aspiration	2 (2.8)	0	3 (2.9)	4 (2.7)	0
Fall	0	0	1 (1.0)	4 (2.7)	0
COVID-19	0	0	3 (2.9)	3 (2.0)	0
Pneumonia	0	0	3 (2.9)	3 (2.0)	0
Intracranial pressure increased	0	0	2 (1.9)	3 (2.0)	0
Aspiration	1 (1.4)	0	2 (1.9)	2 (1.4)	0
Cardio-respiratory arrest	0	0	2 (1.9)	2 (1.4)	0
Chronic respiratory failure	0	0	2 (1.9)	2 (1.4)	0
Respiratory arrest	0	0	2 (1.9)	2 (1.4)	0
Septic shock	0	0	2 (1.9)	2 (1.4)	1 (14.3)
Faecaloma	1 (1.4)	0	1 (1.0)	2 (1.4)	0
Myelitis	1 (1.4)	0	1 (1.0)	2 (1.4)	0
Amyotrophic lateral sclerosis	0	0	1 (1.0)	2 (1.4)	0
Back pain	0	0	1 (1.0)	2 (1.4)	0
Headache	0	0	1 (1.0)	2 (1.4)	0
Nephrolithiasis	0	0	1 (1.0)	2 (1.4)	0
Urinary tract infection	0	0	1 (1.0)	2 (1.4)	0
Respiratory distress	0	0	0	2 (1.4)	0
Dyspnoea	0	2 (5.6)	1 (1.0)	1 (0.7)	0

Number of patients with the event (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

PMDA's view:

Since adverse events in the clinical studies do not tend to clearly differ between the Japanese and overall populations, the safety of tofersen in Japanese patients with SOD1-ALS is evaluable based on the submitted clinical study results in the overall population.

According to the submitted clinical study results, many of the adverse events are related to the primary disease, treatment for the primary disease, or administration procedures. However, adverse events related to myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic occurred during tofersen treatment, and some of them were serious, and 2'-MOE-modified ASOs are known to have a proinflammatory effect as well as effects on the kidney, liver, and platelet as class effects. Given these points, adverse events related to myelitis, radiculitis, optic disc oedema, intracranial

pressure increased, and meningitis aseptic, events related to lumbar puncture, events related to renal dysfunction, events related to hepatic dysfunction, and effects of tofersen on blood coagulation cascade are reviewed in detail in Sections 7.R.3.2 to 7.R.3.6.

Adverse events during tofersen treatment other than the above events are considered to raise no concerns as relevant problems in clinical use of tofersen in view of the incidences in the clinical studies and severity. On the condition that for each of the events described below, appropriate cautions and risk minimization activities be exercised, PMDA concluded that the safety of tofersen in Japanese patients with SOD1-ALS is acceptable.

7.R.3.2 Adverse events related to myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic

In view of findings in the central nervous system (inflammation in the meninges and spinal nerve root as well as vacuolated neurons) in non-clinical studies of tofersen and occurrence of adverse events related to myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic in clinical studies, PMDA asked the applicant to explain occurrence of these events in clinical studies in detail.

The applicant's explanation:

Table 50 shows incidences of adverse events related to myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic[36)] in Studies 101 and 102. In the placebo group, none of the concerned events occurred. On the other hand, these events occurred in 4 of 72 patients in the tofersen group in Part C of Study 101 and 12 of 139 patients in Study 102; in total, 31 events occurred in 16 patients. Of 16 patients, 3 patients discontinued the treatment, 2 patients interrupted the treatment, and 11 events in 8 patients did not resolve. The mechanism of onset of these events remains unclear. These events which represent inflammation in the central nervous system might have been caused by the proinflammatory effect of tofersen, ASO.

36) MedDRA preferred terms (PTs) "myelitis," "myelitis transverse," "neurosarcoidosis," "radiculopathy," "lumbar radiculopathy," "optic disc oedema," "intracranial pressure increased," "meningitis chemical," and "meningitis aseptic" are included.

Table 50. Adverse events related to myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic during tofersen treatment in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

Age (years)	Sex	Race	Mutation	Event	Day of onset[a] (Day)	Severity[b]/ seriousness	Action on tofersen	Duration (days)/ outcome	Causal relationship
Study 101									
2[redacted]	Female	Caucasian	Ala90Thr	Meningitis chemical	147	Grade 3/serious	Discontinued	11/recovered	Related
4[redacted]	Male	Unknown	His121Gln	Lumbar radiculopathy	3	Grade 2/serious	Continued	2/recovered	Related
				Lumbar radiculopathy	59	Grade 2/non-serious	Continued	3/recovered	Related
				Lumbar radiculopathy	115	Grade 2/non-serious	Continued	3/recovered	Related
				Lumbar radiculopathy	142	Grade 1/non-serious	Continued	3/recovered	Related
3[redacted]	Male	Unknown	Ala5Ser	Myelitis transverse	197	Grade 1/serious	Continued	Unrecovered	Related
3[redacted]	Female	Unknown	Gly94Cys	Myelitis	98	Grade 3/serious	Discontinued	Unrecovered	Related
Study 102									
4[redacted]	Male	Caucasian	Glu41Gly	Neurosarcoidosis	95	Grade 3/serious	Discontinued	104/recovered	Unrelated
5[redacted]	Male	Caucasian	Ile114Thr	Meningitis aseptic	91	Grade 2/serious	Continued	25/recovered	Related
				Optic disc oedema	148	Grade 3/serious	Interrupted	191/recovered	Related
7[redacted]	Male	Caucasian	Gly94Ala	Intracranial pressure increased	198	Grade 1/serious	Continued	5/recovered	Related
				Intracranial pressure increased	203	Grade 2/serious	Continued	247/recovered	Related
				Optic disc oedema	203	Grade 1/non-serious	Continued	37/recovered	Related
				Intracranial pressure increased	450	Grade 1/non-serious	Continued	Unrecovered	Related
4[redacted]	Male	Caucasian	Ala5Thr	Radiculopathy	646	Grade 3/serious	Continued	280/recovered	Related
5[redacted]	Female	Caucasian	Asp91Ala	Lumbar radiculopathy	1543	Grade 1/non-serious	Continued	56/recovered	Related
5[redacted]	Male	Caucasian	Ile114Thr	Optic disc oedema	331	Grade 1/non-serious	Continued	70/recovered	Related
				Optic disc oedema	400	Grade 1/non-serious	Continued	187/recovered	Related
				Intracranial pressure increased	422	Grade 2/non-serious	Continued	165/recovered	Related
				Meningitis chemical	646	Grade 2/non-serious	Continued	Unrecovered	Related
4[redacted]	Male	Unknown	Ile114Thr	Intracranial pressure increased	269	Grade 3/serious	Continued	27/recovered	Related
3[redacted]	Female	Unknown	Asn87Ser	Meningitis aseptic	309	Grade 1/non-serious	Continued	Unrecovered	Related
				Optic disc oedema	376	Grade 2/non-serious	Continued	Unrecovered	Related
				Intracranial pressure increased	433	Grade 3/serious	Continued	Unrecovered	Related
				Myelitis	474	Grade 3/serious	Interrupted	87/recovered	Related
4[redacted]	Female	Asian	Gly94Ser	Meningitis aseptic	15	Grade 1/non-serious	Continued	Unrecovered	Related
				Radiculopathy	508	Grade 1/non-serious	Continued	59/recovered	Related
4[redacted]	Female	Caucasian	Ile114Thr	Meningitis chemical	1374	Grade 1/non-serious	Continued	Unrecovered	Related
5[redacted]	Male	Caucasian	Ile114Thr	Intracranial pressure increased	338	Grade 2/non-serious	Continued	Unrecovered	Related
				Optic disc oedema	423	Grade 2/non-serious	Continued	Unrecovered	Related
4[redacted]	Male	Caucasian	Gly148Ser	Intracranial pressure increased	701	Grade 2/non-serious	Continued	30/recovered	Related

a) Number of days from the first dose in Study 101 or Study 102 to onset of the event
b) Severity was rated according to CTCAE version 4.

Patients treated with tofersen 100 mg in Study 101 or 102 were sorted into subgroups according to patient characteristic factors that might affect onset of these adverse events. Table 51 shows the subgroup analysis results. A comparison between subgroups formed according to post-baseline white blood cell count in CSF had limitations because most of the subjects had the concerned count $>5 \times 10^6$/L at least once, but comparisons between subgroups formed according to the other factors showed no clear differences.

Table 51. Incidences of adverse events related to myelitis in subgroups formed according to patient characteristic factors in Studies 101 and 102[36)]
(pooled safety data from Studies 101 and 102, data cutoff in February 2023)

		No. of patients evaluated	Non-serious adverse events	Serious adverse events
Sex	Female	65	4 (6.2)	3 (4.6)
	Male	82	7 (8.5)	7 (8.5)
Age	<65 years	127	10 (7.9)	9 (7.1)
	≥65 years	20	1 (5.0)	1 (5.0)
Race	Asian	10	1 (10.0)	0 (0)
	Caucasian	88	8 (9.1)	5 (5.7)
	Unknown	45	2 (4.4)	5 (11.1)
Duration of disease[a)]	<11.79 months	47	4 (8.5)	4 (8.5)
	>11.79 months	100	7 (7.0)	7 (7.0)
Analysis population	mITT	58	3 (5.2)	5 (8.6)
	Non-mITT	46	4 (8.7)	2 (4.3)
Post-baseline white blood cell count in CSF	$>5 \times 10^6$/L	134	11 (8.2)	10 (7.5)
	$<5 \times 10^6$/L	13	0 (0)	0 (0)
Number of doses of tofersen	1-20 doses	44	0 (0)	3 (6.8)
	20-40 doses	46	5 (10.9)	6 (13.0)
	>40 doses	57	6 (10.5)	1 (1.8)

Number of patients with the event (incidence [%])
a) Stratified by the median

Anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD) occurred only in 1 patient in Study 102. The concerned event was serious and rated as CTCAE Grade 3. The investigator considered that inflammation in the spinal cavity attributable to the study drug potentially led to NMOSD and thus the concerned event was related to the study drug. The clinical course is shown in Table 52. The concerned subject received 48 doses of tofersen before onset of NMOSD, recovered with steroid therapy, and then discontinued the study treatment. At present, except for the concerned subject, none were found positive for autoantibody related to an autoimmune disease such as encephalitis, myelitis, or NMOSD in Study 101 or 102. Whether the long-term tofersen treatment can increase the risk of these events remains unknown. Onset of SOD1-ALS and NMOSD is not considered to share the same mechanism, and no concurrent onset of SOD1-ALS and NMOSD has been reported so far. In view of an ASO's proinflammatory attribute, neurogenic inflammation caused by tofersen is generally considered to be related to onset of NMOSD, but at present, the mechanism of onset of NMOSD, a demyelinating disease, after tofersen treatment remains unclear. NMOSD and myelitis, which were observed during tofersen treatment, have similar clinical characteristics (numbness, weakness), but at present, there is no evidence that these conditions develop through the same mechanism. The applicant will continue to collect the information on NMOSD during tofersen treatment including long-term treatment after the market launch of tofersen as well and take additional safety measures where necessary.

Table 52. Clinical course of subject with NMOSD

Age/sex/race/mutation	4[redacted] year old/female/Asian/p.His47Arg
Course	
[redacted] 20[redacted]	Start of tofersen treatment (tofersen 100 mg intrathecally administered every 2 weeks and then every 4 weeks)
DAY 1571 (January 20XX)	Last dose of tofersen
MONTH 53 (February of the same year)	Numbness started from the right leg and then spread to the left leg and trunk
DAY 1614 (March of the same year)	Hospitalized because of numbness on the left hand and moving difficulty Neurological examination revealed analgesia at T6 or lower parts, abnormal tingling sensation (left upper limb), and decreased tactile sensation (right upper limb). CSF examination revealed increased cell count (36/μL) and increased protein concentration (161 mg/dL). Serology test (ELISA) presented an anti-AQP4 antibody positive result (25.4 U/mL; normal range, 0.0-2.9 U/mL). CBA presented an anti-AQP4 antibody negative result.
DAY 1616 (March of the same year)	MRI (spinal cord) identified a lesion at the fourth to sixth cervical vertebrae (C4 to C6). Steroid pulse therapy started on the same day (2 cycles were performed during hospital stay).
DAY 1628 (March of the same year)	The patient recovered from NMOSD and was discharged. Examination during hospital stay revealed no signs of optic neuritis.
DAY 1661 (April of the same year)	Tofersen treatment discontinued

PMDA asked the applicant to explain their views on necessity of periodic spinal fluid examination or magnetic resonance imaging (MRI) examination to control adverse events such as myelitis, intracranial pressure increased, and meningitis aseptic during tofersen treatment and acceptability of continued tofersen treatment in case of occurrence of any of the concerned adverse events.

The applicant's explanation:
Spinal fluid examination was scheduled before each dose of the study drug and 4 weeks after the last dose in Part C of Study 101 and before each dose of the study drug in Study 102. Additional unscheduled spinal fluid examination was allowed based on the clinical symptoms at the discretion of the investigator. No periodic MRI examination was scheduled, but MRI examination was allowed based on the clinical symptoms at the discretion of the investigator.

Table 53 shows results of the spinal fluid examination in 10 patients who experienced serious adverse events of myelitis, radiculitis, optic disc oedema, intracranial pressure increased, or meningitis aseptic as listed in Table 50. No clear relationship of severity or type of each neurological event to abnormal values in the spinal fluid examination was observed. Of 104 subjects transferred from Part C of Study 101 to Study 102, 82 subjects (78.8%) and 92 subjects (88.5%) had the increased white blood cell count in CSF to $>10 \times 10^6$/L and $>5 \times 10^6$/L, respectively, at least once. In many subjects, the increased white blood cell count in spinal fluid was observed but mostly asymptomatic. The periodic monitoring of white blood cell count in spinal fluid is, therefore, considered little meaningful for the purpose of controlling the risk of adverse events such as myelitis. Patients with ALS may have moving difficulty owing to remarkable muscular weakness or have to be on ventilatory support owing to respiratory failure, and MRI examination requiring any subject to be at rest in supine position can pose physical burden to these patients. Thus, the attending physician should perform the MRI examination based on clinical symptoms where necessary.

Based on the above, in post-marketing settings, spinal fluid or MRI examination may not have to be performed periodically but should be performed when a physician finds it necessary after checking the patient's condition.

In Part C of Study 101 and Study 102, the protocol did not specify the pre-determined actions to be taken in response to onset of adverse events such as myelitis, and physicians decided actions such as discontinuation of the study drug according to symptoms and conditions of each patient. In the clinical studies, most of the patients who experienced adverse events related to myelitis continued the study drug without discontinuation, and SOD1-ALS is a serious progressive disease. In view of the above, tofersen may not have to be always discontinued or temporarily interrupted when any of these events occurs during clinical use of tofersen, and physicians should decide to continue, discontinue, or temporarily interrupt tofersen based on conditions of each patient.

Table 53. Results of spinal fluid examination in subjects who experienced serious myelitis, radiculitis, optic disc oedema, intracranial pressure increased, or meningitis aseptic in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

Age (years)	Sex	Event	Severity[a)]	Spinal fluid examination at the time of event onset		
				White blood cell count (/μL)	Protein (mg/dL)	Intracranial pressure (cmH_2O)
Study 101						
2[redacted]	Female	Meningitis chemical	Grade 3	144	185	-
4[redacted]	Male	Lumbar radiculopathy	Grade 2	9	131	-
3[redacted]	Male	Myelitis transverse	Grade 1	23, 17	53, 58	-
3[redacted]	Female	Myelitis	Grade 3	21	79	-
Study 102						
4[redacted]	Male	Neurosarcoidosis	Grade 3	44	93	-
5[redacted]	Male	Meningitis aseptic	Grade 2	317	95	-
		Optic disc oedema	Grade 3	131	197	16.6-21
7[redacted]	Male	Intracranial pressure increased	Grade 2	23	82	28
4[redacted]	Male	Radiculopathy	Grade 3	9, 16	200	-
4[redacted]	Male	Intracranial pressure increased	Grade 3	43	140	25.5
3[redacted]	Female	Intracranial pressure increased	Grade 3	41	77	38
		Myelitis	Grade 3	38	119	-

a) Severity was rated according to CTCAE version 4.

PMDA's view:

Myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic occurred only when tofersen was used, and thus for most of these events, a causal relationship to tofersen cannot be ruled out. These adverse events including serious events may occur during use of tofersen. Taking into account that 2'-MOE-modified ASOs including tofersen can induce inflammatory reactions (Antisense Drug Technology: Toxicologic Properties Of 2'-Methoxyethyl Chimeric Antisense Inhibitors In Animal And Man. *CRC Press*; 2008.p327-62), tofersen is considered likely to have induced adverse events such as meningitis aseptic, myelitis, radiculitis, optic disc oedema, and intracranial pressure increased, as explained by the applicant.

Myelitis and radiculitis are hardly distinguished from worsening of ALS symptoms based on the clinical conditions, and these events can result in serious outcomes. For example, optic disc oedema associated with intracranial pressure increased would pose a risk of blindness if no appropriate measures are taken. All of the subjects who experienced serious myelitis, radiculitis, optic disc oedema, intracranial pressure

increased, or meningitis aseptic were found to have the increased cell count in spinal fluid examinations. In view of the above review, the package insert should provide caution to ensure that spinal fluid examination and intracranial pressure measurement are periodically performed during tofersen treatment, and that patients' conditions including neurologic symptoms are monitored. Information about myelitis, radiculitis, optic disc oedema, intracranial pressure increased, meningitis aseptic, and abnormal values in spinal fluid examinations reported in the clinical studies should be provided through the package insert. The applicant is required to collect the information with a focus on onset of these events in post-marketing settings as well.

7.R.3.3 Adverse events related to lumbar puncture

PMDA asked the applicant to explain about adverse events related to lumbar puncture:

The applicant's explanation:

Table 54 shows incidences of adverse events related to lumbar puncture[37)] reported in Studies 101 and 102. Incidences of adverse events related to lumbar puncture did not clearly differ between the tofersen group and placebo group or between the population of patients transferred from Part C to Study 102 and the population in Part C. There were no serious adverse events or adverse events leading to treatment discontinuation.

Based on the above, adverse events related to lumbar puncture may occur during tofersen treatment. The applicant will provide information about adverse drug reactions related to lumbar puncture through the package insert. In view of their severity, these events are considered to raise no relevant concerns for its clinical use.

37) Whether the event was related to a lumbar puncture procedure was judged according to the following criteria for the related events: (a) The lumbar puncture procedure and event are timely continuous; (b) the event is included in known patterns of reactions to a lumbar puncture procedure (e.g., bleeding from the puncture site); (c) the lumbar puncture procedure and adverse event are causally related in a biologically justified manner; or (d) for the adverse event, no other causes are found.

Table 54. Incidences of adverse events related to lumbar puncture in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled analysis of Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
All adverse events	58 (80.6)	29 (80.6)	87 (83.7)	126 (85.7)	6 (85.7)
Main adverse events (events reported by ≥4 patients in any group or population)					
Procedural pain	40 (55.6)	21 (58.3)	59 (56.7)	85 (57.8)	1 (14.3)
Headache	22 (30.6)	12 (33.3)	46 (44.2)	66 (44.9)	4 (57.1)
Back pain	9 (12.5)	0	33 (31.7)	48 (32.7)	5 (71.4)
Post lumbar puncture syndrome	13 (18.1)	11 (30.6)	24 (23.1)	36 (24.5)	1 (14.3)
Nausea	4 (5.6)	3 (8.3)	9 (8.7)	14 (9.5)	2 (28.6)
Pain in extremity	6 (8.3)	0	10 (9.6)	13 (8.8)	0
CSF white blood cell count increased	4 (5.6)	0	9 (8.7)	11 (7.5)	0
Dizziness	2 (2.8)	1 (2.8)	8 (7.7)	11 (7.5)	1 (14.3)
CSF protein increased	3 (4.2)	0	7 (6.7)	11 (7.5)	0
Post procedural contusion	1 (1.4)	0	5 (4.8)	5 (3.4)	0
Paraesthesia	3 (4.2)	0	6 (5.8)	7 (4.8)	0
Arthralgia	2 (2.8)	0	4 (3.8)	5 (3.4)	0
Migraine	1 (1.4)	1 (2.8)	3 (2.9)	3 (2.0)	0
Neck pain	2 (2.8)	3 (8.3)	2 (1.9)	3 (2.0)	0
Hypoaesthesia	1 (1.4)	0	2 (1.9)	4 (2.7)	0
Pleocytosis	2 (2.8)	0	2 (1.9)	4 (2.7)	0
Procedural nausea	1 (1.4)	2 (5.6)	3 (2.9)	5 (3.4)	0
Post procedural complication	2 (2.8)	2 (5.6)	2 (1.9)	4 (2.7)	0
Post procedural swelling	0	0	1 (1.0)	4 (2.7)	0

Number of patients with the event (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

PMDA's view:

In the clinical studies, adverse events related to lumbar puncture occurred, but neither serious events nor events leading to treatment discontinuation occurred. All of the patients with these events continued the treatment. During use of tofersen, adverse events related to lumbar puncture may occur but are considered to raise no relevant problems in clinical use of tofersen at present.

7.R.3.4 Renal dysfunction

For nusinersen sodium, an approved ASO, the package insert provides caution to ensure that renal function test is periodically performed during the treatment (package insert of "Spinraza Intrathecal Injection 12 mg") based on reports of renal disorder after administration of other ASOs outside Japan and increased urine protein after administration of nusinersen sodium. PMDA asked the applicant to explain about renal dysfunction during tofersen treatment.

The applicant's explanation:

Table 55 shows incidences of adverse events related to renal and urinary disorders[38)] reported in Studies 101 and 102. Incidences of adverse events related to renal and urinary disorders did not clearly differ between the tofersen group and placebo group in Part C of Study 101, and the adverse event in subjects treated with tofersen 100 mg for which a causal relationship to tofersen could not be ruled out was micturition urgency in 2 subjects.

38) Events coded to MedDRA SOC "Renal and urinary disorders"

In Part C of Study 101, a high creatinine or blood urea nitrogen (BUN) value in a haematology was found in 1.4% or 23.5% of the patients in the tofersen group and 5.9% or 28.1% in the placebo group, respectively, and no clear differences between the groups were observed.

According to the pooled safety data from Studies 101 and 102 (data cutoff in July 2022), of 147 patients treated with tofersen 100 mg, <4% of patients were found to have experienced blood urine present, cells in urine, protein urine, protein urine present, white blood cells urine positive, glucose urine present, and nitrite urine present, among adverse events coded to SOC "Investigations."

Based on the above, the information available to date does not raise a concern about an increased incidence of renal dysfunction owing to tofersen.

Table 55. Incidences of adverse events related to renal and urinary disorders in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled analysis of Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
All adverse events	6 (8.3)	1 (2.8)	21 (20.2)	35 (23.8)	5 (71.4)
Serious adverse events	0	0	3 (2.9)	4 (2.7)	1 (14.3)
Adverse events leading to treatment discontinuation	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Main adverse events (events reported by ≥2 patients in any group or population)					
Nephrolithiasis	0	0	5 (4.8)	7 (4.8)	0
Pollakiuria	1 (1.4)	1 (2.8)	4 (3.8)	6 (4.1)	1 (14.3)
Acute kidney injury	1 (1.4)	0	5 (4.8)	5 (3.4)	0
Micturition urgency	2 (2.8)	0	2 (1.9)	5 (3.4)	0
Haematuria	0	0	1 (1.0)	4 (2.7)	0
Dysuria	0	0	2 (1.9)	3 (2.0)	0
Urinary incontinence	0	0	0	3 (2.0)	0
Calculus urinary	0	0	1 (1.0)	2 (1.4)	1 (14.3)
Chromaturia	0	0	2 (1.9)	2 (1.4)	0
Glycosuria	2 (2.8)	0	2 (1.9)	2 (1.4)	0
Urinary retention	0	0	0	2 (1.4)	0

Number of patients with the event (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

PMDA's view:

In the information available to date, neither adverse events related to renal dysfunction potentially raising clinically relevant concerns nor a definite excursion trend of clinical laboratory values related to renal functions are observed. However, the incidences tended to be slightly higher in the tofersen group than in the placebo group in Part C of Study 101. The pooled analysis of Studies 101 and 102 shows that incidences of adverse events related to renal dysfunction during tofersen treatment were actually high and serious adverse events also occurred. In view of not only these findings but also occurrence of renal dysfunction reported with the other 2'-MOE-modified ASOs, a possibility of occurrence of renal dysfunction during tofersen treatment cannot be ruled out. Therefore, the package insert should include caution to ensure that renal function test is periodically performed during tofersen treatment.

7.R.3.5 Hepatic dysfunction

For nusinersen sodium, an approved ASO, the package insert includes caution to ensure that hepatic function test is periodically performed during the treatment (package insert of "Spinraza Intrathecal Injection 12 mg") based on reports of hepatic disorder after administration of other ASOs outside Japan. PMDA asked the applicant to explain about hepatic dysfunction during tofersen treatment.

The applicant's explanation:

Table 56 shows incidences of adverse events related to hepatobiliary disorders[39)] and laboratory abnormalities related to hepatobiliary disorders[40)] in Studies 101 and 102. Incidences of adverse events related to hepatic dysfunction did not clearly differ between the tofersen group and placebo group in Part C of Study 101, and there were no events for which a causal relationship to tofersen could not be ruled out throughout Studies 101 and 102. One subject who participated in Studies 101 and 102 experienced hepatic function abnormal, and its severity was moderate. More specifically, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased occurred and then resolved, and a causal relationship to tofersen was ruled out for the events.

Of events of hepatobiliary laboratory abnormalities, none were serious, and event leading to treatment discontinuation was only blood alkaline phosphatase (ALP) increased in 1 patient.[41)] There were no events of hepatic dysfunction meeting the Hy's Law criteria for clinical laboratory values (defined according to Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009). In the tofersen group in Part C of Study 101, an ALT value greater than 5 times the upper limits of normal (ULN) and an AST value greater than 3 times ULN occurred in 1 subject each, but most of the changes in the other liver function parameters did not clearly differ between the tofersen group and placebo group.

Based on the above, a risk of hepatic dysfunction owing to tofersen is not indicated.

39) Events coded to MedDRA SOC "Hepatobiliary disorders"

40) Events that are coded to MedDRA SOC "Investigations" and have PTs of alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, gamma-glutamyl transferase increased, transaminases increased, liver function test abnormal, and blood alkaline phosphatase increased

41) Blood alkaline phosphatase increased occurred in 1 subject treated with tofersen 100 mg in Part C of Study 101 and Study 102. The event was rated as Grade 2 in severity according to CTCAE version 4, and a causal relationship to tofersen could not be ruled out for this event, resulting in discontinuation of tofersen treatment. No abnormalities were observed in values on the other liver function test parameters. The blood alkaline phosphatase abnormality did not resolve even 11 months after discontinuation of tofersen.

Table 56. Incidences of adverse events and laboratory abnormalities related to hepatobiliary disorders in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled analysis of Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	0	1 (1.0)	2 (1.4)	0
Adverse events leading to treatment discontinuation	0	0	1 (1.0)	1 (0.7)	1 (14.3)
Adverse events					
Alanine aminotransferase increased	1 (1.4)	0	6 (5.8)	8 (5.4)	0
Aspartate aminotransferase increased	1 (1.4)	0	4 (3.8)	6 (4.1)	0
Hepatic enzyme increased	0	0	3 (2.9)	6 (4.1)	0
Hepatic steatosis	1 (1.4)	0	6 (5.8)	6 (4.1)	2 (28.6)
Gamma-glutamyl transferase increased	0	0	0	2 (1.4)	0
Transaminases increased	1 (1.4)	0	2 (1.9)	2 (1.4)	0
Blood alkaline phosphatase increased	0	0	2 (1.9)	2 (1.4)	1 (14.3)
Cholelithiasis	0	0	2 (1.9)	4 (2.7)	0
Bile duct stone	0	0	0	1 (0.7)	0
Cholecystitis	0	0	1 (1.0)	1 (0.7)	0
Hepatic function abnormal	0	0	0	1 (0.7)	0
Hypertransaminasaemia	0	0	0	1 (0.7)	0
Liver function test abnormal	0	0	0	1 (0.7)	0

Number of patients with the event (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

PMDA's view:

Hepatic dysfunction was reported as a consequence of the class effect of 2'-MOE-modified ASOs (Antisense Drug Technology: Toxicologic Properties of 2'-Methoxyethyl Chimeric Antisense Inhibitors in Animal and Man. *CRC Press*; 2008.p.327-62). In the clinical studies of tofersen, incidences of adverse events related to hepatic dysfunction and proportions of subjects with abnormal liver function test values did not tend to be definitely higher in the tofersen group than in the placebo group, and no events of hepatic dysfunction meeting the Hy's Law criteria for clinical laboratory values were observed. Therefore, the package insert does not have to include any particular caution about hepatic dysfunction at present.

7.R.3.6 Effects on blood coagulation system

For nusinersen sodium, an approved ASO, the package insert includes caution to ensure that platelet count measurement and coagulation test are periodically performed during the treatment (package insert of "Spinraza Intrathecal Injection 12 mg") based on reports of coagulation system abnormalities including severe acute thrombocytopenia after administration of other ASOs outside Japan and platelet count decreased during nusinersen sodium treatment. PMDA asked the applicant to explain effects of tofersen on platelet count and a blood coagulation system.

The applicant's explanation:

Table 57 shows proportions of patients with a platelet count change after the first dose of the study drug in Studies 101 and 102. In Part C of Study 101, changes in platelet count did not clearly differ between

the tofersen group and placebo group, and no clinically meaningful changes in platelet count were observed throughout the study period.

Table 57. Changes in platelet count from baseline in Studies 101 and 102 (pooled safety data from Studies 101 and 102, data cutoff in July 2022)

		Minimum after baseline			Maximum after baseline		
Population	Baseline	Low	Normal	High	Low	Normal	High
Part C of Study 101							
Tofersen 100 mg (n = 72)	Low	0	1 (1.4)	0	0	1 (1.4)	0
	Normal	3 (4.2)	67 (93.1)	0	0	70 (97.2)	0
	High	0	1 (1.4)	0	0	0	1 (1.4)
Placebo (n = 36)	Low	0	0	0	0	0	0
	Normal	1 (2.8)	35 (97.2)	0	0	36 (100)	0
	High	0	0	0	0	0	0
Studies 101 and 102							
Population transferred from Part C of Study 101 to Study 102 (n = 104)[a)]	Low	0	1 (1.0)	0	0	1 (1.0)	0
	Normal	4 (3.8)	98 (94.2)	0	0	99 (95.2)	3 (2.9)
	High	0	1 (1.0)	0	0	0	1 (1.0)
All subjects treated with tofersen (n = 166)	Low	1 (0.6)	2 (1.2)	0	0	3 (1.8)	0
	Normal	9 (5.4)	152 (91.6)	0	0	156 (94.0)	5 (0.3)
	High	0	2 (1.2)	0	0	0	2 (1.2)

Number of patients with changes (incidence [%])

a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

Table 58 shows incidences of adverse events related to "Haemorrhage" and "Embolism and thrombosis"[42)] in Studies 101 and 102. In Part C of Study 101, incidences of events related to haemorrhage, and embolism and thrombosis in the tofersen group were similar to those in the placebo group. In the tofersen group in Part C of Study 101 and Study 102, serious adverse events occurred in 7 patients (pulmonary embolism in 6 patients, deep vein thrombosis in 1 patient), but all of them are considered potentially attributable to decreased flexibility of the lower limbs, which is observed in patients with ALS, and a causal relationship to tofersen was ruled out for all of them.

Based on the above, a risk of events related to haemorrhage, and embolism and thrombosis owing to tofersen is not indicated.

42) Events coded to MedDRA SMQs "Haemorrhage terms (excl laboratory terms)," "Haemorrhage laboratory terms (narrow)," "Embolic and thrombotic events, arterial," "Embolic and thrombotic events, venous," "Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous haemorrhage."

Table 58. Incidences of adverse events related to haemorrhage, and embolism and thrombosis in Studies 101 and 102
(pooled safety data from Studies 101 and 102, data cutoff in February 2023)

	Part C of Study 101		Pooled analysis of Studies 101 and 102		
	Tofersen 100 mg	Placebo	Population transferred from Part C of Study 101 to Study 102[a)]	Population treated with tofersen 100 mg in Study 101 or Study 102	Japanese population
No. of patients evaluated	72	36	104	147	7
All adverse events	11 (15.3)	5 (13.9)	37 (35.6)	53 (36.1)	1 (14.3)
Serious adverse events	4 (5.6)	1 (2.8)	7 (6.7)	7 (4.8)	0
Adverse events leading to treatment discontinuation	1 (1.4)	0	1 (1.0)	1 (0.7)	0
Main adverse events (events reported by ≥2 patients in any group or population)					
Contusion	3 (4.2)	1 (2.8)	15 (14.4)	25 (17.0)	1 (14.3)
Post procedural contusion	1 (1.4)	0	5 (4.8)	5 (3.4)	0
Pulmonary embolism	3 (4.2)	1 (2.8)	6 (5.8)	6 (4.1)	0
Blood urine present	0	0	2 (1.9)	5 (3.4)	0
Deep vein thrombosis	1 (1.4)	2 (5.6)	2 (1.9)	2 (1.4)	0
Epistaxis	2 (2.8)	1 (2.8)	2 (1.9)	4 (2.7)	0
Haematuria	0	0	1 (1.0)	4 (2.7)	0
Infusion site bruising	0	0	2 (1.9)	3 (2.0)	0
Activated partial thromboplastin time prolonged	0	0	1 (1.0)	2 (1.4)	0
Injection site bruising	0	0	2 (1.9)	2 (1.4)	0
Vessel puncture site haematoma	0	0	1 (1.0)	2 (1.4)	0

Number of patients with the event (incidence [%])
a) Includes 95 patients transferred from Part C of Study 101 to Study 102 and 9 patients who received tofersen in Part C but did not enter Study 102

PMDA's view:

Although the number of subjects investigated in the clinical studies is limited, incidences of adverse events related to haemorrhage, and embolism and thrombosis did not tend to be definitely higher in the tofersen group than in the placebo group, and no clear changing trend in platelet count was observed in subjects treated with tofersen. In the clinical studies, however, incidences of serious events were higher in the tofersen group than in the placebo group, and in the pooed analysis of Studies 101 and 102, incidences of adverse events related to haemorrhage, and embolism and thrombosis were actually high. Platelet count decreased and coagulation disorder were reported during treatment of the other ASOs. The above findings raise a concern about potential occurrence of coagulation system abnormalities and platelet count decreased owing to tofersen. In addition, since platelet count decreased and coagulation disorder may result in serious outcomes, the package insert of tofersen should include caution about these events as well.

7.R.4 Intended population and indication

The European Academy of Neurology Guideline on the Management of Amyotrophic Lateral Sclerosis recommends tofersen for patients with progressive ALS caused by *SOD1* gene mutation, while for patients with slowly progressing SOD1-ALS, the guideline states that "it is important to discuss the balance of potential benefits and harms" (*Eur J Neurol*. 2024;00:e16264). In view of the above guideline, PMDA asked the applicant to explain the efficacy and safety of tofersen in patients with slowly progressing SOD1-ALS.

The applicant's explanation:

In both mITT population and non-mITT population, which are populations of patients meeting the prognostic enrichment criteria for rapid disease progression and those not meeting the criteria, results on a change in ALSFRS-R total score from baseline to Week 28 in Part C of Study 101 showed that the efficacy tended to be higher in the tofersen group than in the placebo group in comparison of point estimates, and the differences between the groups were similar (Table 29). Changes in ALSFRS-R total score from baseline to multiple timepoints showed that declines in ALSFRS-R total score from baseline were greater in the mITT population than in the non-mITT population, but in both populations and all timepoints, the result was better in the tofersen group than in the placebo/delayed-start tofersen group in comparisons of point estimates, and differences between the groups did not clearly differ between these two analysis populations (Table 39).

Table 59 shows incidences of adverse events in the mITT population and non-mITT population in Part C of Study 101. Incidences of serious adverse events and adverse events leading to treatment discontinuation were lower in the non-mITT population than in the mITT population. The difference in incidence of adverse events is considered to reflect the general condition associated with disease progression, and none of the results suggested that the safety concern of tofersen in patients with slow progression would outweigh that in patients with rapid progression.

In addition to the above, based on pharmacologic effect of tofersen, the efficacy can be expected in patients harboring either rapid or slow progression-type *SOD1* gene mutation. Therefore, tofersen may be used irrespective of disease progression rate of SOD1-ALS.

Table 59. Incidences of adverse events in Part C of Study 101 by analysis population (safety analysis population)

	mITT		Non-mITT	
	Placebo	Tofersen 100 mg	Placebo	Tofersen 100 mg
No. of patients evaluated	21	39	15	33
All adverse events	20 (95.2)	36 (92.3)	14 (93.3)	33 (100.0)
Death	0	1 (2.6)	0	0
Serious adverse events	4 (19.0)	11 (28.2)	1 (6.7)	2 (6.1)
Adverse events leading to treatment discontinuation	0	3 (7.7)	0	1 (3.0)

Number of patients with the event (incidence [%])

PMDA's view:

Results on the efficacy in mITT population and non-mITT population in Part C of Study 101 showed that differences between the tofersen group and placebo group in patients with slowly progressing SOD1-ALS were generally similar to those in patients with rapidly progressing SOD1-ALS, and the efficacy of tofersen can be expected in patients with slowly progressing SOD1-ALS as well. None of the clinical study results suggested that the safety concern of tofersen in patients with slow progression would outweigh that in patients with rapid progression, and currently available therapeutic options for SOD1-ALS are limited. In view of the above, the intended population of tofersen may not have to be narrowed by the disease progression rate. The indication of tofersen should be specified as slowing the progression of functional impairment in patients with SOD1-ALS.

On the other hand, patients with slow progression may receive tofersen for a longer period than those with rapid progression, and use of tofersen may be accompanied by adverse events such as myelitis and intracranial pressure increased, which potentially lead to serious outcome. Patients eligible for tofersen must be selected by physicians with adequate knowledge and experience in ALS treatment including tofersen who have understood clinical study results including characteristics of the patients enrolled in the clinical studies and carefully evaluated the potential benefit and risk in individual patients. The package insert should include caution to ensure that physicians should select patients eligible for tofersen properly after being thoroughly informed of the clinical study results including patient populations in the clinical studies

7.R.5 Clinical positioning

PMDA asked the applicant to explain the intended clinical positioning of tofersen in treatment for SOD1-ALS.

The applicant's explanation:

At present, treatment for SOD1-ALS is performed as done for ALS in Japan. When an application for tofersen was submitted in Japan, riluzole and edaravone were approved for treatment of ALS in Japan. Later, mecobalamin was additionally approved in September 2024. The other drugs used for symptomatic treatment for ALS include opioids for relief from respiratory distress and suffering and antispasmodics for spasm, and these drugs are used according to conditions of each patient (Practical Guideline for Amyotrophic Lateral Sclerosis 2023, Drafting Committee for Practical Guideline for Amyotrophic Lateral Sclerosis ed.).

Results from Part C of Study 101 conducted in patients with SOD1-ALS show that the efficacy of tofersen can be expected [see Section 7.R.2] and the safety is acceptable [see Section 7.R.3]. Tofersen can offer a new therapeutic option for SOD1-ALS.

PMDA's view:

In view of the review in Sections 7.R.1 to 7.R.4 and the treatment algorithm for ALS, tofersen can offer a new therapeutic option for slowing the progression of functional impairment in patients with SOD1-ALS. To use tofersen in patients with SOD1-ALS, physicians must firstly understand clinical study results including characteristics of the patients enrolled in the clinical studies, carefully evaluate the potential benefit and risk in individual patients, consult the updated information such as guidelines for clinical management of ALS in and outside Japan, and then carefully assess their eligibility for tofersen. The position of tofersen in the treatment algorithm for ALS will be discussed at relevant academic societies with new post-marketing information taken into account when such information becomes available.

7.R.6 Dosage and administration

PMDA asked the applicant to explain the rationale for specifying the dosage regimens in Study 101 in view of non-clinical study results and clinical study results available up to conduct of Part C of Study 101.

The applicant's explanation:
For Parts A and B of Study 101, doses lower than 120 mg, a human equivalent dose to the NOAEL in repeated-dose toxicity studies in monkeys (calculated on the assumption that the CSF volume in humans is approximately 10 times that in monkeys), were specified. More specifically, a single dose of tofersen 10 to 60 mg was intrathecally administered in Part A, and multiple doses of tofersen 20 to 100 mg were intrathecally administered in Part B (3 loading doses every 2 weeks and then 2 doses every 4 weeks). Results in Part B suggest that the tofersen concentration in CSF reached the steady state after the end of the loading doses, and tofersen concentrations in CSF during the subsequent 4-week-interval treatment period did not show accumulation or decreases. Among the doses investigated, tofersen 100 mg achieved the maximum tofersen exposure and decrease in total SOD1 protein concentration in CSF, tended to slow the disease progression as shown by results on many efficacy endpoints when compared with the lower doses, and was found to have acceptable safety.

In Part C of Study 101 and Study 102, tofersen 100 mg, the maximum dose in Part B of Study 101, was administered 3 times every 2 weeks as the loading dose and then every 4 weeks. This study demonstrated the efficacy and safety of tofersen [see Sections 7.R.2 and 7.R.3].

Based on the above, according to the dosage regimen investigated in Part C of Study 101, the proposed dosage and administration was specified as follows: The dosage is 100 mg intrathecally administered 3 times every 2 weeks and then every 4 weeks.

In view of the dosage regimen as well as results on the efficacy and safety obtained in confirmatory Part C of Study 101, PMDA concluded that the dosage and administration of tofersen should be specified according to the dosage regimen in the clinical study as follows: The dosage is 100 mg of tofersen intrathecally administered 3 times every 2 weeks and then every 4 weeks.

7.R.7 Post-marketing investigations

The applicant plans a post-marketing surveillance covering all patients treated with tofersen to evaluate the safety of tofersen in clinical practice in Japan, including the long-term safety.

PMDA's view:
The clinical study results available to date indicate that special attention should be paid to onset of adverse events such as myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic. The long-term data were obtained only from the limited number of patients treated with tofersen. Given these points, the applicant is required to gather safety information through a post-marketing surveillance covering all patients treated with tofersen, including myelitis associated with the long-term tofersen treatment in clinical practice in Japan, as explained by the applicant.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tofersen has efficacy in slowing the progression of functional impairment in patients with SOD1-ALS, and that tofersen has acceptable safety in view of its benefits. Tofersen is clinically meaningful because it offers a new treatment option for patients with SOD1-ALS.

PMDA has concluded that tofersen may be approved if tofersen is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 20, 2024

Product Submitted for Approval

Brand Name	Qalsody Intrathecal Injection 100 mg
Non-proprietary Name	Tofersen
Applicant	Biogen Japan Ltd.
Date of Application	May 21, 2024

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the clinical positioning, dosage and administration, and post-marketing investigations presented in the Review Report (1).

1.1 Efficacy

At the Expert Discussion, the expert advisors made the following comments on the efficacy of tofersen and supported PMDA's conclusions presented in Sections "7.R.1 Evaluation strategy for efficacy of tofersen" and "7.R.2 Efficacy of tofersen" in the Review Report (1).

- The results on a change in ALSFRS-R total score at Week 28, the primary endpoint in Part C of Study 101, do not show a remarkable difference between the placebo group and tofersen group. In view of characteristics of SOD1-ALS, which is a very rare serious progressive disease and has the extremely limited therapeutic options available to date, an additional confirmatory study in a similar patient population is highly unlikely to be accepted by healthcare professionals in and outside Japan. PMDA's strategy to evaluate results in Part C of Study 101 and Study 102 comprehensively is acceptable. As a result of the review on the submitted clinical study results, the efficacy of tofersen can be expected, and it is of significance to provide tofersen to the healthcare professionals in Japan based on the submitted clinical study results.
- Although the number of patients of the Japanese subgroup in Part C of Study 101 is limited, the results did not show any trend clearly different from that in the overall population. Given this finding and other data, the efficacy can be expected in Japanese patients as well.

1.2 Intended population and indication

At the Expert Discussion, the expert advisors made the following comments on the intended population and indication and supported PMDA's conclusion presented in Section "7.R.4 Intended population and indication" in the Review Report (1).

- Results on the efficacy and safety did not greatly differ depending on whether the patient meets the prognostic enrichment criteria for rapid disease progression. The intended population of tofersen may not have to be narrowed uniformly based on the disease progression rate. Physicians intending to use tofersen must carefully evaluate the potential benefit and risk in individual patients, understand clinical study results including characteristics of the patients enrolled in the clinical studies, and then decide whether to use tofersen.

PMDA's view:

In view of the review presented in Section "7.R.4 Intended population and indication" and discussion at the Expert Discussion, the indication should be "Slowing the progression of functional impairment in patients with amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene," and the "Precautions Concerning Indications" section should include caution to ensure that patients eligible for tofersen must be selected by physicians who are thoroughly informed of characteristics of the patients enrolled in the clinical studies such as types of *SOD1* gene mutations and disease progression rates and the study results and fully understand the efficacy and safety of tofersen. Furthermore, the applicant must provide information about the study results and definitions of the mITT population and non-mITT population, which included patients meeting the prognostic enrichment criteria and those not meeting the criteria, respectively, in Part C of Study 101, through the package insert and other documents. The above PMDA's conclusion was supported by the expert advisors. PMDA instructed the applicant to take measures on the above points, and the applicant agreed to respond to them appropriately.

1.3 Safety and post-marketing investigation and risk management plan (draft)

At the Expert Discussion, the expert advisors made the following comments on the safety and post-marketing investigations and supported PMDA's conclusions presented in Sections "7.R.3 Safety of tofersen" and "7.R.7 Post-marketing investigations" in the Review Report (1).

- In view of the obtained clinical study results and seriousness of SOD1-ALS, tofersen has acceptable safety in Japanese patients with SOD1-ALS, provided that safety measures are taken, including raising caution about myelitis, radiculitis, optic disc oedema, intracranial pressure increased, and meningitis aseptic; and tofersen is used by physicians who are familiar with diagnosis and treatment for ALS and capable of adequately managing the risk during tofersen treatment.
- In view of the limited number of patients on long-term tofersen treatment investigated, the applicant must gather information about the risk of events such as myelitis in patients on long-term tofersen treatment in clinical practice in Japan. The applicant should conduct a post-marketing surveillance covering all patients treated with tofersen to gather the relevant information and provide feedback to healthcare professionals promptly.

In view of the review in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and discussion at the Expert Discussion, PMDA has concluded as follows: The risk management plan (draft) for tofersen should include the safety specifications presented in Table 60; the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Tables 61 and 62.

Table 60. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelitis, radiculitis • Optic disc oedema, intracranial pressure increased • Meningitis aseptic	• Renal disorder • Blood coagulation disorder	None
Efficacy specification		
Not applicable		

Table 61. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results surveys (all-case surveillance)	• Organize and disseminate information regarding the proper use (through a proper use guide for healthcare professionals) • Disseminate data gathered during early post-marketing phase vigilance

Table 62. Outline of use-results survey (draft)

Objective	Investigation of safety and efficacy in clinical practice
Survey method	All-case surveillance approach
Population	All patients treated with tofersen
Observation period	Up to 5 years
Planned sample size	187 patients
Main survey items	• Patient characteristics (sex, age, height and weight, comorbidity and past history, duration of disease, *SOD1* gene test result, family history, prior treatment for ALS, etc.) • Concomitant drugs and therapies • Status of tofersen treatment (dose, treatment duration, reason for discontinuation, etc.) • Adverse events • Respiratory care status, ALSFRS-R total score, vital capacity, severity

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval conditions. Since the product is a drug with a new active ingredient and an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Slowing the progression of functional impairment in patients with amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene

Dosage and Administration

The usual adult dosage is 100 mg of tofersen administered intrathecally over 1 to 3 minutes. The first 3 doses are administered every 2 weeks, and the subsequent doses are administered every 4 weeks.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients have been gathered.

Appendix

List of Abbreviations

2'-MOE	2'-*O*-(2-methoxyethyl)
ADA	Anti-drug antibody
ADL	Activities of Daily Living
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALS	Amyotrophic Lateral Sclerosis
ALSAQ-5	ALS Assessment Questionnaire
ALSFRS-R	ALS Functional Rating Scale-Revised
ANCOVA	Analysis of Covariance
AQP4	Aquaporin-4
ASO	Antisense Oligonucleotide
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBA	Cell-based Assay
CMAP	Compound muscle action potential
CQA	Critical Quality Attribute
CSF	Cerebrospinal fluid
EC_{50}	Half-maximal effective concentration
ESI TOF-MS	electrospray ionization time-of-flight mass spectrometry
ELISA	Enzyme-linked Immunosorbent Assay
GT	Glutamyl transferase
HHD	Handheld Dynamometry
HPLC-UV	High performance liquid chromatography with ultraviolet detection
HPLC-UV-MS	High performance liquid chromatography with ultraviolet and mass spectrometry detection
IC_{50}	Half maximal inhibitory concentration
mRNA	Messenger ribonucleic acid
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NMOSD	Neuromyelitis Optica Spectrum Disorder
NMR	Nuclear Magnetic Resonance spectroscopy
PBS	Phosphate-buffered saline
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
Qalsody	Qalsody Intrathecal Injection 100 mg
QbD	Quality by Design
RT-PCR	Reverse transcription polymerase chain reaction
SMQ	Standardized MedDRA Query
SNP	Single nucleotide polymorphism
SOC	System Organ Class
SOD1	Super Oxide Dismutase 1
SOD1-ALS	ALS associated with a mutation in the *SOD1* gene
Study 101	Study 233AS101
Study 102	Study 233AS102
SVC	Slow Vital Capacity
Tofersen	Tofersen
UV-VIS	Ultraviolet-visible spectroscopy