SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Qalsody 100 mg solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 ml vial contains 100 mg of tofersen.

Each ml contains 6.7 mg of tofersen.

Excipient with known effect

Each 15 ml vial contains 52 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colourless to slightly yellow solution with a pH of 6.7 to 7.7.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with tofersen should only be initiated by a physician with experience in the management of ALS.

Qalsody should be administered by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Posology

The recommended dose is 100 mg of tofersen per treatment.

Tofersen treatment should be initiated with 3 loading doses administered at 14-day intervals.

A maintenance dose should be administered once every 28 days thereafter.

Missed or delayed doses

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

Duration of treatment

The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy.

Special populations

Elderly

Experience with the use of tofersen in the elderly is limited. However, from the clinical data available, the efficacy and safety of tofersen are expected to be similar to that of other age groups studied.

There is no evidence for special dose considerations based on age when tofersen is administered.

Renal impairment

Tofersen has not been studied in patients with renal impairment.

Hepatic impairment

Tofersen has not been studied in patients with hepatic impairment.

Paediatric population

The safety and efficacy of Qalsody in paediatric patients below the age of 18 years has not been established. No data are available.

Method of administration

Qalsody is for intrathecal use by lumbar puncture.

- It is recommended to ensure intrathecal access prior to removing the plastic cap from the vial and drawing up the tofersen dose.
- 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 tofersen 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, including bacterial or particulate 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 tofersen.
- Tofersen is administered as an intrathecal bolus injection using a lumbar puncture needle over 1 to 3 minutes.

Procedural preparation instruction:

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

Following injection, standard post-lumbar-puncture care is recommended.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Lumbar puncture procedure

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

Myelitis and/or radiculitis

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

Increased intracranial pressure and/or papilloedema

Serious cases of increased intracranial pressure and/or papilloedema have been reported in patients treated with tofersen. If symptoms consistent with these adverse reactions develop, diagnostic evaluation 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.

Excipients

Sodium

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

Potassium

This medicinal product contains potassium, less than 1 mmol (39 mg) per 15 ml dose, i.e., essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

There are no data on the use of tofersen during breast-feeding in humans. Available pharmacodynamic data in animals have shown excretion of tofersen in milk (see section 5.3). A risk to the newborn/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tofersen therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the potential effects on fertility in humans. Toxicity studies in animals have indicated that tofersen would not appear to have harmful effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The serious adverse reactions in tofersen-treated participants were myelitis (2.7%), increase intracranial pressure and/or papilloedema (2.7%), radiculitis (1.4%) and aseptic meningitis (1.4%). The most common adverse reactions reported in tofersen-treated participants were pain (66%), arthralgia (34%), fatigue (28.6%), CSF white blood cell increased (26.5%), CSF protein increased (26.5%), myalgia (19%) and pyrexia (18.4%).

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and frequency using the following convention: Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥1/10 000 to <1/1 000); Very Rare (<1/10 000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions with Qalsody-treated participants in Study 101 and Study 102

System Organ Class (SOC)	Adverse reaction	Frequency

System Organ Class (SOC)	Adverse reaction	Frequency
Nervous system disorders	CSF white blood cell increased[*]	Very common
	CSF protein increased	Very common
	Papilloedema[‡]	Common
	Neuralgia	Common
	Aseptic meningitis[††]	Common
	Radiculitis[†]	Common
	Myelitis[§]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Musculoskeletal stiffness	Common
General disorders and administration site conditions	Pain[‡‡]	Very common
	Fatigue	Very common
	Pyrexia	Very common

[*] CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis.
[†] Radiculitis includes preferred terms of radiculopathy and lumbar radiculopathy.
[‡] Papilloedema includes preferred terms of papilloedema and intracranial pressure increased. See discussion in Description of selected adverse reactions (ARs).
[§] Myelitis includes preferred terms of myelitis, myelitis transverse, and neurosarcoidosis. See discussion in Description of selected adverse reactions.
[††] Aseptic meningitis includes preferred terms of meningitis chemical and meningitis aseptic. See discussion in Description of selected adverse reactions.
[‡‡] Pain includes preferred terms of pain, back pain, and pain in extremity.

Description of selected adverse reactions

Lumbar puncture procedure

Adverse reactions associated with the administration of tofersen by lumbar puncture have been observed. The adverse reactions commonly associated with lumbar puncture are headache, back pain, post lumbar puncture syndrome, infection. The incidence and severity of these events were consistent with events expected to occur with lumbar puncture.

Myelitis and/or radiculitis

In the clinical studies, 4 participants receiving tofersen 100 mg reported serious reactions of myelitis (2.7%). The number of tofersen doses received before the onset of myelitis ranged from 5 to 15 doses. Two participants were symptomatic and 2 participants were asymptomatic. All 4 participants had abnormal magnetic resonance imaging (MRI) findings related to the event. Two participants discontinued treatment, and the event resolved. In the remaining 2 participants, the event did not lead to discontinuation of treatment (see section 4.4).

Two participants receiving tofersen 100 mg reported serious reactions of radiculitis (1.4%). The number of tofersen doses received before the onset of radiculitis ranged from 1 to 24 doses. Both reactions were symptomatic. One participant had abnormal MRI findings related to the event and one participant had a normal MRI. No participants discontinued treatment, and the reactions resolved with sequelae in one and without sequalae in the second participant (see section 4.4).

Increased intracranial pressure and/or papilloedema

Four participants receiving tofersen 100 mg reported serious reactions of increased intracranial pressure and/or papilloedema (2.7%). The number of tofersen doses received before the onset of increased intracranial pressure and/or papilloedema ranged from 7 to 18 doses. All 4 reactions of increased intracranial pressure and/or papilloedema were symptomatic. Four participants had an MRI with no findings pertinent to the event. One reaction finally led to permanent discontinuation of tofersen, one reaction led to interruption of tofersen treatment. All reactions were manageable with standard of care (see section 4.4).

Aseptic or chemical meningitis

Two participants receiving tofersen 100 mg reported serious reactions of aseptic or chemical meningitis (1.4%). The number of tofersen doses received before the onset of aseptic or chemical meningitis ranged from 5 to 7 doses. Both reactions of aseptic or chemical meningitis were symptomatic. One participant had an MRI with no findings pertinent to the event. One participant discontinued tofersen, and the other participant did not.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

In the event of an overdose, supportive medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

SOD1-ALS is a primarily autosomal-dominant disorder affecting approximately 2% of the ALS population. 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 with a median disease duration of approximately 2.3 years.

Mechanism of action

The human SOD1 gene encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), which catalyses the transmutation of superoxide (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2). In SOD1-ALS patients, mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein, resulting in axonal injury and neurodegeneration.

Tofersen is an antisense oligonucleotide (ASO) 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 (hybridisation). This hybridisation of tofersen to the cognate mRNA results in RNase-H-mediated degradation of the mRNA for SOD1, which reduces the amount of SOD1 protein synthesis.

Pharmacodynamic effects

Total CSF SOD1 protein

Total CSF SOD1 was measured in Studies 101 Part C (VALOR) and 102 as an indirect measure of target engagement.

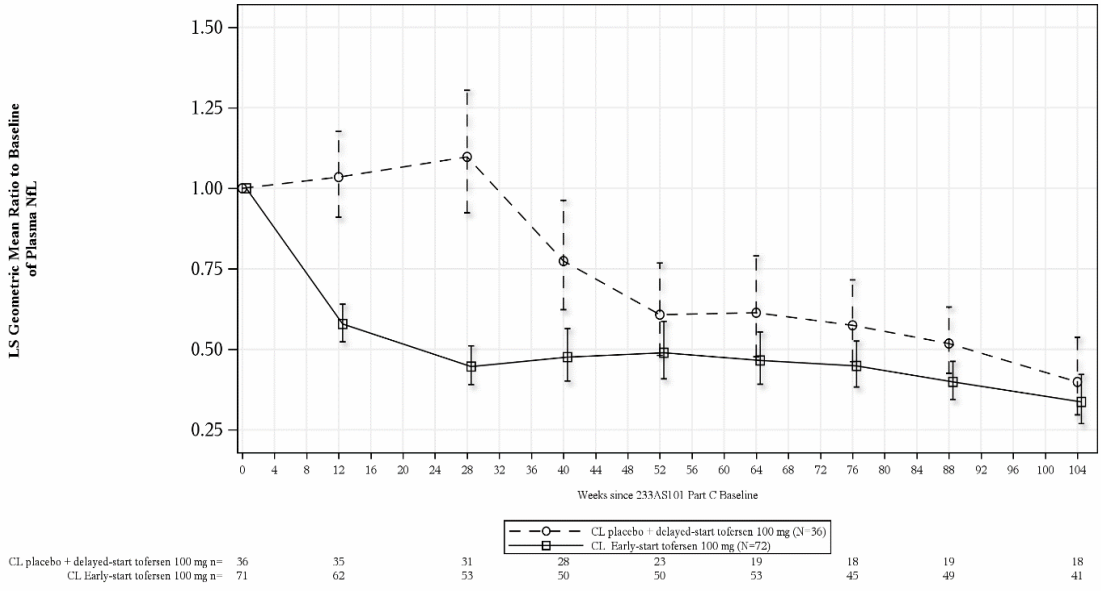
At Week 28 in Study 101 Part C, a reduction in total CSF SOD1 protein of 35% (geometric mean ratio to baseline) in the tofersen-treated group versus a 2% decrease from baseline in the corresponding placebo participants in the ITT population was observed (difference in geometric mean ratios for tofersen to placebo: 34% (95% CI: 23%, 43%). Total CSF SOD1 declined until approximately Day 56, after which the reductions were sustained over time.

Plasma neurofilament light chain (NfL) biomarker

Plasma neurofilament light chain (NfL) was measured in Studies 101 Part C (VALOR) and 102 as a marker of axonal injury and neurodegeneration.

At Week 28 in Study 101 Part C, mean plasma NfL was reduced 55% (geometric mean ratio to baseline) in the tofersen-treated participants (ITT), compared to a 12% increase with placebo (difference in geometric mean ratios for tofersen to placebo: 60% (95% CI: 51%, 67%)). Plasma NfL levels declined until approximately Day 113, after which the reductions were sustained over time. The reductions in CSF NfL were consistent compared to those observed in plasma.

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



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

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

Note 2: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 4.9 pg/mL) in calculations. Multiple imputation is used for missing data.

Note 3: The ITT 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.

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

Cardiac electrophysiology

ECG measurements and the values for the tofersen 100 mg group (n = 41) were similar to placebo group (n = 34) in Study 101 Part C. The incidence of abnormalities in ECG measurements was higher in the tofersen group compared to the placebo group, with 8 participants (11.3%) displaying a maximum increase from baseline in Fridericia formula (QTcF) > 30 to 60 ms in the tofersen group compared to 2 participants (5.6%) in the placebo group. The clinical significance of this imbalance is not known. No participants in the tofersen or placebo group displayed an increase

from baseline in QTcF > 60 ms, and no participants displayed maximum postbaseline QTcF > 480 ms.

Immunogenicity

Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on efficacy or safety was observed. However, data are still limited.

Clinical efficacy and safety

The efficacy of tofersen was assessed in a 28-week randomised, double-blind, placebo-controlled clinical study (Study 101, Part C) in participants aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation confirmed by central laboratory. One hundred eight (108) participants were randomised 2:1 to receive treatment with either tofersen 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 participants who were on a stable dose for at least 30 or 60 days prior to study baseline, respectively.

Baseline disease characteristics in the overall intent to treat (ITT) population were generally similar in the tofersen-treated participants (n=72) and placebo participants (n=36), with a baseline ALS Functional Rating Scale–Revised (ALSFRS-R) total score of 36.9 (SD: 5.9) in the tofersen group and 37.3 (SD: 5.81) in the placebo group. The tofersen group had a shorter median time from symptom onset (11.4 months; range: 1.7, 145.7) as compared to the placebo group (14.6 months; range: 2.4, 103.2), and a higher median baseline plasma NfL level (78.5 pg/mL; range 5 to 329) as compared to the placebo group (64.6 pg/mL; range: 8 to 370).

The primary efficacy endpoint was the change from baseline to Week 28 in the ALSFRS-R total score The results numerically favoured tofersen, but were not statistically significant (ITT population: tofersen-placebo adjusted mean difference [95% CI]: 1.4 [-1.3, 4.1]). Numerically larger differences were observed between tofersen and placebo over 28 weeks in patients with baseline NfL values above median [mean difference (95% CI) 3.9, (-1.0;8.9)] compared to patients with baseline NfL values below median [0.6, (-1.3,4.2)]. Secondary clinical outcomes also did not reach statistical significance.

Paediatric population

The Medicines and Healthcare products Regulatory Agency (MHRA) has waived the obligation to submit the results of studies with tofersen in all subsets of the paediatric population in ALS (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The Medicines and Healthcare products

Regulatory Agency (MHRA) will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The single and multidose pharmacokinetics of tofersen, administered via intrathecal injection, were characterised in plasma and CSF of adult ALS participants with a SOD1 mutation and in autopsy tissue from deceased clinical study participants (n=3).

Absorption

The maximum CSF trough concentration occurred at the third dose, which was the last dose of the loading period. There was little to no accumulation with monthly dosing after the loading phase; the accumulation ratio appears to be less than 2-fold. Tofersen is rapidly transferred from CSF into the systemic circulation, with a median time to maximum concentration (T_{max}) plasma values ranged from 2 to 6 hours post intrathecal (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. 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; and was 40.67 L (130% CV) in the 100 mg dose group. Pharmacokinetic (PK) analysis demonstrates that intrathecally administered tofersen is widely distributed into central nervous system (CNS) tissues and is rapidly transferred from CSF to the systemic circulation.

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.

Biotransformation

Tofersen is metabolised through exonuclease (3'- and 5')-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of 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 median plasma clearance was estimated at 8.32 L/hr (60.6% CV) in study 101 and 102; and was 5.73L/hr 60% CV) at 100 mg dose.

Linearity/non-linearity

In CSF, the pharmacokinetics of tofersen administered IT increase less than dose proportional for dose ranging from 20 mg to 100 mg.

In plasma, the pharmacokinetics of tofersen administered IT increase more than dose proportional for dose ranging from 20 mg to 100 mg.

Immunogenicity

The presence of anti-drug antibodies (ADAs) appeared to decrease plasma clearance by 28.0%.

Characteristics in specific patient populations

Elderly

Of the 166 patients who received tofersen in clinical studies, 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.

Renal impairment

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

Hepatic impairment

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

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies with tofersen have not been performed.

Mutagenesis

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).

Reproductive toxicity

Reproductive toxicology studies were conducted using subcutaneous administration of tofersen in mice and rabbits. In a mice fertility and embryo-fetal development study, 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. No tofersen-related adverse effects on embryo-foetal development were observed in mice and rabbits (at exposures more than 40-times the human exposure at MRHD). 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). Tofersen was detected in mouse milk samples from all tofersen-dosed animals. Tofersen is not pharmacologically active in mice and rabbits, which limits the validity of these studies, as harmful effects associated with SOD1 down-regulation cannot be evaluated therein.

Microscopic evaluation of reproductive tissues from both males and females in the 13-week and 39-week non-human primate (NHP) toxicology studies in which tofersen is pharmacologically active revealed no effects on the reproductive tissues.

Toxicology

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 behaviour 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 human equivalent dose (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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate

Potassium chloride

Calcium chloride dihydrate

Magnesium chloride hexahydrate

Sodium chloride

Sodium dihydrogen phosphate dihydrate

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

42 months

Temporary storage conditions

The vial of Qalsody in its original carton can be stored for up to 14 days at room temperature (store below 30°C).

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For temporary storage conditions of unopened vials of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml clear Type I glass vial with chlorobutyl rubber stopper and an aluminium overseal with flip-off plastic button.

Qalsody is available in a pack of 1 vial.

6.6 Special precautions for disposal

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

For single use only.

Vial preparation instructions:

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

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

7 MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 22407/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/07/2025

10 DATE OF REVISION OF THE TEXT

22/07/2025