swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Qalsody

International non-proprietary name:	tofersen, tofersen sodium
Pharmaceutical form:	Solution for injection
Dosage strength(s):	6,7 mg/ml
Route(s) of administration:	intrathecal administration
Marketing authorisation holder:	Biogen Switzerland AG
Marketing authorisation no.:	68577
Decision and decision date:	temporary authorisation in accordance with Art. 9a TPA approved on 19.12.2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for tofersen, tofersen sodium in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 29 October 2021

Temporary authorisation for human medicinal products
The authorisation was granted as a temporary authorisation in accordance with Article 9*a* TPA by Swissmedic "ex officio".

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dosage is 100 mg/15 mL (6.7 mg/mL) of Qalsody per treatment.
Qalsody treatment should be initiated with three (3) loading doses administered at 14-day intervals.
A maintenance dose should be administered every 28 days thereafter.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	7 March 2024
Formal control completed	18 March 2024
List of Questions (LoQ)	16 July 2024
Response to LoQ	7 November 2024
Preliminary decision 1	4 February 2025

Response to preliminary decision 1	21 May 2025
Preliminary decision 2	13 August 2025
Response to preliminary decision 2	13 October 2025
Final decision	19 December 2025
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

ALS is a rare disease. The global prevalence of ALS is estimated to be approximately 4.42 per 100,000. ALS associated with mutations in the SOD1 gene (SOD1-ALS) represents approximately 2% of the ALS population, resulting in an estimated prevalence of SOD1-ALS of approximately 1,000 cases in EU.

ALS is a progressive, and ultimately fatal, neurodegenerative disease that causes loss of upper and lower motor neurons and their axons within the cortex, brainstem, spinal cord, and peripheral nervous system. The loss of motor neurons leads to progressive loss of muscle mass, strength, and function in bulbar, respiratory, and limb muscles, typically leading to paralysis and ultimately death from respiratory failure within approximately 3 years of symptom onset.

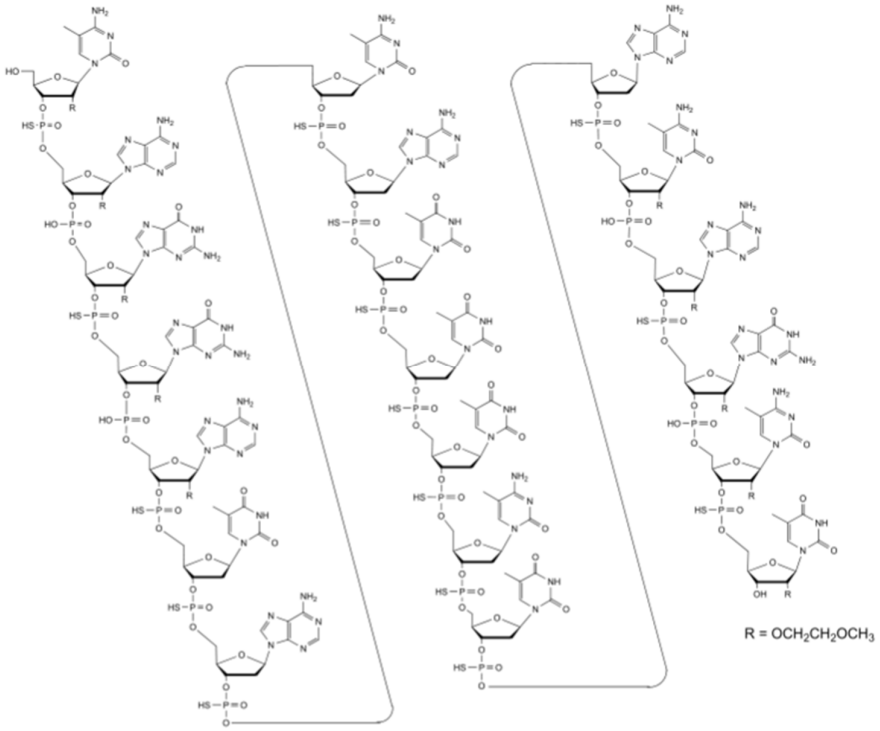
There are limited treatment options for ALS. Functional decline and death are inevitable unless tracheostomy and mechanical ventilation are elected to support life, although these interventions do not stop or slow the decline in physical independence. Symptomatic management includes treatment options for pain, cramps, excess saliva, spasticity, fatigue, pseudobulbar affect, anxiety, and insomnia; therapy (physical, occupational, and speech); and ventilation assistance. Respiratory management encompasses a large part of care for patients.

In Switzerland, riluzole and edaravone are the only pharmacological treatments approved for the treatment of amyotrophic lateral sclerosis (ALS). Nevertheless, these disease-modifying treatments for ALS are unsatisfactory. There is a significant unmet medical need for effective therapies that preserve function and/or prolong life for people living with ALS.

4 Quality aspects

4.1 Drug substance

INN: tofersen
Molecular mass: 7127.86 amu
Tofersen drug substance is a synthetic antisense oligonucleotide (ASO) with 20-base residues (20-mer). The ASO contains 15 phosphorothioate diester and 4 phosphate diester linkages.
Molecular structure:



The chemical structure of tofersen was elucidated by a combination of ion-pair high performance liquid chromatography, 1H-/13C-/31P-NMR, TOF-MS, LC-TOF-MS, MS/MS, Tm ,CD and UV spectroscopy. NMR results were consistent with the expectations for the active substance structure. Also, accurate mass, sequence analysis, and melting temperature indicate the correct primary structure.

Manufacture

The drug substance is manufactured by solid-phase synthesis, using well defined starting materials. Choice of starting materials has been justified; the vendors have been disclosed. The synthesis and purification of the drug substance is described in sufficient detail, including a flow diagram, narrative of each step and appropriate in-process controls.
It has been confirmed that no materials of biological origin are used in the manufacturing process.

Specification and analytical procedures

In order to ensure consistent tofersen quality, the specifications include all relevant test parameters and are based on characterisation studies and compendial requirements. Acceptance criteria are based on the results of development and commercial batches, and on data from release and stability studies. Detailed information on the analytical procedures and method validation reports have been provided. Impurities in the drug substance have been adequately discussed.

Container closure system

The drug substance is stored in an appropriate container closure system.

Stability

Appropriate stability data have been presented. A satisfactory storage condition and retest period was established on the basis of the results.

4.2 Drug product

Description and composition
Qalsody is a sterile, preservative-free, aqueous solution intended for intrathecal administration. The clear, colourless to slightly yellow solution contains 6.7 mg/mL tofersen in phosphate buffer, at pH 7.2. The other ingredients are disodium phosphate, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride, sodium phosphate dihydrate, water for injection.

Manufacture
The drug product manufacturing process consists of drug product compounding, sterile filtration, aseptic filling into vials, and packaging. The manufacturing process is described in sufficient detail, including a flow diagram and narrative for each step, and is considered adequate. The process is sufficiently validated, and appropriate in-process controls are performed.

Specification and analytical procedures
Release specifications have been defined on the basis of the characteristics of the drug substance and the drug product, compendial requirements for the dosage form, and the results of release and stability studies conducted with development and commercial batches in order to ensure a consistent quality.
The analytical methods used have been adequately described and appropriately validated in accordance with current ICH guidelines.

Container closure system
Qalsody final drug product presentation is a ready-to-use aqueous solution for injection in a sterile vial.

Stability
The product is stable for the proposed shelf life of 42 months under the defined storage conditions (2-8°C), including up to 14 days at room temperature, as demonstrated by the stability data provided for several development and commercial-scale batches.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Amyotrophic lateral sclerosis (ALS) is a serious neurodegenerative disease caused by loss of motor neurons. This results in loss of muscle mass and death from respiratory failure within 3 to 5 years after diagnosis. In about 2% of the ALS population, the disease is attributed to mutations of the SOD1 gene. The SOD1 gene encodes a copper/zinc superoxide dismutase, which catalyses the dismutation of superoxide radicals (O2-), yielding hydrogen peroxide. It is believed that pathogenic SOD1 mutations induce a toxic gain of function, but the exact mechanism linking mutations in SOD1 to neurodegeneration remains unclear. It has been speculated that misfolded states of the SOD1 protein induce the ALS pathology.

Tofersen (ISIS 666853, BIIB067) is an intrathecally (IT) administered, 20-base residue antisense oligonucleotide (ASO) developed to target the 3′ untranslated region (3′-UTR) of the human SOD1 mRNA by Watson-Crick base pairing. Ten of the 20 sugar residues are 2-deoxy-D-ribose and the remainder are 2′-O-(2-methoxyethyl)-D-ribose (2′-MOE). Five 2′-MOE nucleosides are located at the 5′ and 3′ ends of the ASO, flanking 10 DNA nucleotides. All the cytosine bases are methylated at the 5′ position. The hybridisation of tofersen to the SOD1 mRNA results in RNase-H-mediated degradation, which reduces the levels of SOD1 mRNA and protein, potentially providing a therapeutic benefit for SOD1-ALS patients.

5.1 Pharmacology

Using an in vitro screen in cells, tofersen was selected out of 2’000 different ASOs targeting SOD1 mRNA. Analyses of databases and sequencing of SOD1 genes in 331 ALS patients confirmed that the tofersen 3′-UTR mRNA target sequence is conserved in the human population. The tofersen sequence contains 1, 4, 6, 7 mismatches as compared to nonhuman primate (NHPs, cynomolgus monkey), rabbit, rat and mouse SOD1 mRNA target sequences, respectively. In vitro potency assays in the human SH-SY5Y neuroblastoma cell line and the epidermal carcinoma-derived A431 cell line identified SOD1 mRNA IC_{50} values of 1.1 µM and 0.65 µM, respectively. In primary cynomolgus monkey hepatocytes, an IC_{50} value of 0,98 µM was determined.

The ability of tofersen to knock down SOD1 mRNA was analysed in vivo in hSOD-1-G93A transgenic mice and rats, which express supraphysiological levels of human SOD1 mRNA and protein, and in wildtype NHP. Single bolus intracerebroventricular (ICV) injection of tofersen in transgenic mice resulted in ED_{50} values of hSOD1 mRNA knockdown of 64 µg (lumbar cord), 44 µg (cervical cord) and 144 µg (cerebral cortex), and EC_{50} values of 0.87 µg/g (lumbar cord) and 7.9 µg/g (cortex). Single IT injection of tofersen in transgenic rats resulted in ED_{50} values of hSOD1 mRNA knockdown of 48 µg (lumbar cord), 93 µg (cervical cord) and 534 µg (caudal cortex), and EC_{50} values of 1.4 µg/g (lumbar cord) and 2.3 µg/g (cervical cord). In transgenic rats, reduced SOD1 mRNA and protein levels were observed in the central nervous system (CNS) and cerebrospinal fluid (CSF) up to 8 weeks after IT tofersen injection. In NHP, tofersen reduced SOD1 mRNA in a dose-dependent manner throughout the CNS, with a determined EC_{50} of 20.7 µg/g.

Proof-of-concept survival studies were performed in transgenic mice with single ICV injections (300 µg tofersen) or two ICV injections (2x 100 µg or 2x 300 µg tofersen) before onset of disease, which was defined as >10% body weight loss. Tofersen treatment delayed disease onset. Median post-treatment survival time was prolonged by up to 34 days (single ICV injection) or 37 days (two ICV injections). Besides the delayed disease onset / prolongation of median survival, the following tofersen-dependent beneficial effects were noted: improved motor performance as assessed by rotarod, improvements in electrophysiological parameters, protection from neuro-muscular junction loss, reduced development of slow muscle fibre clusters (less denervation), less inflammation in the CNS as analysed by GFAP and IBA-1 staining, dose-dependent reductions of native and misfolded SOD1 protein in CNS, and dose-dependent reduction of phosphoneurofilament heavy chain (pNfH) serum levels (a marker of neurodegeneration).

With respect to the secondary pharmacodynamics of tofersen, potential off-targets and the ability to stimulate chemokine production were assessed. Tofersen showed no potential to stimulate the TLR9 receptor and no IL-8 or IP-10 was detectable in supernatants of tofersen-treated hTLR9 expressing 293XL-hTLR9A cells. Computational analyses of the human transcriptome did not identify any off-targets with fewer than 2 mismatches. 27 off-targets were identified with 2 mismatches. These genes were either not expressed in the CNS, were not altered by tofersen treatment, or were only minimally reduced by tofersen treatment compared to on-target SOD1 mRNA inhibition in human cells.

With respect to safety pharmacology, cardiovascular, respiratory, and CNS parameters were assessed in cells in culture (hERG assay), in rats after a single IT tofersen administration, and in NHPs after multiple IT tofersen administrations. In HEK-293 cells that had been stably transfected with the hERG gene, the IC_{50} for the inhibitory effect of BIIB067 on hERG potassium current could not be calculated, but was estimated to be greater than 34 µM, which is > 100x the plasma C_{max} concentration at the clinically relevant therapeutic dose of 100 mg tofersen. In animals, no cardiovascular effects were reported. In rats, 3 mg (1500 mg HED) tofersen resulted in transient tactile hypersensitivity, and decreased arousal, gait, mobility and respiration. In NHPs, 35mg resulted in transient muscle cramping and intermittent tremor and impairment of patellar and foot grip reflexes.

5.2 Pharmacokinetics

A hybridisation-based ELISA used for quantification of tofersen in monkey CSF, plasma, and tissues, and in mouse and rabbit plasma was adequately and successfully validated. Qualified HPLC and liquid LC/MS assays were used to quantify concentrations of tofersen in the mouse and rat tissues. Metabolites and chain-shortened ASOs were identified and quantified using HPLC in the mouse tissues and LC-MS/MS in the monkey tissues.

Absorption

In mice, tofersen was rapidly absorbed into the circulation after SC administration, with a T_{max} of 0.5-1 hour. Systemic exposure increased with dose. Tofersen plasma levels declined within 2 days due to tissue distribution. In pregnant rabbits, SC-administered tofersen was also rapidly absorbed, with a T_{max} of 1-2 hours. In female and male NHPs, IT-administered tofersen resulted in a multiphasic decline in the CSF, with rapid distribution to the CNS and a slow elimination phase with a $T_{1/2}$ of 20-45 days. In plasma, dose-dependent C_{max} was reached 1-4 hours after tofersen administration. Plasma levels also declined in a multiphasic manner, with an initial decline within 2 days, followed by slow elimination with a dose-dependent plasma $T_{1/2}$ of 22-51 days. Plasma exposure increased in a greater than dose-proportional manner. *In vitro* studies showed a high plasma protein binding (>95%).

Distribution

The submitted data on the systemic distribution of tofersen were limited. Based on the class of ASO, systemic tofersen distribution in many organs can be anticipated, with the highest levels in the liver and kidneys. A dose-dependent distribution pattern was seen in all species. In mice, tofersen is rapidly and extensively distributed from plasma to liver and kidneys following SC administration. Tofersen was detected in mouse milk samples from lactating animals following SC tofersen administration. IT administration of tofersen in NHPs resulted in rapid and broad distribution from CSF to CNS, with the highest concentrations close to the injection site. CNS tissue concentrations were at least 90x higher than CSF levels after the initial distribution phase. $T_{1/2}$ for the CNS was 31-40 days. Tofersen increases in NHPs were greater than dose-proportional for the liver and less than dose-proportional for the kidney cortex. The submitted liver and kidney data showed a $T_{1/2}$ in the liver of 15-20 days and a $T_{1/2}$ in the kidney of 18-22 days.

Metabolism

Tofersen metabolism has been evaluated in mice and monkeys. The results are consistent with previous experience with similar classes of ASOs. The identified ASO metabolites in the liver and

kidney are consistent with nuclease-mediated metabolism. A low percentage of liver and kidney chain-shortened oligos (5' and 3') was identified. In mice, intact tofersen was most abundant 12 weeks after dosing, with 81% in the liver and 89% in the kidneys. In NHPs, intact tofersen was the most abundant type of oligonucleotide, accounting for around 92% of the total drug-related peak area in kidney cortex tissue.

Excretion
No specific nonclinical studies were performed to investigate tofersen excretion. Bibliographic data for similar classes of ASOs indicate that tofersen and its metabolites are excreted mostly by the urinary pathway.

Pharmacokinetic drug interactions
In in vitro studies, it was shown that tofersen is not an inhibitor (10 and 100 µM of tofersen) or a substrate (1 and 10 µM of tofersen) when tested in a standard set of transporters. Furthermore, in vitro studies with cryopreserved human primary hepatocytes showed that tofersen is neither an inducer nor an inhibitor of CYP450-mediated oxidative metabolism. Tofersen is therefore unlikely to compete with other drugs for metabolic pathways involving CYP450 enzymes.

5.3 Toxicology

The toxicology assessment included GLP-compliant single-dose and repeated-dose studies in mice, rats and NHPs, in vitro and in vivo genotoxicity studies and reproductive and developmental studies in mice, rats and rabbits. In addition, an impurity qualification study was performed in NHPs.

In a single-dose GLP toxicology study in rats involving IT doses of tofersen of up to 3 mg (1.5 g human equivalent dose, HED), transient acute tactile hypersensitivity was noted 25 minutes after tofersen administration. In addition, decreases in arousal, gait, mobility, respiration, and sensorimotor observations were seen 3 hours post-dose. The NOAEL in this study was defined as 1 mg tofersen.

In mice, two GLP-compliant repeat-dose toxicology studies (12 weeks, 26 weeks) were performed using SC administration of tofersen once every two weeks. In both studies, the NOAEL was defined as 150 mg/kg/dose (the highest administered dose). Major findings included known class-related effects of ASO uptake, such as dose-dependent Kupffer cell vacuolation in the liver, macrophage vacuolation in many tissues, and the presence of basophilic granules in kidney tubular epithelial cells. At the end of the recovery period, macrophage vacuolation was still observed in several tissues, but was not associated with inflammatory, degenerative or necrotic changes. Furthermore, some of the haematological and clinical chemistry changes observed at the highest dose, such as lower mean platelet counts or higher plasma AST levels, were not fully reversed at the end of the recovery period.

In NHPs, two GLP-compliant repeat-dose toxicology studies (13 weeks + 13 weeks recovery, 9 months + 6 months recovery) were performed with IT administration of tofersen (4, 12, and 35 mg, bi-weekly administration for the first month, then monthly administration). The treatment did not result in adverse neurobehavioral findings in the 13-week study. On several occasions, one female monkey in the 35 mg group of the 9-month study developed transient muscle cramping immediately after dosing as well as intermittent tremors. These required diazepam treatment to resolve. Some additional animals in the 35 mg group of the 9-month study showed transient impairments of the patellar and foot grip reflexes. The major microscopic findings were class effects typically observed in the brain, spinal cord and lymph nodes after IT treatment with ASOs as a result of cellular ASO uptake, cellular activation and cytokine production. The findings included macro- and microvesicular vacuolation of neurons, vacuolated macrophages in the brain and lymph nodes, and mononuclear cell infiltrates in the brain and spinal cord. No evidence of reversibility was noted for the microvesicular vacuolation of neurons or the mononuclear cell infiltrates in the brain and spinal cord. Given the lack of any evidence of neuronal or lymphoid cell degeneration and the absence of clinical/neurological abnormalities, none of the tofersen-related microscopic findings were considered adverse, and the NOAEL was 35 mg in

the 13-week toxicology study and 12 mg in the 9-month toxicology study. Based on these data, a safety margin of 1.2x can be calculated for a 100 mg human dose of tofersen. This is acceptable in view of the severity of ALS and the medical need to be filled.

A bacterial reverse mutation assay, an in vitro chromosome aberration assay, and an in vivo erythrocyte micronucleus assay failed to show any genotoxic potential for tofersen. As regards carcinogenicity, no preneoplastic or neoplastic lesions were observed in preclinical toxicology studies. A 2-year carcinogenicity study in mice was ongoing at the time of approval.

Reproductive and developmental toxicity studies were performed in mice and rabbits with repeated SC administration of tofersen at doses of 0, 3, 10, and 30 mg/kg. No adverse effects on male or female fertility and no adverse effects on embryo-foetal development were observed in a combined fertility / embryo-foetal study in mice. Histopathology findings in male mice included vacuolated macrophages in the testes and epididymis (10mg/kg), and apoptosis of epithelial cells (30mg/kg). Minimal to mild seminiferous tubular degeneration, seminiferous tubule dilatation and spermatid retention, and increased prostate weight were also observed for the 30 mg/kg/dose level. The NOAEL was defined as 10mg/kg (males) and 30mg/kg (females). An embryo-foetal study in rabbits did not reveal any adverse effects, and the NOAEL was defined as 30 mg/kg. A peri-/postnatal development study in mice did not identify adverse effects on F0 females and F1 generation. Tofersen was detected in the milk. No tofersen was measurable in the liver or brain of pups. The NOAEL in this study was 30mg/kg (50x human exposure). Since tofersen is notably not active in mice and rabbits, reproductive and developmental toxicity due to SOD1 knockdown could not be evaluated.

An impurity qualification study was performed in NHPs with IT administration of a 10 mg dose of 3 different mixtures of tofersen impurities over 13 weeks (total of 5 doses). The tofersen impurity mixtures were well tolerated and produced no adverse effects. The NOAEL of this study was defined as 10 mg.

5.4 Nonclinical conclusions

Tofersen inhibits human and NHP SOD1 mRNA and protein expression in cells in culture and in animals. In transgenic mice and rats, tofersen treatment delays disease onset and prolongs survival, while inhibiting biomarkers such as CMAP decline and serum pNfH increase. However, tofersen treatment does not rescue hSOD1 transgenic animals.

The pharmacokinetics profile that was established is comparable to other ASOs of similar chemistry.

The safety of tofersen has been assessed in mice, rats, rabbits, and NHPs. Tofersen is not pharmacologically active in mice, rats, and rabbits, which precludes the identification of harmful effects associated with SOD1 knock-down in these species. With one female NHP experiencing transient muscle cramping and tremors at an IT dose of 35 mg and requiring diazepam treatment to control them, the NOAEL in NHPs was 12 mg, yielding a small safety margin of 1.2x as compared to a human dose of 100 mg. Taking into the account the severity of ALS and the lack of treatment options, however, this can be accepted. No critical effects were observed in genotoxicity studies, reproductive and developmental toxicity studies in mice and rabbits, and an impurity qualification in NHPs. Therefore, the nonclinical assessment does not preclude an approval of tofersen for the treatment of SOD1-ALS in humans.

6 Clinical aspects

6.1 Clinical pharmacology

The drug product is an aqueous solution for intrathecal (IT) injection, and the intended dosing regimen is 100 mg of tofersen, administered as 3 loading doses once every 2 weeks followed by a maintenance dose once every 4 weeks.

ADME

Absorption and Distribution

IT injection into the CSF allows tofersen to be administered in close proximity to the site of action within the CNS. The distribution of radioactively labelled tofersen was studied by SPEC/CT imaging in healthy adults using the same administration procedure as in the patient population. Furthermore, CNS tissue samples from patients who died during the course of the OLE study were analysed. Based on the SPECT/CT result, CNS tissue concentration data, and non-clinical in vivo data, tofersen concentration follows a concentration gradient from the injection site towards brain structures. The highest abundance of tofersen is found in the lumbar region of the spinal cord at the site of injection, which is considered the primary target region. A lower local concentration in the brain tissue can be expected. After the loading phase, no further accumulation is observed in the CSF.
Following IT bolus administration, a fast transfer into systemic circulation was observed, with a median time to maximum concentration (T_{max}) of 2 to 6 hours post-dose. High variability in systemic exposure was observed, and C_{max} appears to be dose-dependent. The systemic circulation is a secondary compartment and systemic exposure is therefore not considered to be relevant for the pharmacodynamic activities of tofersen.

Metabolism

Oligonucleotides are known to be primarily metabolised by exo- and endonucleases. Tofersen does not contain a lipophilic moiety for enhanced target organ distribution, therefore no additional metabolic pathway is expected.

Elimination

Due to the limitations of the sparse C_{trough} data for CSF, the PopPK CSF model was described by a one-compartment model with bolus injection and first-order elimination. The observed variability of tofersen was high. The geometric mean of the estimated half-life in CSF based on the PopPK model is approx. 32 days.

Special populations

The effect of renal and hepatic impairment on the PK of tofersen was not investigated, however, no effect on tofersen exposure and exposure-effect relationship is expected based on the route of administration and route of elimination.
Furthermore, no relevant age- or gender-related effect on exposure was observed. The age range investigated was 24 to 76 years.

Immunogenicity

It was found that the presence of antibodies decreased the plasma CL by 42.9%. The occurrence of ADA is not expected to produce notable effects on CSF PK since ADAs have limited penetration through the blood brain barrier into the CSF compartment.

s

The exposure-response relationship of tofersen was investigated on the observed SOD1 protein concentration in CSF and plasma NfL concentration. The observed levels are described in the efficacy section of the SwissPAR.

The effect of tofersen on the CSF SOD1 protein and plasma NfL concentration was described by E_{max} models, assuming a direct effect of tofersen on the synthesis of SOD1 or NfL. The models were able to adequately describe the clinical data, and no covariates were identified. A high inter-patient variability was observed. The mean EC_{50} values were, however, below the observed C_{trough} values.

6.2 Dose finding and dose recommendation

Parts A and B of study 233AS101 were designed to evaluate the safety, tolerability, PK, PD, and exploratory efficacy.

In Part A, participants received a single dose of 10, 20, 40, and 60 mg with 15 weeks of follow-up. In Part B, participants received a multiple ascending dose of 4 dose levels of tofersen (20, 40, 60, and 100 mg) administered for approximately 12 weeks (3 loading doses on days 1, 15, and 29 plus 2 maintenance doses on days 57 and 85).

Single ascending dose (SAD)
No meaningful change in exploratory clinical function assessments (ALSFRS-R scores, SVC, EIM, MUNIX, and HHD) were observed between baseline and day 57 following a single dose of tofersen at any dose level. Additionally, no changes in PD biomarkers were observed after a single dose. Interpretation of data from these clinical endpoints and PD data was limited by the short duration of treatment and small number of participants in each group.

Overall, intrathecal administration of 10, 20, 40, and 60 mg of tofersen was well tolerated. There were no deaths or SAEs during the SAD portion of the study. The incidence of AEs was similar across the different dosing groups and placebo. All reported AEs were mild or moderate in severity. About half of all participants experienced AEs considered by the investigator to be related to the LP procedure, most frequently procedural pain. Other AEs reported were musculoskeletal/connective tissue disorders and nervous system disorders. There were no clinically significant findings for clinical laboratory tests, vital signs, physical/neurological examinations, ECG, or C-SSRS.

Multiple ascending dose (MAD)
Several exploratory clinical function endpoints (i.e., ALSFRS-R, SVC, HHD, ALSAQ-5, FSS, and EQ-5D-3L) and exploratory biomarkers (i.e., CSF and plasma pNfH and NfL) exhibited trends suggesting a slowing of decline and underlying disease activity with BIIB067 100 mg as compared to placebo, but these failed to reach statistical significance. A tendency towards dose-dependent reduction in SOD1 protein in CSF was observed, but the finding is confounded by the elevated baseline SOD1 apparent in higher dose level cohorts.

Other exploratory endpoints (MUNIX, EIM, SF-36, ZBI) were inconclusive at this time. Interpretation of data in the post-treatment follow-up period (after day 85) is limited due to the magnitude of missing data in the placebo group; specifically, ≤ 50% of the 12 placebo participants completed all post-baseline SVC and HHD assessments.

Overall, intrathecal administration of 20, 40, 60, and 100 mg of tofersen was well tolerated. 3 deaths not considered related to the study treatment occurred during the MAD portion of the study (1 each in the placebo, 20 mg, and 60 mg treatment groups).

8 SAEs were reported in 7 participants across all treatment groups. A correlation with the dose could not be established. 2 SAEs (CSF protein increased, CSF white blood cell count increased) were assessed as related to the study treatment. The only SAE to occur in more than 1 participant was respiratory failure. All participants experienced AEs. The most frequently reported were procedural pain, headache, post LP syndrome, and fall. The incidence of AEs was similar across the placebo and tofersen treatment groups. With the exception of the non-treatment-related deaths, no AEs resulted in

withdrawal from the study. The majority of AEs were mild or moderate in severity, rates were similar across the placebo and tofersen treatment groups. About one quarter of reported AEs were considered by the investigator to be related to the study treatment, with slightly more treatment-related AEs occurring in the highest dose groups (60 mg and 100 mg). Increases in CSF protein and CSF WBCs were the most common treatment-related AEs. Additional participants exhibited abnormalities in these CSF parameters that were not reported as AEs. These participants did not have symptoms consistent with meningitis or meningeal inflammation, and none of these abnormalities led to treatment discontinuation. The majority of participants across all groups experienced AEs considered by the investigator to be related to the LP procedure. These were most frequently categorised as procedural pain, post LP syndrome, and headache. Other AEs reported were musculoskeletal/connective tissue disorders and nervous system disorders. There were no clinically significant findings for clinical laboratory tests, vital signs, and physical and neurological examinations. 2 participants, 1 in the placebo group and 1 in the tofersen 20 mg treatment group, displayed adverse ECG abnormalities identified as sinus tachycardia and atrial flutter, respectively. 2 participants, 1 in the placebo group and 1 in the BIIB067 100 mg group, had treatment-emergent suicidal ideation according to C-SSRS; however, neither reported suicidal behaviours. A total of 4 participants in the BIIB067 40 mg group and 6 participants in the BIIB067 100 mg group had treatment-emergent ADAs.
Overall, no meaningful change in clinical function assessments was observed between baseline and day 57 following a single dose of tofersen at any dose level (SAD), but trends were observed suggesting a slowing of decline and underlying disease activity with tofersen 100 mg as compared to placebo. However, these did not reach statistical significance (MAD).

Overall, intrathecal administration of 20, 40, 60, and 100 mg of tofersen was well tolerated. Eight SAEs were reported in 7 participants across all treatment groups (MAD). A correlation with the dose could not be established. The incidence of AEs was similar across the placebo and tofersen treatment groups.

Therefore, neither a minimum effective dose nor a maximum tolerated dose, or any change of efficacy and safety profile across different dose levels, could be determined. It is not possible to conclude an optimal dose for tofersen on the basis of the clinical data from participants in Part A (SAD) and Part B (MAD) of study 233AS101. The 100 mg tofersen dose for Part C was selected on the basis of PK/PD data from participants in Part A (SAD) and Part B (MAD) and translatory considerations. The dose of 100 mg was selected as the highest dose to be tested in humans based on the observed NOAEL of 12 mg in toxicological studies in primates (human equivalent dose: 120 mg based on monkey-to-human CSF volume scaling).

6.3 Efficacy

Pivotal studies
Design
Study 101 Part C was a phase 3, randomised, double-blind, placebo-controlled study designed to assess the efficacy and safety of tofersen 100 mg versus placebo over 6 months. Initially designed to enrol 60 participants and subsequently amended to enrol 99 participants following regulatory feedback, a total of 108 participants with weakness attributable to ALS and a confirmed SOD1 mutation were randomised 2:1 to receive tofersen or placebo for approximately 24 weeks (3 loading doses followed by 5 maintenance doses).

The prespecified primary analysis population, or mITT population, comprised the subset (n = 60) of participants who met the prognostic enrichment criteria for rapid disease progression based on their SOD1 mutation type and pre-randomisation ALSFRS-R slope (also referred to as the enriched or faster progressing/faster progressor subgroup). All other participants (n = 48) were classified as the non-mITT population (also referred to as the other or slower progressing/slower progressor subgroup).

Objectives
The primary endpoint was change in ALSFRS-R total score from baseline to week 28. Secondary endpoints were change in SVC from baseline to week 28 (day 197), changes in HHD megascore to assess muscle strength, as measured by the HHD device, from baseline to week 28 (day 197), time to death or permanent ventilation (≥ 22 hours of invasive or non-invasive mechanical ventilation per day for ≥ 21 consecutive days), and time to death.

With a functional measure (ALS Functional Rating Scale-Revised; ALSFRS-R) as the primary efficacy endpoint, a respiratory function measurement (slow vital capacity; SVC), a muscle strength measure (hand-held dynamometry; HHD), and a survival and time to failure analysis (time to death or permanent ventilation) as the secondary efficacy endpoint, and an electrophysiological assessment (motor unit number index; MUNIX), additional biomarkers, and a QoL measure as exploratory endpoints, the chosen primary and secondary endpoints are in accordance with the applicable EMA and FDA guidelines on the clinical investigation of medicinal products for the treatment of ALS.

The protocol underwent a number of major amendments, the most important being the change of the analyses focusing on the NfL levels and not the pre-randomisation slope. Thus, NfL levels cannot be considered as prespecified, but represent a post-hoc analysis.

Treatment administered
100 mg of tofersen or placebo, administered 8 times (3 loading doses once every 2 weeks and 5 maintenance doses once every 4 weeks) by intrathecal administration. Prior to injection, approximately 10 mL of CSF were collected for analysis. A total volume of 15 mL tofersen or placebo was administered over a 1- to 3-minute bolus injection.

Study population
A total of 108 participants were randomised (tofersen 100 mg, n = 72; placebo = 36), 60 of whom met prognostic enrichment criteria for faster disease progression and were included in the mITT population (tofersen 100 mg = 39; placebo = 21).

Study 101 Part C enrolled adults with weakness attributable to ALS and a confirmed SOD1 mutation. Participants were enrolled at sites across Belgium, Canada, Denmark, France, Germany, Italy, Japan, the UK, and the USA. A total of 42 unique SOD1 mutations were included in the study, the commonest being p.Ile114Thr (N = 20), p.Ala5Val (N = 17), p.Gly94Cys (N = 6), and p.His47Arg (N = 5).

Concomitant riluzole and/or edaravone was permitted for participants who were on a stable dose for at least 30 or 60 days prior to study baseline, respectively. In the overall ITT, approximately 62% of participants were receiving riluzole, and 8% were receiving edaravone at baseline.

Baseline and disease characteristics were balanced across treatment arms for riluzole and/or edaravone use and characteristics reflective of disease stage. However, baseline plasma NfL levels were approximately 15% to 25% higher in the tofersen group compared to the placebo group, suggesting that these participants were progressing more quickly at baseline. Consistently, the rate of decline on ALSFRS-R from screening to day 15 (approximately a 42-day period) was higher in the tofersen group compared to the placebo group.

Primary efficacy endpoint
In the mITT population of pivotal study 101 Part C, a statistically insignificant difference of 1.2 favouring tofersen was observed at the primary efficacy endpoint of ALSFRS-R change from baseline at week 28 (-7.0-point decline in the tofersen group and -8.1-point decline in the placebo group; JRT + MI p = 0.9689). In the course of the disease, at least, the literature describes a clinical relevance with a difference of at least 8 points. The Forest plot results for ALSFRS-R total score change from

baseline versus placebo at week 28 showed consistent trends favouring tofersen across sensitivity, additional, and supplementary analyses. However, all confidence interval whiskers pass through the y-axis of no effect, and the data are statistically insignificant. Hence, sensitivity analyses of the primary outcome consistently failed to show an effect for tofersen in SOD1-ALS patients.

233AS101 Part C: Forest plot of ALSFRS-R total score change from baseline to Day 197 - mITT population
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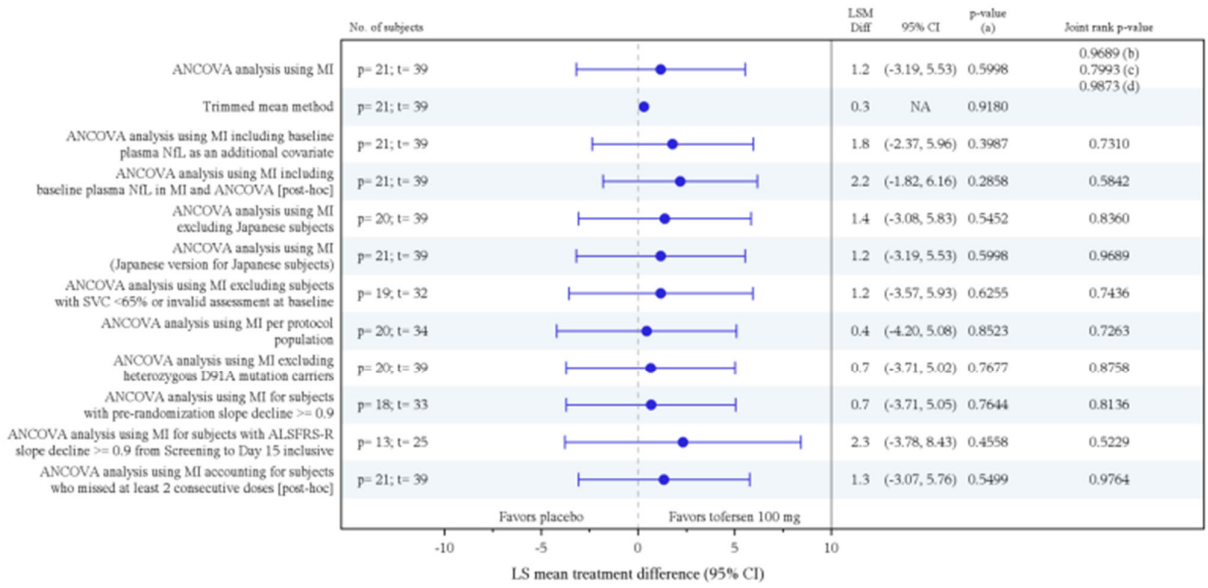


Relevant secondary endpoints

In the mITT population, a reduction in total CSF SOD1 protein was observed at week 28 in the tofersen group compared to the placebo group (38% difference in geometric mean ratios for tofersen to placebo; nominal $p < 0.0001$).

In the mITT population, a reduction in plasma NfL was observed at week 28 in the tofersen group compared to the placebo group (67% difference in geometric mean ratios for tofersen to placebo; nominal $p < 0.0001$).

Although there was a consistent numerical trend in secondary endpoints in tofersen's favour, no efficacy could be demonstrated (either in the per protocol or post-hoc analyses) in any of the clinical secondary endpoints 'SVC', 'HDD' ('Time to Death or Permanent Ventilation' or 'Time to Death' could not be estimated due to the small number of events observed (1 death in the tofersen group)).

Exploratory endpoints

Among the exploratory endpoints, nominally significant reductions were observed for plasma and CSF levels of pNfH and CSF levels of NfL, and in one subscale of quality-of-life variables (EQ-5D-5L utility scale). However, since the focus of the analyses was shifted to the exploratory endpoint of NfL levels as the result an amendment, this cannot be considered as 'prespecified' in terms of the initial protocol. To date, NfL has not been established as a validated surrogate endpoint for predicting clinical efficacy. Furthermore, the results from the VALOR RCT did not provide grounds to conclude that a reduction in plasma NfL can translate into a clinical benefit.

In summary, the pivotal study 101 Part C did not provide confirmatory evidence that tofersen is effective in SOD1-ALS patients.

Participants who completed study 101 had the opportunity to be followed up in study 102. During the transition from pivotal study 101 to open-label, long-term follow-up study 102, selection biases occurred. Since these had an unknown effect on the results, they jeopardised interpretability and generalisability of the results. In summary, both treatment groups deteriorated slightly in the 2nd

interim analyses over 24 weeks in respect of ALSFRS-R and SVC, and remained fairly consistent in respect of the HHD megascore values. Median survival time could not be estimated due to the limited number of events. All these observations were independent of prior treatment group, i.e., 24 weeks of follow-up (2nd interim data) in the open-label extension study 233AS102 did not provide confirmatory evidence that tofersen is effective in SOD1-ALS patients.

In the OLE study, the biomarker data showed higher variability and lower PD response compared to the patients on active drug in study 101 Part C. The observed SOD1 GMR to baseline for SOD1 was higher, at 0.86 (95% CI 0.70 – 1.05) in patients switching from placebo to tofersen compared to 0.71 (95% CI 0.62 – 0.83) and 0.60 (95% CI 0.54 – 0.67) for mITT and non-mITT in study 233AS101 Part C, respectively. A similar observation was made for plasma NfL, where the GMR to baseline was 0.56 (95%CI 0.48 – 0.66) in patients switching from placebo to tofersen compared to 0.40 (95% CI 0.33 – 0.48) and 0.50 (95% CI 0.44 – 0.56) for mITT and non-mITT in study 233AS101 Part C, respectively. SOD1 and NfL levels appeared to remain stable in the patients who remained on 100 mg tofersen.

Additional efficacy data
To permit long-term follow-up of patients, 88% of patients (95/108) (Qalsody 100 mg: n = 63; placebo: n = 32) were enrolled in study 2, an open-label extension study with a blinded dose-escalation phase in patients who had previously participated in study 1 Part C. In study 2, all patients received Qalsody 100 mg. At the start of treatment with Qalsody, the mean SVC value as a percentage of the target value for patients in the placebo/delayed-start group was 68.7 (SD: 25.8; range: 21.6 to 113.7), while total ALSFRS-R score was 30.9 (SD: 9.2; range: 12 to 44).

Median follow-up across the two studies at the time of the interim analysis (data cut-off (16 January 2022) was 1.7 years (range: 0.08 to 2.82 years) in patients who participated in study 1 Part C. At the time of the interim analysis, 62% (67/108) of patients were still participating in study 2.

At the time of the combined interim analysis of study 1 Part C and study 2, 12 (16.7%) patients who had started Qalsody 100 mg in the ITT population in study 1 Part C (early-start [ES] group) and 8 (22.2%) patients who started Qalsody 100 mg in study 2 (placebo/delayed-start [DS] group) had either died or were on permanent ventilation. Earlier initiation of treatment with Qalsody (ES group) was associated with an apparent reduction in the risk of death or permanent ventilation (HR [95% CI]: 0.36 [0.14; 0.94]) and the risk of death (HR [95% CI]: 0.27 [0.08; 0.89]). The median time to event could not be estimated.

Earlier initiation of treatment with Qalsody (early-start group) was associated with a reduction in the decline in ALSFRS-R, SVC value as a percentage of target value, and HHD mega score over 52 weeks from the start of study 1 Part C compared with placebo/later initiation of treatment with Qalsody (DS group).

6.4 Safety

Overall safety database
This section focuses on AEs that emerged during treatment with tofersen in participants with SOD1-ALS including AEs, SAEs, and deaths in participants in study 101 Part C based on the 16 July 2021 data cut and study 102 based on the 15 July 2022 data cut-off date.

The AE profile of tofersen is summarised by integrated safety analysis pools (15 July 2022 data cut) and in the following order.

1) Participants in study 101 Part C who received either tofersen 100 mg or placebo (pool RC with RC1 = tofersen 100 mg and RC2 = placebo)
2) Overall tofersen experience (pool ABCL)

a) All participants who received tofersen 100 mg in either study 101 Part B or C or in study 102 (pool ABCL1)
b) Total tofersen all doses: all participants exposed to tofersen regardless of dose; participants who did not continue into study 102 are included (pool ABCL2)

Adverse events

Overview

Most participants in study 101 and study 102 experienced AEs. Many of the commonly reported AEs in participants treated with tofersen were consistent with events occurring in the natural history of ALS. Most AEs were mild to moderate in severity across both studies. There was an identical incidence of LP-related events in the pivotal study between tofersen 100 mg-treated participants and placebo-treated participants. In the pivotal study, only participants in the tofersen-treated group reported AEs leading to study treatment interruption, study treatment withdrawal, and study withdrawal; there were no such events in the placebo group. Early-start tofersen (CL1) and delayed-start tofersen (CL2) participants had similar rates of AEs. Although early-start tofersen participants (CL1) demonstrated higher rates of SAEs compared to delayed-start tofersen participants (CL2), the early-start group (CL1) demonstrated a lower incidence of AEs leading to study withdrawal and of AEs with fatal outcome.

- In study 101 Part A, the percentage of participants experiencing at least 1 treatment-emergent AE was 93.3% in the overall tofersen-treated groups (versus 40.0%in the placebo group). There were no SAEs, deaths, or AEs that led to discontinuation of study treatment or withdrawal from the study.
- In study 101 Part B, all participants experienced at least 1 AE in both the placebo and the overall tofersen-treated groups. Two participants (5.3%) from the overall tofersen-treated group (1 participant from the 60 mg tofersen-treated group and 1 participant from the 20 mg tofersen-treated group) and 1 participant from the placebo-treated group experienced a fatal AE.
- In study 101 Part C, the percentage of participants experiencing at least 1 AE was similar across groups. SAEs were reported more frequently in the tofersen 100 mg-treated participants than the placebo-treated participants, and 4 of the tofersen 100 mg-treated participants experienced SAEs assessed as treatment related. Three participants from the tofersen 100 mg-treated group, and no participants from the placebo-treated group, experienced AEs that led to study withdrawal. One participant in the tofersen 100 mg-treated group experienced the fatal AE of congestive cardiac failure, but this was assessed as unrelated to tofersen.
- Of the 147 participants in the tofersen 100 mg population (ABCL1 pool) and the 166 participants in the total tofersen population at all doses (ABCL2), nearly all participants experienced AEs, and rates of events were similar between these 2 pools in regard to severity, LP-related events, and events leading to study treatment and study withdrawal. As of the 15 July 2022 data cut-off date, 40.1% of tofersen 100 mg-treated participants across study 101 and 102 (ABCL1) reported at least 1 SAE, and 12.9% of tofersen 100 mg-treated participants (ABCL1) experienced fatal AEs. The majority of tofersen 100 mg-treated participants (ABCL1) had at least 1 AE that was assessed as treatment-related. In the total tofersen group at all doses (ABCL2), 6.6% of participants experienced SAEs assessed as related to tofersen; all such events were consistent with the neuroinflammatory SAEs described in more detail in section 2.2, with the exception of 1 participant with the SAEs of gastritis and pancreatitis and 1 participant with an SAE of back pain.

Common adverse events

Tofersen was generally well tolerated. Most AEs were mild or moderate in severity and did not lead to tofersen discontinuation or dose interruption. The AEs leading to tofersen discontinuation or interruption were often related to the LP procedure or were secondary to ALS, and were not commonly assessed as related to tofersen.

In study 101 Part C, the AEs of pain in extremity, back pain, myalgia, and fatigue more commonly occurred (≥5% difference between groups) within 24 hours in the tofersen 100 mg-treated group (RC1) than in the placebo group (RC2).

As of 15 July 2022, the most common AEs (i.e., reported in >15% of participants) in participants receiving 100 mg of tofersen (ABCL1) were headache, dizziness, procedural pain, post lumbar puncture syndrome, fall, contusion, back pain, pain in extremity, arthralgia, myalgia, muscle spasms, COVID-19, nasopharyngitis, nausea, constipation, fatigue, pyrexia, increased CSF protein, and increased CSF white blood cell count. The frequency of the most common AEs decreased over time with continued exposure, and no new events emerged with longer-term tofersen exposure. AEs of grade 3 severity or higher occurred in 39.5% of participants, where most of these events were SAEs. Finally, when accounting for all participants who received tofersen at any dose across studies 101 and 102 (ABCL2), the rates of pulmonary embolism were equivalent to those in the placebo-controlled period and did not increase over time as participants' exposure to tofersen increased. Pulmonary embolism is a common occurrence in ALS patients and is attributable to the underlying disease. The rates of pulmonary embolism in tofersen-treated participants in studies 101 and 102 were also similar to the rates of pulmonary embolism observed in the overall ALS population.

In study 101 Part C, 38.9% of participants in the tofersen 100 mg group (RC1) had at least 1 AE assessed by the investigator as related to tofersen, compared to 5.6% of participants in the placebo group (RC2). Related AEs with an incidence of ≥5% in tofersen-treated participants were headache, pain in extremity, myalgia, and procedural pain. In the tofersen 100 mg-treated group (ABCL1), 63.9% of participants reported AEs that were considered to be related to tofersen. Related AEs with an incidence of ≥5% were increased CSF protein (20.4%), headache (13.6%), increased CSF white blood cell count (12.2%), pain in extremity (16.3%), pleocytosis (8.2%), paraesthesia (5.4%), myalgia (10.2%), and fatigue (5.4%). Respiratory, thoracic, and mediastinal disorders had the highest incidence of grade ≥ 3 AEs in the ABCL1 group. However, no respiratory events, with the exception of oropharyngeal pain experienced by 1 participant in the ABCL1 group, were considered to be tofersen-related.

In study 101 Part C, 80.6% of participants in the tofersen group (RC1) and the same figure in the placebo group (RC2) reported at least one AE assessed as related to the LP. The most common AEs with an incidence of ≥5% in tofersen-treated participants were procedural pain, post-lumbar puncture syndrome, headache, back pain, pain in extremity, nausea, and increased CSF white blood cell count. In the tofersen 100 mg-treated group (ABCL1), 85.0% of participants reported AEs that were considered by the investigator to be related to the LP. LP-related AEs with an incidence of ≥10% were procedural pain (56.5%), headache (43.5%), post-lumbar puncture syndrome (23.1%), and back pain (29.9%). The SOC of injury, poisoning, and procedural complications had the highest incidence of AEs related to the LP (65.3%).

Other relevant safety aspects

Deaths

As of 15 July 2022, 22 deaths have been reported in tofersen-treated participants in the tofersen CDP, 19 of whom were receiving tofersen 100 mg. In addition, 1 death due to respiratory failure secondary to ALS was reported in the placebo-treated group of study 101 Part B. None of the deaths have been assessed as treatment-related.

There were no deaths in study 101 Part A. In study 101 Part B, 1 participant in the tofersen 20 mg group with a history of obesity and sleep apnoea died due to an event of cardiovascular disorder, and 1 participant in the tofersen 60 mg group died due to respiratory failure secondary to ALS. No deaths were assessed by the investigator as related to the study treatment.

In study 101 Part C, 1 participant whose medical history included longstanding coronary artery disease and other comorbidities died due to congestive cardiac failure (day 114). This death was assessed by the investigator as unrelated to the study treatment.

In study 102, 12 participants died due to respiratory failure and 2 died of respiratory arrest; these were assessed as associated with ALS disease progression. Some of these events were associated with either the voluntary withdrawal of non-invasive ventilation or the participant declining to initiate non-invasive ventilation. Other deaths occurred in participants who had been dependent on non-invasive ventilation for several months and/or were receiving hospice or palliative care due to advanced ALS disease. One participant died from fatal events of ALS and one from euthanasia. Finally, 1 participant died due to a fatal event of septic shock.

Adverse events that led to discontinuation of study treatment or withdrawal from study
In the total tofersen experience at all doses (ABCL2), 27 of 166 participants (16.3%) reported AEs that led to discontinuation of study treatment, and 28 of 166 participants (16.9%) reported AEs that led to withdrawal from the study. Most AEs that led to study treatment discontinuation and study withdrawal were associated with the underlying ALS disease. Many of the AEs leading to discontinuation of study treatment and/or withdrawal from the study resulted in death.
SAEs of gastritis, pancreatitis, vocal cord paralysis, and pneumonitis aspiration all occurred in 1 participant and led to discontinuation of study treatment; however, the participant remained in the study. One participant reported an SAE of pulmonary embolism in study 101 Part C that led to study treatment discontinuation; however, the participant continued in the study and ultimately resumed treatment with tofersen in study 102. One participant reported a non-serious AE of dyspnoea that led to discontinuation of study treatment and subsequent withdrawal from the study. One participant reported non-serious AEs of salivary hypersecretion and muscular weakness that led to discontinuation of study treatment; the AE of muscular weakness led to the participant's subsequent withdrawal from the study. One participant reported an SAE of pneumonia that did not lead to study treatment discontinuation, but led to study withdrawal. None of these events were assessed as treatment-related.

AEs leading to study treatment interruption occurred in 15.0% of tofersen 100 mg-treated participants (ABCL1). Each AE (PT) that led to study treatment interruption occurred in only 1 participant apart from the AEs of COVID-19 and deep vein thrombosis, which occurred in 5 and 2 participants, respectively.

Non-serious adverse drug reactions
In study 101 Part C, 12 participants (16.7%) in the tofersen 100 mg-treated group (RC1) had CSF laboratory abnormalities compared to 1 participant (2.8%) in the placebo-treated group (RC2).

34.0% of the integrated dataset of tofersen 100 mg-treated participants (ABCL1) had AEs related to CSF laboratory abnormalities, including 24.5% with increased CSF protein, 16.3% with increased CSF white blood cell count, and 8.8% with pleocytosis. Many of the events of increased CSF white blood cell count and increased CSF protein in the tofersen 100 mg-treated participants (ABCL1) were assessed by the investigator as treatment-related.

While the PTs of increased CSF white blood cell and pleocytosis occur in different SOCs (Investigations and Nervous system disorders, respectively), they represent the same phenomenon and were therefore combined into the ADR of increased CSF white blood cell. In the non-clinical non-human primate GLP toxicology studies, increases in CSF white blood cells, red blood cells, microalbumin, and total protein concentrations were seen, as were mononuclear cell infiltrates in the meninges. In light of the non-clinical and clinical findings, the increased rate of AEs in the tofersen 100 mg-treated participants compared to the placebo participants in study 101 Part C, and the proinflammatory nature of ASOs, increased CSF white blood cell and increased CSF protein are events with a likely causal relationship to tofersen and are therefore listed as non-serious ADRs.

Pain and other non-serious adverse drug reactions
AEs of pain in extremity, back pain, fatigue, arthralgia, myalgia, pain, musculoskeletal stiffness, and neuralgia all occurred more frequently in the tofersen 100 mg-treated participants (RC1) than in placebo-treated participants (RC2) in study 101 Part C, indicating a likely causal relationship to tofersen treatment rather than the LP procedure.

Pyrexia was identified as a non-serious ADR after multiple participants had positive rechallenge experiences after receiving tofersen, with no confounders identified, and had events of pyrexia in close proximity to the timing of drug exposure.

There was no significant rate of study treatment interruption, study treatment withdrawal, or study withdrawal secondary to these non-serious ADRs. Most of these non-serious ADRs were reported as mild to moderate in severity, and none were reported as life-threatening or resulting in a fatal outcome.

Serious adverse drug reactions
Serious ADRs from the clinical trials of tofersen are myelitis, radiculitis, aseptic meningitis, and papilloedema.

In the overall tofersen 100 mg experience (ABCL1 pool), 6 participants experienced SAEs of myelitis or radiculitis. 4 out of 147 participants (2.8%) who received 100 mg tofersen in study 101 Part C or study 102 (ABCL1) reported events of myelitis and 2 out of 147 participants (1.4%) reported SAEs of radiculitis. In the tofersen clinical programme, 4 relevant SAEs of papilloedema with increased intracranial pressure have been reported. A review of the clinical trial data as of 15 July 2022 identified 3 participants who reported non-serious events of increased intracranial pressure, 3 participants who reported non-serious events of papilloedema, and 1 participant who reported a non-serious event of increased CSF pressure. All AEs and SAEs related to papilloedema/ increased intracranial pressure were reported in participants who received tofersen 100 mg; no such events were reported in the placebo group. In study 101 and 102, there was 1 SAE of chemical meningitis and 1 SAE with PT of aseptic meningitis. 3 participants reported non-serious AEs of aseptic meningitis with PTs of chemical meningitis (2) and aseptic meningitis (1). Two of the non-serious events of meningitis (1 event of chemical meningitis and 1 event of aseptic meningitis) occurred in participants with AEs/SAEs of increased intracranial pressure /papilloedema.

These events are consistent with CNS inflammation and may be secondary to the proinflammatory effects of ASOs; however, the mechanism of these inflammatory events is not yet well understood.

Laboratory findings
No significant trends in haematology values, including haemoglobin, haematocrit, white blood cells, neutrophils, and lymphocytes, were detected in the integrated safety data set. In the ABCL1 pool, AEs reported as "Investigations" or "Blood and lymphatic system disorders" related to haematological results were rare, with rates of ≤3%. None of these AEs were assessed by the investigator as related to tofersen.

No patterns or trends were observed in abnormalities in blood chemistry.

In study 101 Part C, CSF leukocytes shifted to high in 78.3% of participants receiving tofersen 100 mg versus 25.0% of participants who received placebo, and CSF protein shifted to high in 67.4% of participants who received tofersen 100 mg versus 30.0% of participants who received placebo. CSF leukocytes and CSF protein shifted to high in over 85% of the participants who received tofersen 100 mg in the CDP (ABCL1) , with nearly all participants (91.2%) having at least 1 CSF leukocyte value >5 × 10^6 /L and 79.6% of participants having at least 1 value >10 × 10^6 /L. CSF protein levels were found to be elevated at baseline in some participants. There was a gradual rise in CSF protein levels

initially in participants who received tofersen; this stabilised over time with continued tofersen exposure. CSF glucose shifts to low were more common in the placebo-treated participants in study 101 Part C than the tofersen 100 mg-treated participants. CSF glucose shifts to high occurred at similar rates in the placebo-treated and tofersen 100 mg-treated participants in study 101 Part C and to larger magnitudes in the tofersen-treated participants. CSF erythrocyte shifts to high occurred in the majority of all participants across the tofersen CDP and at similar rates in the tofersen 100 mg-treated participants and placebo-treated participants in study 101 Part C. Infrequent AEs with PTs of abnormal CSF cell count and increased CSF cell count were not specific for whether these were related to CSF RBC, CSF WBC, or both. There were otherwise no specific AEs in the Investigations SOC related to CSF erythrocytes, and there was 1 participant in the overall tofersen 100 mg-treated group with an AE of cerebral haemorrhage.

In study 101 Part C, 2 (2.8%) participants who received tofersen 100 mg (RC1) were ADA-positive prior to their first dose. Of those 2 participants, 1 participant was ADA-positive after receiving tofersen 100 mg and 1 was negative. A total of 21 (29.2%) participants who received tofersen 100 mg had treatment-emergent ADAs. Of the 22 participants with a positive ADA after a dose of tofersen 100 mg, 19 (26.4%) had a persistent ADA response and 3 (4.2%) had a transient ADA response.
Of the participants who received tofersen 100 mg across studies 101 and 102 (N=147; ABCL1), 9 (6.1%) participants were ADA-positive prior to their first dose of 100 mg (participants may have had a lower dose of tofersen previously). Of the 9 subjects with a positive baseline, 8 (5.4%) were positive after receiving tofersen 100 mg. A total of 85 (57.8%) participants had treatment-emergent ADAs. Of the 93 participants with a positive ADA after a dose of tofersen 100 mg, 76 (51.7%) had a persistent ADA response and 17 (11.6%) had a transient ADA response. However, no impact of tofersen ADA was observed on the incidence of serious neurological ADRs (myelitis, radiculitis, papilloedema, aseptic meningitis). In the overall tofersen 100 mg-treated group (ABCL1), 4 participants (2.7%) with serious neurologic ADRs had positive ADA status, while 6 (4.1%) had negative ADA status.

6.5 Final clinical benefit risk assessment

Beneficial effects and respective uncertainties
The pharmacokinetic parameters of tofersen have been sufficiently described in plasma and CSF. Based on the SPECT/CT result, the CNS tissue concentration data and non-clinical in vivo data, tofersen appears to have a strong concentration gradient from the injection site towards brain structures. Furthermore, there is an apparent concentration gradient from tissue in close proximity to the surface towards deeper brain tissues. The impact of this gradient on the pharmacodynamic response remains unclear. In addition, the provided biomarker analysis of NfL primarily reflects motor neuron death. However, potential mode of action-related negative effects caused by the induction of motor neuron dysfunction due to diminished SOD1 levels cannot be assessed with the provided biomarker data.

There is a mechanistic basis for the potential treatment effect of tofersen. It is biologically plausible that by reducing SOD1, tofersen has disease-modifying effects, which can be measured by an appropriate neurodegeneration biomarker, i.e., NfL.

In pivotal study 101 Part C however, no statistically significant difference in the primary efficacy endpoint ALSFRS-R change from baseline to week 28 was observed. Nor was efficacy demonstrated (either in the per protocol or post-hoc analyses) in any of the key secondary endpoints “SVC”, “HDD”, “Time to death or permanent ventilation” or “Time to death”. There was, however, a consistent numerical trend in secondary endpoints favouring tofersen.

Among the exploratory endpoints, significant reductions were observed for plasma and CSF levels of pNfH and CSF levels of NfL, and in one subscale of quality-of-life variables (EQ-5D-5L utility scale). However, since an amendment in February 2022 focused the analyses on the NfL levels rather than the pre-randomisation slope, this cannot be considered to be “prespecified” in terms of the initial

protocol and prior to the final database lock and unblinding. To date, NfL has not been established as a validated surrogate endpoint for predicting clinical efficacy. Whether a reduction in NfL in tofersen-treated patients with SOD1-ALS is reasonably likely to result in a clinical benefit for these patients will be evaluated in an ongoing study phase 3 randomised, double-blind, placebo-controlled trial in individuals who are carriers of the SOD1 genetic mutation who do not yet have symptoms (study 233AS303). Efficacy data from study 233AS303 have not been included in this submission. Data are not expected before 2028.

In summary, pivotal study 101 Part C did not provide confirmatory evidence that tofersen is effective in SOD1-ALS patients.

Participants who completed study 101 had the opportunity to be followed up in study 102. During the transition from pivotal study 101 to open-label, long-term follow-up study 102, selection biases occurred. These had an unknown effect on the results and jeopardised interpretability and generalisability. In summary, both treatment groups deteriorated slightly in the 2nd interim analyses over 24 weeks in respect to ALSFRS-R and SVC, and remained fairly consistent in respect to the HHD megascore values. Median survival time could not be estimated due to the limited number of events. All these observations were independent of prior treatment group, i.e., 24 weeks of follow-up (2nd interim data) in the open-label extension study 233AS102 did not provide confirmatory evidence that tofersen is effective in SOD1-ALS patients.

However, at week 52 of the open-label extension study, clinical outcome measures of strength, clinical function, quality of life (QoL), and survival consistently favoured early-start tofersen (i.e., participants who started tofersen 6 months prior to the placebo/delayed-start group) with nominally statistically significance. Additionally, data from real-world studies suggest that tofersen has a positive effect on SOD1 ALS, at least in a subgroup of patients. The results of the open-label extension study are difficult to interpret due to unknown patient flows and dropouts of patients included in study 102, resulting in unpredictable biases.

Additionally, real-world studies addressing the clinical benefits of tofersen in ALS were performed. These studies showed relative stabilisation, with some evidence of improvement in measures of clinical and motor function and/or patient-reported quality of life.

Unfavourable effects and respective uncertainties

Overall, the safety profile of tofersen is considered acceptable. Serious ADRs of myelitis/radiculitis, papilloedema and aseptic meningitis have been observed in patients who received 100 mg tofersen IT monthly. CSF laboratory abnormalities, including pleocytosis and elevated protein, were commonly observed with tofersen. In most cases, these were asymptomatic and not treatment-limiting. The relationship of these laboratory findings to serious neurological events is not well understood. Non-serious ADRs of pain, fatigue, arthralgia, myalgia, increased CSF WBC, increased CSF protein, musculoskeletal stiffness, and neuralgia were identified. These were generally mild to moderate in severity and not treatment-limiting. Although lumbar-puncture-related events were common in both placebo and tofersen-treated participants, they were generally mild to moderate in severity, managed through standard of care, and not treatment-limiting.

Benefit-risk balance

Tofersen administration did not result in a statistically significant difference from placebo on the primary efficacy endpoint, the change from baseline to week 28 in “ALSFRS-R total score”. Nor was efficacy demonstrated in any of the key secondary endpoints “SVC”, “HDD”, “Time to death or permanent ventilation” or “Time to death”. Among exploratory endpoints, nominally significant reductions were observed for plasma and CSF levels of pNfH and CSF levels of NfL. However, since an amendment focused the analyses on the exploratory endpoint of NfL levels, this cannot be considered to be “prespecified” in terms of the initial protocol. To date, it has not been shown that a reduction in neurofilaments predicts an improvement in clinical endpoints. In conclusion, although

there was a trend in favour of tofersen treatment, pivotal phase 3 study 101 Part C did not provide confirmatory evidence at week 28 that tofersen is effective in SOD1-ALS patients.

In the 2nd interim analyses over 24 weeks of the open-label extension study 233AS102, results for ALSFRS-R, SVC, HHD megascore and time to death were independent of the prior treatment group, i.e., the open-label extension study 233AS102 did not provide evidence at week 24 of follow-up, that tofersen is effective in SOD1-ALS patients.

At week 52 of the open-label extension study, clinical outcome measures of strength, clinical function, quality of life (QoL), and survival consistently favoured early-start tofersen with nominally statistically significance. Additionally, data from real-world studies suggest that tofersen has a positive effect on SOD1 ALS.

Serious AEs of myelitis/radiculitis, papilloedema, and aseptic meningitis have been observed with tofersen administration. CSF laboratory abnormalities were commonly observed, but were asymptomatic and not treatment-limiting in most cases. Non-serious ADRs of pain, fatigue, arthralgia, myalgia, increased CSF WBC, increased CSF protein, musculoskeletal stiffness, and neuralgia were identified, but were generally mild to moderate and not treatment-limiting.

In summary, the clinical programme with tofersen 100 mg IT monthly did not provide confirmatory evidence that tofersen is effective in patients with SOD1 ALS. However, additional data from the open-label extension (OLE) study and real-world data suggest a significant therapeutic benefit as required for a temporary authorisation under Article 18 TPLO, criterion c. Criterion d requires that the applicant is able to submit the necessary data before the expiry of the temporary authorisation, which leads to corresponding conditions. It is undisputed that SOD1 ALS leads to serious invalidity and severe suffering resulting in death, and that no alternative and equivalent medicinal product is authorised or available in Switzerland (criteria a and b of Article 18 TPLO)). Methodological uncertainties related to the interpretation of these results, based on pooled post hoc analyses, remain.

Treatment with tofersen is burdensome for patients due to the repeated lumbar punctures required. tofersen can also cause serious neuroinflammatory reactions. Based on clinical data available to date, these reactions appear to be manageable. However, there are too few cases to date to make definitive conclusions about the safety profile of tofersen.

Based on the overall available evidence, the benefit-risk ratio of tofersen for the treatment of adult patients with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1), is considered probably favourable. However, the available data are not considered to be sufficient for a marketing authorisation, as originally requested by the applicant. Confirmatory evidence of the efficacy of tofersen and robust statements on its safety profile are still to be provided. Therefore, temporary authorisation is granted ex officio.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Qalsody was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected new or serious adverse reactions. See «Undesirable effects» section for advice on the reporting of adverse reactions.

QALSODY™

Composition

Active substances

Tofersen.
Tofersen is a chimeric MOE gapmer mixed backbone antisense oligonucleotide (ASO) inhibitor of human SOD1 messenger ribonucleic acid (mRNA). Tofersen is a 20-base residue (20-mer) oligonucleotide that contains 15 phosphorothioate diester and 4 phosphate diester linkages.

Excipients

Disodium phosphate, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection.
Qalsody contains 52.35 mg sodium and 1.76 mg potassium per vial (15 ml).

Pharmaceutical form and active substance quantity per unit

Solution for injection for intrathecal administration.
One vial (15 ml) contains 100 mg of tofersen (6,7 mg/ml).
The solution is clear and colorless to slightly yellow with a pH of approximately 7.2 (range: 6.7-7.7).

Indications/Uses

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

Dosage/Administration

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

Recommended dosage

The recommended dosage is 100 mg/15 mL (6.7 mg/mL) of Qalsody per treatment.
Qalsody treatment should be initiated with three (3) loading doses administered at 14-day intervals.
A maintenance dose should be administered every 28 days thereafter.

Special dosage instructions

Patients with hepatic disorders

Qalsody has not been studied in patients with hepatic impairment.

Patients with renal disorders

Qalsody has not been studied in patients with renal impairment.

Elderly patients

A total of 13,3 % (22/166) ALS patients were 65 years of age and older and 1,2 % (2/166) subjects were 75 years of age and older at initiation of treatment in clinical trials. There is no evidence for special dosage considerations based on age when Qalsody is administered.

Children and adolescents

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

Missed or delayed doses

If the second loading dose is delayed or missed, Qalsody should be administered as soon as possible, and the third loading dose should be administered 14 days later.
If the third loading dose is delayed or missed, Qalsody should be administered as soon as possible, and the first maintenance dose should be administered 28 days later.
If a maintenance dose is delayed or missed, Qalsody should be administered as soon as possible. Subsequent maintenance doses should be administered every 28 days from the last dose.

Mode of administration

Aseptic technique must be used when preparing and administering Qalsody intrathecally.
For information about the preparation and administration of Qalsody, refer to section «Other information, *Instructions for handling».*

Contraindications

None.

Warnings and precautions

Lumbar puncture procedure

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

Myelitis and or radiculitis

Serious events of myelitis and radiculitis have been reported in patients treated with Qalsody. If symptoms consistent with these adverse events develop, diagnostic workup and treatment should be initiated according to the standard of care.

Increased intracranial pressure and/or Papilledema

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

Thrombocytopenia and coagulation abnormalities

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

Renal toxicity

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

Natrium

This medicinal product contains 52 mg sodium per 15 ml solution for injection, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Kalium

This medicinal product contains potassium, but less than 1 mmol (39 mg) per 15 ml solution for injection, i.e. it is essentially ‘potassium-free’.

Interactions

In vitro studies indicated that Qalsody was not an inducer or inhibitor of CYP450-mediated oxidative metabolism; therefore, it should not interfere with other medicinal products that interact with these metabolic pathways.
In vitro studies indicated that the likelihood for interactions with tofersen due to competition with or inhibition of transporters is low. *In vitro* studies also indicated that Tofersen was not a substrate of BCRP and MDR1 efflux or MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters, nor is it an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC, BCRP, BSEP, and MDR1 transporters.
The co-administration of other intrathecal medicinal products with Qalsody has not been evaluated and the safety of these combinations is not known.

Pregnancy, lactation

Pregnancy

There are no data from clinical trials on the use of Qalsody during pregnancy. The benefit of treatment with Qalsody versus potential risk should be discussed with women of childbearing age or women who become pregnant during therapy.
Microscopic evaluation of reproductive tissues from both male and female animals in the 13-week and 39-week NHP toxicology studies revealed no effects on the reproductive tissues. There were no effects on embryo-fetal development. Female general toxicity and reproductive/developmental NOAEL for tofersen was 30 mg/kg/dose, the highest dose tested (see «Preclinical data»).

Lactation

There are no data on the use of Qalsody during lactation in humans. It is unknown whether tofersen or its metabolites are excreted in human milk. A risk to the newborn or infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Qalsody therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Tofersen was detected in mouse milk samples from all tofersen-dosed animals. There were no tofersen-related effects on either the maternal dams or offspring.

Fertility

There are no data available on the potential effects on fertility in humans. In toxicity studies in animals, no effects on male or female fertility were observed (see «Preclinical data»).

Effects on ability to drive and use machines

Studies on the effects on the ability to drive or use machines during treatment with Qalsody have not been performed.

Undesirable effects

The safety of Qalsody 100 mg was evaluated in 147 SOD1-ALS subjects. The median patient exposure was 148.4 weeks (range 4 to 245 weeks). Qalsody was evaluated in the placebo-controlled trial 1 and in the open label extension trial 2. Of these patients, approximately 44,2 % were female; 55,8 % were male; 59,9 % were White; 6,8 % were Asian. The mean age at trial entry was 49,8 years (range 23 to 78 years).
Very common adverse reactions (≥ 10 %) by preferred term reported in Qalsody-treated subjects were pain, myalgia, arthralgia, fatigue, CSF white blood cell increased, CSF protein increased, and pyrexia.
The corresponding frequency category for each adverse drug reaction is based on the following convention: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare

(≥ 1/10’000, < 1/1000); Very rare (< 1/10’000); not known (cannot be estimated from available data).

ADRs are presented by MedDRA system organ class (SOC), frequency, and ADR.

Table 1: Adverse Drug Reactions (ADRs) with Qalsody *Treated Patients in Trial 1 and Trial 2*

System Organ Class (SOC)	Preferred term	Trial 1 Part C		Trial 1 and Trial 2	
		Placebo (n = 36) n/N (%)	Qalsody 100 mg (n = 72) n/N (%)	Qalsody 100 mg (n = 147) n/N (%)	Frequency
Nervous system disorders	CSF white blood cell increased*	0/36 (0)	10/72 (13,9)	39/147 (26,5)	Very common
	CSF protein increased	1/36 (2,8)	6/72 (8,3)	39/147 (26,5)	Very common
	Papilledema‡	0	0	7/147 (4,8)	Common
	Neuralgia	0/36 (0)	4/72 (5,6)	7/147 (4,8)	Common
	Aseptic Meningitis††	0/36 (0)	1/72 (1,4)	6/147 (4,1)	Common
	Radiculitis†	0/36 (0)	1/72 (1,4)	4/147 (2,7)	Common
	Myelitis§	0/36 (0)	2/72 (2,8)	4/147 (2,7)	Common
Musculoskeletal and connective tissue disorders	Arthralgia	2/36 (5,6)	10/72 (13,9)	50/147 (34,0)	Very common
	Myalgia	2/36 (5,6)	10/72 (13,9)	28/147 (19,0)	Very common
	Musculoskeletal stiffness	0/36 (0)	4/72 (5,6)	10/147 (6,8)	Common
General disorders and administration site conditions	Pain‡‡	8/36 (22,2)	30/72 (41,7)	97/147 (66,0)	Very common
	Fatigue	2/36 (5,6)	12/72 (16,7)	42/147 (28,6)	Very common
	Pyrexia	1/36 (2,8)	3/72 (4,2)	27/147 (18,4)	Very common

* CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis.

† Radiculitis includes preferred terms of radiculopathy and lumbar radiculopathy.

‡ Papilledema includes preferred terms of papilledema and intracranial pressure increased. See discussion in Description of selected adverse events (AEs).

§ Myelitis includes preferred terms of myelitis, myelitis transverse, and neurosarcoidosis. See discussion in Description of selected adverse events.

†† Aseptic meningitis includes preferred terms of meningitis chemical and meningitis aseptic. See discussion in Description of selected adverse events.

‡‡ Pain includes preferred terms of pain, back pain, and pain in extremity.

Note: Table 1 represents cases of serious and non-serious ADRs.

Description of specific adverse reactions and additional information

Myelitis and/or radiculitis

Six Qalsody-treated subjects experienced serious events of myelitis or radiculitis while receiving Qalsody 100 mg treatment in the clinical trials. Two subjects discontinued treatment, and both events resolved. In the remaining 4 subjects, the events did not lead to discontinuation of treatment (see «Warnings and precautions»).

Increased intracranial pressure and/or Papilledema

A total of 4 serious events in Qalsody-treated subjects involving elevated intracranial pressure and/or papilledema were reported in trial 2. No events led to discontinuation of Qalsody, and all were manageable with standard of care (see «Warnings and precautions »).

Aseptic or chemical meningitis

One subject experienced a serious event of chemical meningitis which led to discontinuation of Qalsody. One additional serious event of aseptic meningitis occurred in trial 2 and did not lead to discontinuation of Qalsody. Nonserious ADRs of CSF white blood cell increased and CSF protein increased have also been reported with Qalsody.

Immunogenicity

As with all antisense oligonucleotides, there is a potential for immunogenicity. The detection of antibody formation strongly depends on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity (including neutralizing antibodies) in an assay can be influenced by various factors. These include test methodology, sample handling, timing of sample collection, concomitant medication, and underlying diseases.
The immunogenic response to Qalsody was evaluated in 166 patients with post-baseline plasma samples for anti-drug antibodies (ADAs). Overall, 97 Qalsody-treated patients (58,4 %) developed treatment-emergent ADAs (of which 14 were transient and 83 were persistent). Given the relatively small number of participants in each group and individual disease heterogeneity, it is difficult to draw conclusions regarding the effects of ADAs on efficacy. No discernible effects of ADAs on safety (incidence of AEs including hypersensitivity, anaphylactic reaction, and angioedema) have been observed. Medical review of individual cases of serious neurological events also showed no association with ADA status (see «Pharmacokinetics»).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose associated with Qalsody were reported in clinical trials.
In the event of overdose, medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

Properties/Effects

ATC code

N07XX22

SOD1 ALS

SOD1-ALS is a primarily autosomal-dominant disorder representing approximately 2% of the ALS population. In these patients, mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein. Over 200 unique SOD1 mutations associated with ALS have been identified. The natural history of SOD1-ALS is therefore highly variable.

Mechanism of action

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

Pharmacodynamics

CSF SOD1 protein

Total CSF SOD1, an indirect measure of target engagement, was formally tested in trial 1 part C After 28 weeks, a reduction in total CSF SOD1 protein of 35 % (geometric mean ratio to baseline) in the Qalsody-treated group versus a 2 % decrease from baseline in the corresponding placebo subjects in the ITT population was observed (difference in geometric mean ratios for Qalsody to placebo: 34 %; 95% CI: 23%, 43%). Total CSF SOD1 declined until approximately week 8, after which the reductions were sustained.

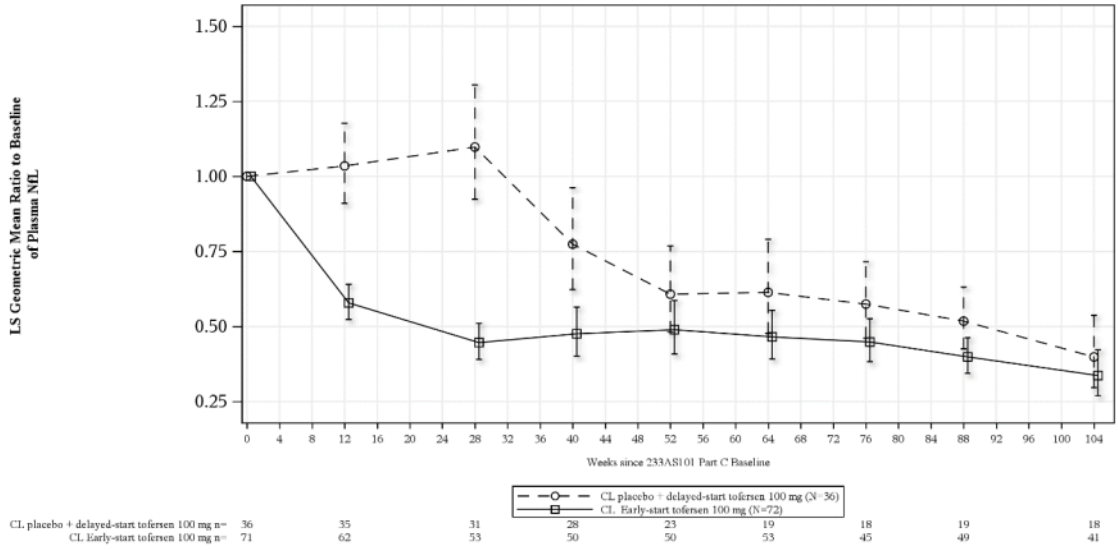
Plasma NfL (neurofilament light chain) biomarker

Plasma NfL, a blood-based biomarker of axonal injury and neurodegeneration, was tested in trial 1 part C.
At Week 28 in trial 1 part C, mean plasma NfL was reduced 55 % (geometric mean ratio to baseline) in the Qalsody-treated subjects (ITT), compared to a 12 % increase with placebo (difference in geometric mean ratios for Qalsody to placebo: 60 %; 95% CI: 51%, 67%). Plasma NfL declined until approximately week 16, after which the reductions were sustained. The reductions in phosphorylated

neurofilament heavy chain (pNfH) were consistent compared to NfL as were reductions in CSF compared to plasma.

Figure 1: Trial 1 part C: plasma NfL adjusted geometric mean ratio to baseline values by trial week for the ITT population

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



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

Note 1: Baseline is defined as day 1 value prior to the clinical trial drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

Note 2: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 4,9 pg/mL) in calculations. Multiple imputation is used for missing data.

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

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

Cardiac Electrophysiology

ECG measurements and the values for the Qalsody 100 mg group (n = 41) were similar to placebo group (n = 34) in trial 1 part C. The incidence of abnormalities in ECG measurements was slightly higher in the Qalsody group compared to the placebo group, with 8 subjects (11,3 %) displaying a maximum increase from baseline in Fridericia formula (QTcF) > 30 to 60 ms in the Qalsody group compared to 2 subjects (5,6 %) in the placebo group. No subjects in the Qalsody or placebo group displayed an increase from baseline in QTcF > 60 ms, and no subjects displayed maximum postbaseline QTcF > 480 ms.
Results of this analysis suggested the absence of a concentration dependent QTcF prolongation with Qalsody by demonstrating that there is a lack of QTcF prolongation for the 5^{th} to 95^{th} percentiles of the observed Qalsody concentration range (1,14 to 1440 ng/mL). The slope of the Qalsody concentration effect was estimated to be approximately zero, indicating the Qalsody concentration is not a clinically relevant predictor of QTcF and Qalsody is not anticipated to prolong the QTcF interval.

Clinical efficacy

The efficacy of Qalsody was assessed in a 28-week randomized, double-blind, placebo-controlled clinical trial (trial 1, part C) in subjects aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation confirmed by central laboratory. One hundred eight (108) subjects were randomized 2:1 to receive treatment with either Qalsody 100 mg or placebo for 24 weeks (3 loading doses followed by 5 maintenance doses). Forty-two (42) unique SOD1 mutations were evaluated, with the most common being p.Ile114Thr (n = 20), p.Ala5Val (n = 17), p.Gly94Cys (n = 6), and p.His47Arg (n = 5). Concomitant riluzole and/or edaravone use was permitted for subjects who were on a stable dose for at least 30 or 60 days prior to trial baseline, respectively.
The prespecified primary analysis population (n = 60, modified intent to treat [mITT]) had a trial 1 SVC ≥ 65 % of predicted value as adjusted for sex, age, and height (from the sitting position) at screening and met prognostic enrichment criteria for rapid disease progression, defined based on their prerandomization ALS Functional Rating Scale–Revised (ALSFRS-R) decline slope and SOD1 mutation type as follows:

- One of the following SOD1 mutations and a pre-randomization ALSFRS-R decline slope ≥ 0.2 points per month (calculated as [48 minus baseline ALSFRS-R total score]/time since symptom onset):
  p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly
  OR
- SOD1 mutation other than those listed above with pre-randomization ALSFRS-R decline slope ≥ 0.9 points per month (calculated as [48 minus baseline ALSFRS-R total score]/time since symptom onset)

The non-mITT population (n = 48) had an SVC ≥ 50 % of predicted value as adjusted for sex, age, and height (from the sitting position) at screening.

Baseline disease characteristics in the overall intent-to-treat (ITT) population were generally similar in the Qalsody-treated subjects and placebo-treated subjects, with slightly shorter time from symptom onset and higher plasma NfL at baseline in the tofersen group (Table 2).

Table 2: Baseline disease characteristics in trial 1, part C

Baseline and disease characteristics*	**ITT (n = 108)**	
	Placebo (n = 36)	**Qalsody 100 mg (n = 72)**
Site of onset n(%)		
Bulbar	3 (8)	3 (4)
Lower limbs	26 (72)	46 (64)
Upper limbs	7 (19)	20 (28)
Respiratory	0	1 (1)
Multiple sites	0	2 (3)
Riluzole Use‡ Yes n (%)	22 (61)	45 (63)
Edaravone Use†,‡ Yes n (%)	3 (8)	6 (8)
Time from symptom onset (months): median (min, max)	14,6 (2,4, 103,2)	11,4 (1,7, 145,7)
ALSFRS-R baseline total score:		
Mean (SD)	37,3 (5,81)	36,9 (5,91)
Range: min, max	24, 47	15, 48
% predicted SVC at baseline:		
mean (SD)	85,1 (16,53)	82,1 (16,59)
Range: min, max	54,8, 120,4	46,7, 134,7
Plasma NfL at baseline (pg/mL)		
mean (SD)	89,7 (86,5)	100,4 (82,8)
Geometric mean	56,6	66,6
Range: min, max	8, 370	5, 329

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

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

† All subjects receiving edaravone were also receiving riluzole.

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

The primary efficacy analysis was the change from baseline to Week 28 in the ALSFRS-R total score in the mITT population, analyzed using the joint rank test to account for mortality in conjunction with

multiple imputation (MI) to account for missing data for withdrawals other than death. The results numerically favored Qalsody but were not statistically significant (Qalsody-placebo adjusted mean difference [95 % CI]: 1.2 [-3,2; 5,5]).

In the ITT population during the 28-week follow-up period, the median time to death and/or permanent ventilation was not estimable due to the limited number of events observed. In the Qalsody group, 1,4 % of subjects died compared to 0,0 % in the placebo group. In the Qalsody and placebo groups, 5,6 % of subjects died or had an event of permanent ventilation.

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

Table 3: Effect of Qalsody from trial 1, part C baseline for the ITT population

Endpoint	**Trial 1 part C*** Change from baseline to Week 28 Qalsody (n = 72) versus placebo (n = 36)
Change from baseline on ALSFRS-R total score	
Adjusted means: Tof; Placebo	-4,1; -6,2
Qalsody-placebo: adjusted mean difference (95 % CI)	2,1 (-0,3, 4,5)
Nominal p-value (ANCOVA+MI)	0,0904
Change from baseline on %-predicted SVC	
Adjusted means: Tof; placebo	-7,3; -15,8
Qalsody-placebo: adjusted mean difference (95 % CI)	8,5 (1,8, 15,2)
Nominal p-value (ANCOVA+MI)	0,0128
Change from baseline on HHD megascore	
Adjusted means: Tof; placebo	-0,23; -0,32
Qalsody-placebo: adjusted mean difference (95 % CI)	0,10 (-0,04, 0,23)
Nominal p-value (ANCOVA+MI)	0,1547

* Post-hoc analyses adjusting for baseline plasma NfL

Notes:

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

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

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

Integrated results of trial 1 part C and trial 2

To allow for long-term follow up of these subjects, at the end of trial 1 part C, 88 % of subjects (95/108) (Qalsody 100 mg: n = 63; placebo: n = 32) enrolled in trial 2, an open-label extension trial with a blinded loading dose period for subjects who previously participated in trial 1 Part C. In trial 2, all subjects received Qalsody 100 mg. At the time of Qalsody initiation, subjects in the placebo/delayed-start group had a mean percent-predicted SVC value of 68,7 (SD: 25,8; range 21,6 to 113,7) and total ALSFRS-R score of 30,9 (SD: 9,2; range: 12 to 44).
The median follow-up across the 2 trials at the time of the interim analysis, for subjects who participated in trial 1 part C, was 1,7 years (range: 0,08 to 2,82 years). At the time of the interim analysis, 62 % (67/108) of subjects remained ongoing in trial 2. An accounting of subject disposition is below in Table 4.

Table 4: Subject disposition of integrated analysis of trial 1 Part C and trial 2 for the ITT population

Subjects	**Early-start Qalsody 100 mg (n = 72)**	**Placebo/delayed-start Qalsody 100 mg (n = 36)**
Dosed in trial 1 Part C n (%)	72 (100)	36 (100)
Dosed in trial 2* n (%)	63 (88)	32 (89)
Completed trial 1 Part C but not enrolled in trial 2 n (%)	1 (1)	1 (3)
Ongoing in trial 2* n (%)	49 (68)	18 (50)
Died while on trial n (%)	8 (11)	6 (17)
Withdrew from trial n (%) AE Consent withdrawn Death Disease progression	22 (31) 2 (3) 4 (6) 8 (11) 8 (11)	17 (47) 0 4 (11) 6 (17) 7 (19)

* Interim analysis for trial 2

At the time of the interim analysis, across trial 1 part C and trial 2 combined, there were 12 (16,7 %) subjects with death or permanent ventilation in those who initiated Qalsody 100 mg in trial 1 part C ('early-start' (ES) group) in the ITT population and 8 (22,2 %) in those who initiated Qalsody 100 mg in trial 2 ('placebo/delayed-start' (DS) group). Earlier initiation of Qalsody (ES group) was associated with an apparent reduction in the risk of death or permanent ventilation (HR [95 % CI]: 0,36 [0,14; 0,94]) and risk of death (HR [95 % CI]: 0,27 [0,08; 0,89]). Median time-to-event was not estimable. Earlier initiation of Qalsody (ES group) was associated with a reduction in decline on ALSFRS-R, SVC percent-predicted, and HHD megascore over 52 weeks from the start of trial 1 Part C as compared to placebo/delayed initiation of Qalsody (DS group); see Table 5, Figure 2, Figure 3, and Figure 4.

Table 5: Analyses of clinical outcome measures for trial 1 part C and trial 2 integrated data at Week 52 for the ITT population*

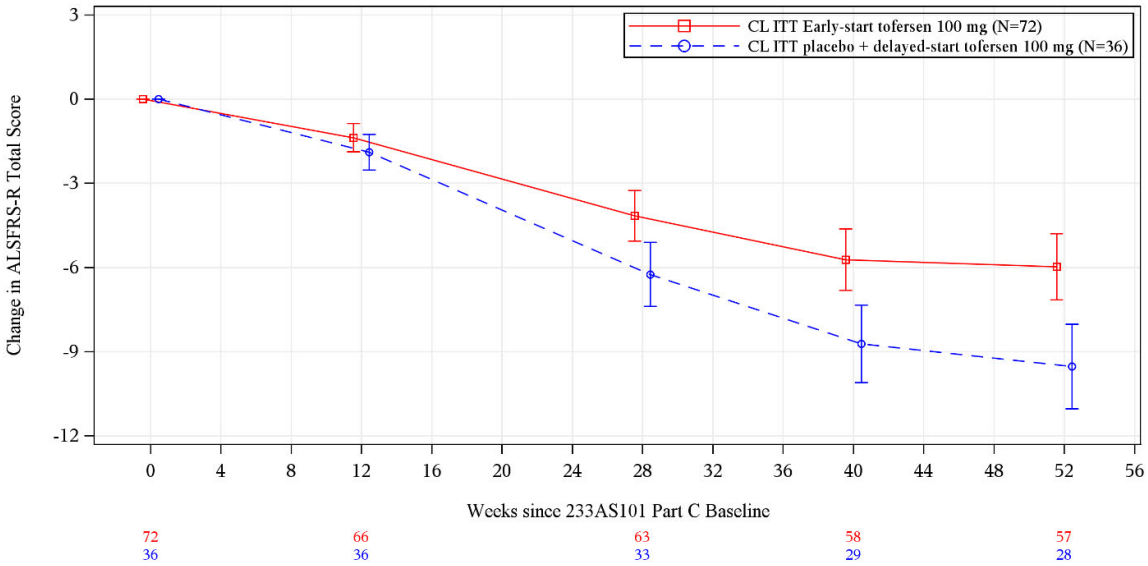
Endpoint	Trial 1 part C & Trial 2†		
	Early-start Qalsody 100 mg (n = 72) Adjusted mean	Placebo/delayed -start Qalsody 100 mg (n = 36) Adjusted mean	Adjusted mean difference (95 % CI) Nominal p-value
ALSFRS-R total score change from trial 1 part C baseline to Week 52	-6,0	-9,5	3,5 (0,4; 6,7) 0,0272
SVC %-predicted change from trial 1 part C baseline to Week 52	-9,4	-18,6	9,2 (1,7; 16,6) 0,0159
HHD megascore change from trial 1 part C baseline to Week 52	-0,17	-0,45	0,28 (0,05; 0,52) 0,0186

* Interim analysis for trial 2

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

Notes: Baseline is defined using trial 1 Part C baseline. For ITT analyses the multiple imputation model is based on all subjects in the ITT population and includes baseline plasma NfL, treatment, use of riluzole or edaravone, relevant baseline value and post-baseline values.

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



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

Note 1: Baseline is defined as day 1 value prior to the clinical study drug and presented as Day 1. If Day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

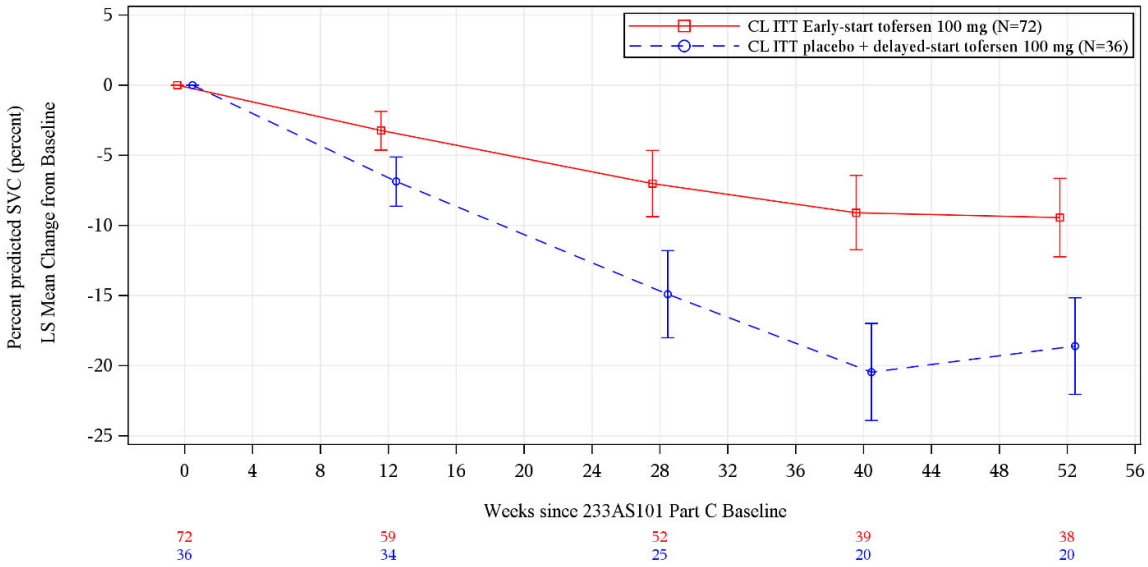
Note 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

Note 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.

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

Note 5: Subjects that were randomized to placebo in Trial 1 Part C and continued to Trial 2 received Qalsody after Week 28.

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



Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square; ATS = the American Thoracic Society.

Note 1: Baseline is defined as Day 1 value prior to the clinical trial drug and presented as Day 1. If Day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

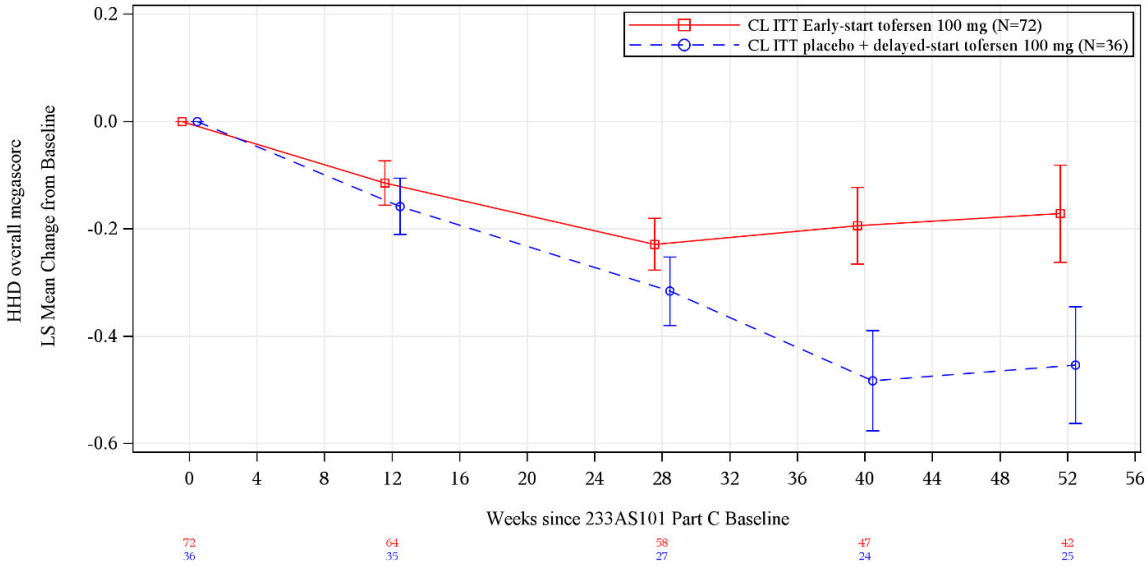
Note 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.

Note 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.

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

Note 5: Subjects that were randomized to placebo in Trial 1 Part C and continued to Trial 2 received Qalsody after Week 28.

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



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

Note 1: Baseline is defined as Day 1 value prior to the clinical trial drug and presented as Day 1. If Day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

Note 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

Note 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Note 5: Subjects that were randomized to placebo in Trial 1 Part C and continued to Trial 2 received Qalsody after Week 28.

Pharmacokinetics

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

Absorption

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

Distribution

Tofersen administered intrathecally was extensively distributed within the CNS, achieving therapeutic levels in the target spinal cord tissues, confirmed by results from autopsy tissue from tofersen-treated patients (n=3) and from pharmacokinetic (PK) analysis. The median plasma AUC at 100 mg (Study 101 Part C data) after first dose was 13973.1 ng/mL*h; median maximum plasma concentration (Cmax) was 824.3 ng/mL, which occurred at between 4-6 hours post dose. The median plasma volume of distribution was estimated at 50.9L (119% CV) in study 101 and 102.

Plasma Protein Binding
Tofersen is highly bound to human plasma proteins (≥ 98% bound) at clinically relevant or higher plasma concentrations (0.1 and 3 µg/ml), which limits glomerular filtration and reduces urinary excretion of the active substance. The likelihood of drug-drug interactions due to competition with plasma protein binding is very low.

Metabolism

Tofersen is metabolized predominantly through exonuclease (3' and 5')-mediated hydrolysis and is not a substrate for CYP450 enzymes.

Elimination

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

Immunogenicity

The presence of anti-drug antibodies (ADAs) decreased plasma clearance by 32 %. The occurrence of ADAs is not expected to produce notable effects on CSF PK. ADAs had no relevant impact on the measured SOD1 protein or on NfL.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of tofersen in patients with hepatic impairment has not been studied.

Renal impairment

The pharmacokinetics of tofersen in patients with renal impairment has not been studied.

Elderly patients

Of the 166 patients who received Qalsody in clinical trials, a total of 22 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in clinical PK were observed between these patients, but data are limited.

Children and adolescents

Tofersen has not been studied in pediatric patients.

Sex/Gender

Population pharmacokinetic analysis shows that sex of the patient does not affect the pharmacokinetics of Tofersen.

Body surface area

The body surface area (BSA) was identified as a covariate of plasma clearance of tofersen but does not have an effect on tofersen CSF PK profile hence the effect of body surface area is considered not clinically relevant.

Preclinical data

Evidence of myelitis was not observed in the nonclinical toxicology studies for tofersen. However, vacuolation of neurons in brain and spinal cord as well as mononuclear cell infiltrates in spinal

cord/nerve roots were seen with tofersen as well as with other ASOs. None of these findings were associated with degenerative changes in the brain or spinal cord.
Tofersen demonstrated a very low potential for cardiac IKR (hERG channel) inhibition (IC_{50} > 34 µM) and did not produce adverse effects in cardiovascular safety pharmacology endpoints in nonhuman primates at the highest dose tested (35 mg).

Repeated dose toxicity

In a repeat-dose toxicology study (9 months), intrathecal administration of tofersen to adult cynomolgus monkeys was generally well-tolerated. The exception was a female in the high dose group (35 mg; equivalent to 350 mg per IT injection in humans) that had behavior described as muscle cramping, head/neck dorsiflexion, and opisthotonos-like-back-arching posture after IT dosing. Electroencephalogram (EEG) indicated the absence of seizure. The no observed adverse effect levels (NOAELs) in the repeat-dose chronic toxicology studies were 150 mg/kg subcutaneous administration in the mouse and 12 mg intrathecal administration in the 9-month nonhuman primate. Using the nonhuman primate as the most sensitive species, a dose of 12 mg converts to the HED of 120 mg (based on the monkey-to-human CSF volume scaling). The safety margin (1,2-fold) for the IT doses in monkeys to IT doses in humans is based on the converted HED with consideration of volume difference in CSF (approximately 10-fold between human and monkeys). Therefore, no toxicity effects were seen at dose levels equivalent to 120 mg in humans.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies with tofersen have not been performed.

Reproductive toxicity

Reproductive toxicology studies were conducted using subcutaneous administration of tofersen in mice and rabbits. No impact on fertility, embryo-fetal development, or pre-/postnatal development was observed. Male mice in the high dose group of 30 mg/kg (> 50 times the human exposure [AUC] following 100 mg tofersen) had minimal to mild seminiferous tubular degeneration, seminiferous tubule dilatation, spermatid retention, apoptosis of epithelial cells, increased cellular debris in the testes, and hypospermia in the epididymis. However, there were no tofersen-related adverse effects on mating and fertility or sperm parameters. In female mice, there was no tofersen-related mortality or early delivery and there were no effects on mating or fertility. In a perinatal/postnatal reproduction study in mice, there were no adverse effects on the F0 females or on the growth and development of

the F1 pups at the highest dose evaluated (30 mg/kg). Translation of mouse fertility data to humans is limited based on the lack of cross-reactivity of Tofersen to SOD1 in rodents.
Tofersen was evaluated in embryo-fetal development studies in animals and demonstrated no evidence of teratogenicity.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8 °C).
Do not freeze.
Store in the original packaging in order to protect the contents from light.
The vial of Qalsody in its original carton to protect from light can be stored for up to 14 days at a temperature not to exceeding 30° C.
Unopened vials of Qalsody can be removed from and returned to the refrigerator, if necessary.
Unopened vials can be removed from the original carton for not more than 6 hours per day at room temperature for a maximum of 6 days.

Instructions for handling

Vial preparation instructions:

- The refrigerated vial should be allowed to warm to room temperature (25 °C) prior to administration without external heat sources.
- The vial containing Qalsody should not be shaken.
- Solution should be visually inspected prior to removal of Qalsody from the vial. The solution should be essentially free of visible particles. Only clear and colorless to slightly yellow solution should be administered. If not, the vial must not be used.

Procedural preparation instructions

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

- Prior to removing the vial's cap on the aluminum overseal, readiness of patient should be confirmed. Unopened vial can be returned to the refrigerator (see section *Shelf life after opening* for total time permitted).
- Patients should be evaluated prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture to avoid serious procedural complications.

Administration

- Just prior to administration, the plastic cap should be removed from the vial and a nonspinal anesthesia needle attached to the syringe for the purpose of withdrawing Qalsody from the vial. The syringe needle is inserted into the vial through the center of the overseal to withdraw the required dose of 15 mL (equivalent to 100 mg) from the vial.
- Qalsody must not be diluted.
- External filters are not required.
- It is recommended that approximately 10 mL of cerebrospinal spinal fluid (CSF) is removed using a lumbar puncture needle prior to administration of Qalsody.
- Qalsody is administered as an intrathecal bolus injection using a lumbar puncture needle over 1 to 3 minutes.
- Qalsody contains no preservatives. Once drawn into the syringe, the solution should be administered immediately (within 4 hours since removal from refrigeration) at room temperature; otherwise, it must be discarded.
- Any unused contents of the single-dose vial should be discarded.
- spilled Qalsody must be inactivated with disinfectant.
- emptied vials and consumables that have come into contact with Qalsody must be disposed of as contaminated medical waste.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68577 (Swissmedic).

Packs

Pack containing 1 vial. A

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

Product in container closure system is sterile and non-pyrogenic

Marketing authorisation holder

Biogen Switzerland AG, 6340 Baar

Date of revision of the text

December 2025