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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR

QALSODY (TOFERSEN)

RMP version number:	1.0
Data lock point (DLP) for this RMP:	28 Feb 2023
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QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable - no other versions of the Qalsody EU RMP are currently under evaluation.

Details of currently approved RMP

Not applicable for initial marketing authorisation application submission.

Rationale for submitting an updated RMP

Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP

Not applicable for initial marketing authorisation application submission.

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PART VII - ANNEXES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS-R	Revised ALS Functional Rating Score
ASO	antisense oligonucleotide
ATC	Anatomical Therapeutic Chemical
CNS	central nervous system
CSF	cerebrospinal fluid
DCT	data collection tool
DLP	data lock point
EC	ethics committee
eCTD	Electronic Common Technical Document
ECG	electrocardiogram
EEA	European Economic Area
EEG	electroencephalogram
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
HED	human equivalent dose
HLT	High Level Term
IBD	International Birth Date
ICH	International Council for Harmonisation
INN	International Non-proprietary Name
IT	intrathecal
LP	lumbar puncture
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MOE	methoxyethyl
NA	not applicable
NEC	not elsewhere classified
NHP	non-human primate

Abbreviation	Definition
NOEL	no observed effect level
OCT	optical coherence tomography
PD	pharmacodynamics
PIL	Patient Information Leaflet
PK	pharmacokinetics
PL	Package Information Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	serious adverse event
SC	subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOD1	superoxide dismutase 1
SVC	slow vital capacity
US	United States
VTE	venous thromboembolism
WBC	white blood cell

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Tofersen (formerly known as BIIB067)
Pharmacotherapeutic group(s) (ATC Code)	N07XX22
Marketing Authorisation Applicant	Biogen Netherlands B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	One
Invented name(s) in the European Economic Area (EEA)	Qalsody
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Antisense oligonucleotides (ASO)
	Summary of mode of action: All superoxide dismutase 1 (SOD1) variants associated with amyotrophic lateral sclerosis (ALS) are assumed to cause SOD1 gain-of-function, i.e., they lead to an overabundance of mutant SOD1 protein that is believed to underlie the pathogenicity of SOD1-ALS. Tofersen reduces levels of the substrate for protein translation, an event that is upstream from all pathological mechanisms implicated in SOD1-ALS (all of which occur at the post-translation stage).
	Important information about its composition: Tofersen is a 20-base residue (20-mer) 5-10-5 2′-MOE mixed backbone oligonucleotide.
Hyperlink to the Product Information	1.3.1 SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	**Current:** Tofersen is indicated for the treatment of adults with ALS associated with a mutation in the SOD1 gene.
Dosage in the EEA	**Current:** The recommended dosage is 100 mg/15 mL of tofersen per treatment. Tofersen treatment should be initiated with 3 loading doses administered at 14-day intervals. A maintenance dose should be administered every 28 days thereafter.

Pharmaceutical form(s) and strengths	**Current:** *Form:* Solution for injection *Strength:* One vial contains 100 mg tofersen
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of Amyotrophic Lateral Sclerosis

Epidemiology data for the treatment of ALS, associated with a mutation in the SOD1 gene is provided in the sections below.

Incidence and Prevalence of ALS

A recent systematic review of the literature and meta-analysis study reports pooled prevalence rates (per 100,000 persons) and incidence rates (per 100,000 person-years) as 6.22 and 2.31 for Europe, 5.20 and 2.35 for North America, 3.41 and 1.25 for Latin America, 3.01 and 0.93 for Asian countries excluding Japan, and 7.96 and 1.76 for Japan, respectively [Brown 2021]. The global prevalence of ALS is estimated to be approximately 4.42 per 100,000 [Xu 2020].

SOD1-ALS estimates

Estimates of prevalent and incident ALS cases with a mutation in the SOD1 gene indicate 607 prevalent and 228 incident SOD1-ALS cases across 11 European countries in 2020 [Brown 2021]. These estimates suggest a prevalence rate of 0.12 per 100,000 population and incidence rate of 0.04 per 100,000 person-years for SOD1-ALS in Europe.

Demographics of the population in the proposed indication and risk factors for the disease

Based on the United States (US)-based National ALS Registry (covering the period Oct 2010 to Dec 2011), ALS was reported most commonly in white males, non-Hispanics, and persons aged 60 to 69 years. The age groups with the lowest number of persons with ALS were age 18 to 39 years and age > 80 years. Males had a higher prevalence rate of ALS than females overall and across all data sources[Mehta 2014]. In Europe, the mean age of onset of ALS has been reported as varying from 50 to 65 years, with the median age of onset of 64 years old, with only 5% of cases having an onset < 30 years of age [Kiernan 2011; Logroscino 2010; O'Toole 2008].

There is no known definitive cause of ALS. Though clinically indistinguishable, ALS has historically been classified as familial (5% to 10% of ALS cases) or sporadic (~90% to 95% of ALS cases) based on the presence or absence of a known family history [Byrne 2011; Zarei 2015]. Several potential risk factors for ALS have been identified: Male gender, older age, and family history of ALS increase the likelihood of developing the disease [Longinetti and Fang 2019]. Prior exposure to heavy metals (e.g., lead) has also been associated with an increased risk for ALS [Armon 2009; Kamel 2002; Roelofs-Iverson 1984], and certain occupations (e.g., military service) have been identified as potential risk factors as well [Sutedja 2009; Tai 2017]. Nutritional intake, exposure to infectious agents, physical activity, and trauma also have been identified as possible risk factors [Beghi 2010; Chen 2007; Chiò 2009; Fang 2011; Piazza 2004; Takei 2017; Wang 2011]; however, most risk factor studies have had small sample sizes or

have been conducted in limited geographic areas in populations that might not be representative of the overall population.

In 1993, the first mutations associated with ALS were found within the gene encoding the enzyme SOD1. Today, ALS associated with mutation in the SOD1 gene (hereafter referred to as SOD1-ALS) is thought to represent approximately 2% of the ALS population, including patients with and without a known family history [Ranganathan 2020; Shepheard 2021].

Bali et al described a mean age of onset of SOD1-ALS (49.7 ± 12.3 years) as generally similar to the broad ALS population, though this can vary meaningfully across individual SOD1 mutation types [Bali 2017]. Rare cases of juvenile-onset muscular weakness and/or atrophy in SOD1 mutation carriers have been reported [De La Torre 2019; Hayward 1998; Ikeda 1995; Rezania 2003].

The main existing treatment options

There is 1 treatment for ALS approved in Europe (riluzole) currently. No genetically targeted therapies for ALS have been approved.

Riluzole, the most widely approved ALS treatment, received its first global approval for treatment of ALS in 1995 (US) based on 2 studies that demonstrated that the time to tracheostomy or death was longer for patients receiving riluzole compared with placebo by approximately 90 days. Although riluzole improved survival in both studies, measures of muscle strength and neurological function did not show a benefit. It received the first European Union (EU) approval in 1996.

Two other treatments (edaravone and sodium phenylbutyrate/ursodoxicoltaurine) are in use globally, though approvals vary by region.

Edaravone received its first global approval for the treatment of ALS in 2015 (Japan) based on a single study in Japanese patients with ALS of Grade 1 or 2 in the Japan ALS Severity Classification. After 24 weeks of treatment, the decline in Revised ALS Functional Rating Score (ALSFRS-R) scores from baseline was significantly less in edaravone-treated patients than with placebo (2.49-point difference); no effect on survival was observed. A study conducted in a more progressed subset of the population did not show a statistically significant effect with administration of edaravone. Edaravone is not currently licensed for use in Europe.

Sodium phenylbutyrate/ursodoxicoltaurine (AMX0035; tradename Albrioza) received its first approval for the treatment of ALS in 2022 (Canada). This product is not currently licensed for use in Europe.

To date, no data are available on the safety and effectiveness of these treatments specifically in the SOD1-ALS population.

As ALS progresses, the only other methods of treatment available to patients are designed to relieve symptoms and improve quality of life.

Given the seriousness of the disease and the modest efficacy of available therapies, there remains a high unmet medical need for safe and effective treatments for SOD1-ALS.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

ALS is a serious neurodegenerative disease that causes loss of upper and lower motor neurons within the cortex, brainstem, and spinal cord [Bunton-Stasyshyn 2015; Wijesekera and Leigh 2009]. People with ALS experience progressive loss of muscle mass, strength, and function in bulbar, respiratory, and limb muscles, typically leading to death from respiratory failure within 3 to 5 years of onset [Brown and Al-Chalabi 2017; Bunton-Stasyshyn 2015; Lechtzin 2018].

ALS may present in any anatomical region and spread throughout the body with variable speeds and patterns in different patients. Approximately 80% of patients with ALS initially experience symptoms in their limbs (limb-onset), while approximately 20% present with bulbar (bulbar-onset) or generalized symptoms. Spread of symptoms typically occurs from a single site toward highly connected anatomical regions[Walhout 2018]. Loss of upper motor neurons in the motor cortex results in muscle stiffness and spasticity, while loss of lower motor neurons in the brainstem and spinal cord results in spontaneous fasciculations followed by atrophy [Kiernan 2011].

The natural history of SOD1-ALS is highly variable across SOD1 mutation types. The most current and comprehensive overview of the natural history stems from a retrospective cohort study that reviewed records from 175 SOD1-ALS patients across 15 institutions in North America, which found that the rapidity of disease progression varies substantially across mutation types, with disease durations ranging from less than a year to over 20 years (mean 4.6 ± 6.0 years) [Bali 2017; Cudkowicz 1997]. For example, the p.Ala5Val (A5V;A4V) mutation, the most prevalent variant in North America, was associated with a median survival of 1.2 years and mean disease duration of 1.4 ± 0.9 years; no A5V carriers (n = 35) survived to Year 4 post-onset [Bali 2017]. In contrast, the p. Gly42Asp (G42D;G41D) mutation has a mean disease duration of 23.5 ± 14.0 years [Bali 2017]. Available data suggest mutations in the SOD1 gene increase the propensity for the protein to aggregate, and mutations that show high aggregation propensities appear to be associated with shorter disease duration [Prudencio 2009].

Despite the heterogeneity in disease progression, the underlying pathophysiology of the disease, attributable to accumulation of toxic SOD1 protein, is thought to be consistent across gain of function SOD1 mutation types. As such, effective reduction of SOD1 protein, irrespective of genotype, has the potential to alter the disease course of patients with SOD1-ALS.

Important co-morbidities

Retrospective cohort studies have shown that the incidence in certain concomitant diseases and comorbidities is significantly different in the ALS-affected population in comparison to the general population [Zarei 2015]; however, none of the most commonly reported comorbidities (as discussed below) were concluded to influence disease course or survival [Körner 2013].

Depression is one of the most common secondary symptoms associated with ALS. Previous studies have reported a prevalence of depression of 4% to 56% depending on the assessment measure [Zarei 2015].

Of the diseases most likely to be found in ALS patients prior to their diagnosis, a higher incidence in neurological disorders has been noted when compared to the general population

[Turner 2016]. Similarly, patients with ALS were at higher risk of a receiving a diagnosis of depression both prior to and after ALS diagnosis [Roos 2016]. An effect of depression on disease course or survival was not observed [Körner 2013].

Reduced lower extremity mobility in ALS patients is hypothesized to increase the risk of VTE. Reports of increased incidence of VTE in patients with ALS have been consistent in the literature with annual incidence rates ranging from 3.31% in a retrospective study [Elman 2005], to 8.5% [Caballero-Eraso 2022] and 11.2% [Gladman 2014] in 2 prospective studies.

Suicidality is exhibited at a higher rate in ALS patients compared with the general population [Verschueren 2019]. In a study of 71 ALS patients, 39% expressed either passive or active suicidal ideation, with a higher risk of suicidality in patients with depressive symptoms and increased disability [Verschueren 2019]. A study of US veterans identified a 3-fold higher risk of death from suicide in veterans with ALS compared to those without ALS [Lund 2021]. Euthanasia and physician-assisted suicide are only legal in certain countries and certain states in the US; in the Netherlands, where euthanasia is legal, approximately 20% of ALS patients die by euthanasia or physician-hastened death [Ganzini 1998; Lund 2021; Norris 2020; Veldink 2002].

In cohort studies examining comorbidities prior to ALS diagnosis, there were modest association with prior cardiovascular disease and no association with traditional vascular risk factors such as hypertension, body mass index, and lipid levels [Kioumourtzoglou 2015; Körner 2013; Sutedja 2011].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity Studies	
Single-dose toxicity study A single-dose toxicity study was conducted in rats using IT dose administration at dose levels of 0.1, 0.3, 1, and 3 mg. There was 1 unscheduled death (male) in the 3 mg dose group, which died approximately 45 minutes following dosing. No adverse gross or microscopic findings were attributed to tofersen at the doses and concentrations tested. A transient acute tactile hypersensitivity reaction was noted within approximately 25 minutes from the end of dosing in all animals receiving 3 mg tofersen. No similar clinical observations were noted on subsequent days suggesting a transient effect.	None – Mortality was observed at human equivalent dose (HED) of 1500 mg. Acute tactile hypersensitivity reaction in the highest studied dose group (3 mg) was considered to be a transient effect as similar clinical observations were not noted on subsequent days. This observation is not considered to be of relevance to human use at the proposed tofersen dosing regimen. In addition, decreases in arousal, gait, mobility, respiration, and sensorimotor observations were seen in the 3 mg dose group in the functional observation battery test at 3 hours post dose.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Repeat-dose toxicity studies Repeat-dose toxicology studies were conducted in mice using SC administration and in cynomolgus monkeys using IT administration. In the mouse studies, no test article-related effects were identified from assessments of clinical observations, SC injection site observations, food consumption, body weights, or ophthalmic examinations. Administration of tofersen produced minor non-adverse changes in hematology and clinical chemistry parameters at 150 mg/kg/dose and ≥ 6 mg/kg/dose, respectively; there were also organ weight changes, macroscopic findings, and microscopic findings (generally consistent with those expected with ASO administration) at ≥ 6 mg/kg/dose. None of these findings were considered adverse. In the 13-week monkey toxicology study, there was transient reduced movement in 2 female monkeys in the highest dose group (35 mg) which was not considered adverse. In the 9-month study, adverse clinical observations were noted for 1 female administered 35 mg; this female exhibited neurological signs after the second dose, which were characterized by transient muscle cramping (seen immediately after dosing on multiple days), prolonged recovery from anesthesia, and intermittent tremors (during the last months of the dosing phase). Treatment with diazepam was required on several dosing occasions. An EEG of this animal after the last dose revealed altered post-dose signals (with effects on high-frequency bands), but it confirmed that muscle cramping during EEG recording was not a seizure and could have been related to arousal. An interaction with narcosis was possible. Overall, repeated IT administration of tofersen for 9 months was well tolerated at doses up to 12 mg, which was determined to be the no observed adverse effect level in the cynomolgus monkey. Tofersen-related effects in clinical pathology consisted of non-adverse changes in microalbumin and total protein concentrations in cerebrospinal fluid (CSF) from Day 85 onward (females administered ≥ 12 mg and males ≥ 4 mg). These changes were accompanied by increases in white and/or blood cell counts in individual animals at all dose levels of tofersen and at 1 or more timepoints.	The adverse clinical observations in the high-dose group (35 mg) female (350 mg HED) in NHPs provide an adequate safety margin to the relevant tofersen dose in humans. **Clinical Pathology** While the non-clinical findings of increased microalbumin and total protein concentrations in the CSF were considered non-adverse, adverse events (AEs) of CSF white blood cell increased and CSF protein increased were reported at an increased frequency in tofersen 100 mg-treated participants compared to placebo-treated participants in Study 233AS101 and are therefore listed as non-serious ADRs.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Reproductive/Developmental Toxicity	
Male and female fertility In a fertility study, SC administration of tofersen to male mice once every other day (28 days prior to mating and during and after cohabitation until scheduled euthanasia) at doses of 3, 10, and 30 mg/kg resulted in 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 at 30 mg/kg (55 times the human exposure [area under concentration] following 100 mg tofersen). However, there were no tofersen-related effects on mating and fertility or sperm parameters. In female mice, there were no effects on mating or fertility.	The microscopic findings that were observed in the 30 mg/kg group were considered adverse but the findings at the 10 mg/kg/dose were considered non-adverse because vacuolated macrophage infiltration in testis and epididymis were minimal to mild; no additional microscopic findings (i.e., apoptosis, degeneration, or hypospermia) were noted in this group. Tofersen was not found to have any adverse effects on either male or female fertility, and no impact on human fertility is anticipated.
Embryofetal and perinatal/postnatal development Tofersen did not result in any effects on embryofetal survival or fetal body weights, and it did not produce any fetal external, visceral, or skeletal malformations or variations in either mice or rabbits.	Tofersen had no adverse effects on embryofetal development in mice or rabbits nor perinatal/postnatal development in mice; however, as tofersen does not bind to rodent SOD1 due to 7 base-pair mismatches, the effects of a knockdown of SOD1 protein on embryofetal development in humans are unknown. Results from SOD1 knockdown models indicate that a potential hazard (reduction in fertility) has been identified, however, based on physiologically based PK modeling there is no expectation of complete knockdown of SOD1 following administration of 100 mg tofersen in the clinic.
Lactation Tofersen was detected in mouse milk samples from all tofersen-dosed animals following dose administration on Lactation Day 13. However, maternal exposure did not lead to adverse effects in the offspring.	Tofersen was detected in mouse milk samples following dose administration; however, no toxicologically relevant exposure was noted, and consequently no adverse effects are anticipated.
Genotoxicity	
The genotoxic potential of tofersen has been evaluated in vitro using a bacterial reverse mutation assay (Ames test) and chromosomal aberration assay in a Chinese Hamster Ovary cell line, and in vivo using a mouse micronucleus test. All genotoxicity test results were negative.	None – no evidence of genotoxicity has been observed in non-clinical studies, therefore, no adverse effects in humans are anticipated.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Carcinogenicity	
Carcinogenicity studies have not been conducted with tofersen in accordance with ICH S1A guidelines. Results from the IT repeat-dose toxicology studies in monkeys show no indication of immune or endocrine dysfunction. Furthermore, no proliferative effects, as demonstrated by a lack of preneoplastic or neoplastic lesions, were observed in mice (12-week and 26-week) or in the NHPs (13-week and 9-month).	None – no evidence of an increased carcinogenic risk, therefore, no adverse effects in humans are anticipated.
Safety Pharmacology and Other Toxicity-Related Information	
In the monkey repeat IT bolus dose studies, CNS function was assessed for general sensomotory aspects, cerebral reflexes (pupillary, orbicularis oculi, cornea) and spinal reflexes (anal, patellar, foot grip) and a standard neurobehavioral observation battery, using a modified version of a primary observation test described by Irwin (including body temperature) [Irwin 1968]. Respiratory function was assessed for blood gas parameters. Cardiovascular function was assessed for ECG and blood pressure on non-anesthetized temporarily restrained animals. Tofersen demonstrated a very low potential for cardiac rapid delayed rectifier (IKR) [human Ether-à-go-go-Related Gene channel] inhibition (IC50 > 34 µM). There was no effect of tofersen on any cardiovascular measurement, respiration, or body temperature following single or repeated IT dose administrations. There were transient changes in lower spinal reflexes in monkeys following IT bolus administration of doses > 12 mg per dose, which were observed 4 hours post dose and resolved by 8 hours post dose. The general neurological examinations (general sensory, motor function, and cerebral reflexes) were normal in the 13-week and 9-month toxicology studies with the exception of a 35 mg female in the 9-month toxicology study which exhibited neurological signs (transient muscle cramping and intermittent tremors). An EEG of this animal confirmed that muscle cramping during EEG recording was not a seizure and could have been related to arousal.	**Cardiovascular and Respiratory** None – no evidence of adverse effects on the cardiovascular or respiratory systems were identified in non-clinical studies, therefore, no adverse effects in humans are anticipated. **CNS** None – transient changes in lower spinal reflexes were non-adverse, and the effects in the high-dose group (35 mg) female (350 mg HED) provide an adequate safety margin.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Drug-drug interactions In vitro studies with cryopreserved human primary hepatocytes indicate that tofersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism and should not compete with other drugs for this metabolic pathway. Tofersen is highly bound to mouse and human plasma proteins at clinically relevant or higher plasma concentrations (0.1 and 30 µg/mL), which limits glomerular filtration and reduces the urinary excretion and renal clearance of the drug. However, the protein binding in plasma for this class of ASOs is relatively weak and the binding sites for these types of hydrophilic drugs differ from the binding sites of low molecular weight hydrophobic drugs [Watanabe 2006]. Therefore, the likelihood of drug-drug interactions due to competition with the plasma protein binding is very low. Tofersen is not an in vitro substrate of BCRP and MDR1 efflux or MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters. Tofersen is also not an in vitro inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC and BCRP, BSEP and MDR1 transporters. Therefore, the likelihood of drug interactions due to competition or inhibition of these transporters is very low.	None – no drug-drug interaction potential has been observed.
Phototoxicity In the 13- and 9-month IT repeated dose toxicity study in cynomolgus monkeys, there were no observations of phototoxicity (erythema, pruritis, and edema).	None – no phototoxicity potential has been observed.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The evaluations of safety presented in this EU RMP (in support of the overall benefit-risk assessment of tofersen) focus on the review of integrated data from 2 clinical studies conducted in participants with SOD1-ALS:

- Study 233AS101 is a completed study comprising 3 parts: Part A (Phase 1/2; single ascending dose), Part B (Phase 1/2; multiple ascending dose), and Part C (pivotal Phase 3), from which substantial evidence of safety and efficacy was obtained.
- Study 233AS102 is a Phase 3, ongoing, open-label, long-term extension for participants who completed Study 233AS101.

Final data from Study 233AS101 and interim data from Study 233AS102 (cut-off date: 28 Feb 2023) have been pooled to inform the long-term benefit-risk profile of tofersen.

As of 28 Feb 2023, 166 participants received at least 1 dose of tofersen in the pooled safety dataset (Table 3). A further breakdown of these data by age group and sex (Table 4), dose (Table 5), and race (Table 6) is also provided (see 2.7.4 Summary of Clinical Safety).

Table 3: Study Drug Exposure by Duration – Safety Population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B, and C subjects) tofersen treated period	
	tofersen 100 mg (N = 72)	**placebo (N = 36)**	**tofersen 100 mg (N = 104)**	**Total tofersen 100 mg (N = 147)**	**Total tofersen all doses (N = 166)**
Total Duration of Exposure (weeks)					
≤ 12	2 (2.8)	0	4 (3.8)	4 (2.7)	13 (7.8)
> 12 to 24	5 (6.9)	1 (2.8)	7 (6.7)	9 (6.1)	12 (7.2)
> 24 to 36	65 (90.3)	35 (97.2)	9 (8.7)	11 (7.5)	14 (8.4)
> 36 to 48	0	0	4 (3.8)	7 (4.8)	8 (4.8)
> 48 to 60	0	0	2 (1.9)	3 (2.0)	2 (1.2)
> 60 to 72	0	0	3 (2.9)	3 (2.0)	4 (2.4)
> 72 to 84	0	0	3 (2.9)	3 (2.0)	3 (1.8)
> 84 to 96	0	0	7 (6.7)	7 (4.8)	8 (4.8)
> 96 to 108	0	0	6 (5.8)	7 (4.8)	7 (4.2)
> 108 to 120	0	0	3 (2.9)	7 (4.8)	3 (1.8)
> 120 to 132	0	0	8 (7.7)	8 (5.4)	9 (5.4)
> 132 to 144	0	0	3 (2.9)	3 (2.0)	4 (2.4)
> 144 to 156	0	0	7 (6.7)	8 (5.4)	7 (4.2)
> 156 to 168	0	0	9 (8.7)	9 (6.1)	10 (6.0)
> 168 to 180	0	0	7 (6.7)	8 (5.4)	8 (4.8)
>180 to 192	0	0	14 (13.5)	16 (10.9)	17 (10.2)
> 192 to 204	0	0	7 (6.7)	11 (7.5)	9 (5.4)
> 204 to 216	0	0	1 (1.0)	8 (5.4)	5 (3.0)
> 216 to 228	0	0	0	12 (8.2)	3 (1.8)
> 228 to 240	0	0	0	1 (0.7)	1 (0.6)

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B, and C subjects) tofersen treated period	
	tofersen 100 mg (N = 72)	**placebo (N = 36)**	**tofersen 100 mg (N = 104)**	**Total tofersen 100 mg (N = 147)**	**Total tofersen all doses (N = 166)**
> 240 to 252	0	0	0	2 (1.4)	4 (2.4)
> 252 to 264	0	0	0	0	1 (0.6)
> 264 to 276	0	0	0	0	4 (2.4)
> 276 to 288	0	0	0	0	5 (3.0)
> 288 to 300	0	0	0	0	3 (1.8)
> 300 to 312	0	0	0	0	1 (0.6)
> 312 to 324	0	0	0	0	1 (0.6)
≥ 24	65 (90.3)	35 (97.2)	93 (89.4)	135 (91.8)	142 (85.5)
≥ 52	0	0	80 (76.9)	116 (78.9)	119 (71.7)
≥ 76	0	0	74 (71.2)	109 (74.1)	112 (67.5)
≥ 104	0	0	61 (58.7)	95 (64.6)	97 (58.4)
Total Duration of Exposure (weeks)					
n	72	36	104	147	166
Mean (SD)	27.1 (4.16)	27.9 (2.33)	115.9 (62.48)	130.7 (69.58)	128.3 (85.20)
Median	28.1	28.1	125.6	148.4	131.7
Q1, Q3	27.9, 28.3	28.0, 28.3	59.4, 172.4	70.9, 189.0	40.1, 188.0
Min, Max	8, 34	17, 33	4, 205	4, 245	4, 316

NOTE 1: Duration of exposure (in weeks) = ((last date) - (date of first dose) + 1)/7. Missed doses are ignored, and last date stands for the last available visit date subjects stayed in each of 101 Parts A, B, and C, and the earliest date between last available date and interim cutoff date for 102. All gaps between 233AS101 EOS visit and 233AS102 screening visit are removed in this calculation.
NOTE 2: For categorical summaries, the percentages are calculated based on the total number of subjects in each pooled group.
Source: biib067/rmp/jun2023/t-ex-expos.sas Run Date: 13JUN2023

Table 4: Study Drug Exposure by Age Group and Gender – Safety Population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period				CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period		ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period			
	tofersen 100 mg (N = 72)		placebo (N = 36)		tofersen 100 mg (N = 104)		Total tofersen 100 mg (N = 147)		Total tofersen all doses (N = 166)	
		Subject years		Subject years		Subject years		Subject years		Subject years
Age categories (years), n (%)										
18-< 35	10 (13.9)	5.17	2 (5.6)	1.02	11 (10.6)	25.33	15 (10.2)	39.22	19 (11.4)	43.00
35-< 50	32 (44.4)	17.02	15 (41.7)	8.10	44 (42.3)	106.61	59 (40.1)	155.22	67 (40.4)	173.88
50-< 65	21 (29.2)	10.78	14 (38.9)	7.33	34 (32.7)	74.12	53 (36.1)	137.71	58 (34.9)	148.87
65-< 75	8 (11.1)	3.94	5 (13.9)	2.79	14 (13.5)	25.41	18 (12.2)	33.26	20 (12.0)	38.19
≥ 75	1 (1.4)	0.46	0		1 (1.0)	0.46	2 (1.4)	3.41	2 (1.2)	4.89
Age (years)										
n	72		36		104		147		166	
Mean (SD)	48.1 (12.64)		51.2 (11.57)		49.5 (12.31)		49.8 (12.00)		49.2 (11.97)	
Median	47.5		51.5		48.5		49.0		49.0	
Q1, Q3	39.0, 57.0		44.5, 58.5		40.0, 58.0		41.0, 58.0		41.0, 57.0	
Min, Max	23, 78		28, 73		23, 78		23, 78		21, 78	
Sex										
n	72 (100)		36 (100)		104 (100)		147 (100)		166 (100)	
Male	43 (59.7)		19 (52.8)		60 (57.7)		82 (55.8)		91 (54.8)	
Female	29 (40.3)		17 (47.2)		44 (42.3)		65 (44.2)		75 (45.2)	

NOTE1: For categorical summaries, the percentages are calculated based on the total number of subjects in each pooled group.
NOTE 2: The subject years present the total entire follow-up time among the subjects in the analysis population, which is calculated as the sum of the time from the first dose until the last day of each subject divided by 365.25.
Source: biib067/rmp/jun2023/t-subyrs-byage.sas Run Date: 13JUN2023
Source: biib067/rmp/jun2023/t-demog-gen.sas Run Date: 13JUN2023

Table 5: Study Drug Exposure by Dose – Safety Population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B, and C subjects) tofersen treated period	
	tofersen 100 mg (N = 72)	placebo (N = 36)	tofersen 100 mg (N = 104)	Total tofersen 100 mg (N = 147)	Total tofersen all doses (N = 166)
Number of dose (<100 mg) received per subject					
1-5	NA	NA	NA	NA	22 (13.3)
6-10	NA	NA	NA	NA	4 (2.4)
11-15	NA	NA	NA	NA	12 (7.2)
16-20	NA	NA	NA	NA	12 (7.2)
21-25	NA	NA	NA	NA	2 (1.2)
Number of dose (100 mg) received per subject					
1-5	6 (8.3)	NA	8 (7.7)	12 (8.2)	12 (7.2)
6-10	66 (91.7)	NA	16 (15.4)	19 (12.9)	19 (11.4)
11-15	0	NA	5 (4.8)	7 (4.8)	7 (4.2)
16-20	0	NA	6 (5.8)	6 (4.1)	6 (3.6)
21-25	0	NA	9 (8.7)	12 (8.2)	12 (7.2)
26-30	0	NA	8 (7.7)	10 (6.8)	10 (6.0)
31-35	0	NA	11 (10.6)	15 (10.2)	15 (9.0)
36-40	0	NA	9 (8.7)	9 (6.1)	9 (5.4)
41-45	0	NA	15 (14.4)	19 (12.9)	19 (11.4)
46-50	0	NA	15 (14.4)	18 (12.2)	18 (10.8)
51-55	0	NA	2 (1.9)	12 (8.2)	12 (7.2)
56-60	0	NA	0	7 (4.8)	7 (4.2)
61-65	0	NA	0	1 (0.7)	1 (0.6)
n	72	NA	104	147	147

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B, and C subjects) tofersen treated period	
	tofersen 100 mg (N = 72)	**placebo (N = 36)**	**tofersen 100 mg (N = 104)**	**Total tofersen 100 mg (N = 147)**	**Total tofersen all doses (N = 166)**
Mean (SD)	7.4 (1.25)		28.2 (15.54)	30.9 (17.03)	30.9 (17.03)
Median	8.0		31.0	33.0	33.0
Q1, Q3	7.0, 8.0		13.5, 42.0	14.0, 46.0	14.0, 46.0
Min, Max	3, 8		2, 52	2, 61	2, 61
Total daily dose received per subject (mg)					
n	72	36	104	147	166
Mean (SD)	4.0 (0.47)	0.0 (0.00)	3.6 (0.81)	3.7 (0.98)	3.1 (1.14)
Median	4.1	0.0	3.6	3.6	3.4
Q1, Q3	4.0, 4.1	0.0, 0.0	3.4, 3.7	3.4, 3.8	2.7, 3.7
Min, Max	2, 5	0, 0	1, 8	1, 11	0, 8
Cumulative dose received (mg)					
n	72	36	104	147	166
Mean (SD)	743.1 (125.40)	0.0 (0.00)	2817.3 (1553.98)	3094.6 (1703.05)	2861.1 (1939.29)
Median	800.0	0.0	3100.0	3300.0	3100.0
Q1, Q3	700.0, 800.0	0.0, 0.0	1350.0, 4200.0	1400.0, 4600.0	900.0, 4500.0
Min, Max	300, 800	0, 0	200, 5200	200, 6100	10, 6460

NOTE 1: Duration of exposure (in weeks) = ((last date) - (date of first dose) + 1)/7. Missed doses are ignored, and last date stands for the last available visit date subjects stayed in each of 101 Parts A, B, and C, and the earliest date between last available date and interim cutoff date for 102. All gaps between 233AS101 EOS visit and 233AS102 screening visit are removed in this calculation.
NOTE 2: For categorical summaries, the percentages are calculated based on the total number of subjects in each pooled group.
Source: biib067/iss/iss-bla4/t-ex-expos.sas Data Cutoff: 28FEB2023 Run Date: 24MAY2023

Table 6: Study Drug Exposure by Race Group – Safety Population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period				CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period		ABCL: Overall 233AS101 and 233AS102 (Parts A, B, and C subjects) tofersen treated period			
	tofersen 100 mg (N = 72)		placebo (N = 36)		tofersen 100 mg (N = 104)		Total tofersen 100 mg (N = 147)		Total tofersen all doses (N = 166)	
	n (%)	Subject years	n (%)	Subject years	n (%)	Subject years	n (%)	Subject years	n (%)	Subject years
Race										
American Indian or Alaska Native	0		0		0		0		0	
Asian	5 (6.9)	2.52	4 (11.1)	2.16	9 (8.7)	23.64	10 (6.8)	25.82	10 (6.0)	26.59
Black or African American	1 (1.4)	0.54	0		1 (1.0)	3.62	1 (0.7)	3.62	1 (0.6)	3.62
Native Hawaiian or Other Pacific Islander	0		0		0		1 (0.7)	4.29	1 (0.6)	5.13
White	44 (61.1)	22.65	25 (69.4)	13.43	66 (63.5)	129.52	88 (59.9)	189.75	102 (61.4)	211.89
Not Reported	21 (29.2)	11.11	7 (19.4)	3.65	27 (26.0)	72.08	45 (30.6)	138.37	50 (30.1)	153.85
Other	1 (1.4)	0.54	0		1 (1.0)	3.05	2 (1.4)	6.97	2 (1.2)	7.74

NOTE 1: For categorical summaries, the percentages are calculated based on the total number of subjects in each pooled group.
NOTE 2: The subject years present the total entire follow-up time among the subjects in the analysis population, which is calculated as the sum of the time from the first dose until the last day of each subject divided by 365.25.
Source: biib067/rmp/jun2023/t-subyrs-byrace.sas Run Date: 13JUN2023

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The tofersen clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (e.g., to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (e.g., in order to protect trial participants from potential risks associated with investigational product administration) or were good clinical practice (GCP) related (e.g., to ensure that proper follow-up was possible).

A review of the key exclusion criteria in pivotal studies, and an assessment of their relevance to be considered as areas of missing information are presented in Table 7.

Table 7: Discussion of key exclusion criteria in relation to the assessment of missing information

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of or positive test result for human immunodeficiency virus	To avoid factors that may confound interpretation of data.	No	The exclusion was not due to a specific safety concern with tofersen.
History of or positive test result for hepatitis C virus antibody or hepatitis B virus	To avoid factors that may confound interpretation of data.	No	The exclusion was not due to a specific safety concern with tofersen.
Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period	To avoid factors that may confound interpretation of data.	No	The exclusion was not due to a specific safety concern with tofersen.
Current or recent use, or anticipated need, in the opinion of the Investigator, of copper (II) (diacetyl-bis (N4-methylthiosemicarbazone)) or pyrimethamine	To avoid factors that may confound interpretation of data.	No	The exclusion was not due to a specific safety concern with tofersen. No drug-drug interactions are anticipated based on the in vitro studies.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy	To avoid factors that may confound interpretation of data.	No	The exclusion was not due to a specific safety concern with tofersen.
Female participants who are pregnant or currently breastfeeding	It is not known if tofersen will have any effect on an unborn baby. In addition, it is unknown if tofersen is secreted in human milk.	No	The exclusion was not due to a specific safety concern with tofersen.
Significant cognitive impairment, clinical dementia, or unstable psychiatric illness	To identify individuals physically and mentally able to complete the rigors of a clinical study.	No	The exclusion was not due to a specific safety concern with tofersen.
History of allergies to a broad range of anesthetics	To identify individuals who could undergo LP with anesthetics.	No	The exclusion was not due to a specific safety concern with tofersen.
Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally	To identify individuals who could undergo LP.	No	Participants enrolled in the study with the normal partial thromboplastin time, prothrombin time, international normalized ratio, and platelet count.
Anticipated need for administration of any antiplatelet or anticoagulant medication that cannot be safely held before and/or after an LP	To identify individuals who could undergo LP.	No	The exclusion was not due to a specific safety concern with tofersen.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter	To ensure appropriate distribution of tofersen in the CNS.	No	This exclusion criterion is related to the operational aspects of the study and was not due to a specific safety concern with tofersen.
Clinically significant abnormalities in hematology or clinical chemistry parameters	To identify individuals physically and mentally able to complete the rigors of a clinical study.	No	The exclusion was not due to a specific safety concern with tofersen.
Clinically significant 12-lead ECG abnormalities	To identify individuals physically and mentally able to complete the rigors of a clinical study.	No	The exclusion was not due to a specific safety concern with tofersen.
History of drug abuse/alcoholism within 6 months before enrollment	To avoid factors that may confound interpretation of data,	No	The exclusion was not due to a specific safety concern with tofersen.
Prior or current treatment with small interfering RNA (siRNA), stem cell therapy, or gene therapy	To avoid factors that may confound interpretation of data	No	The exclusion was not due to a specific safety concern with tofersen.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 8.

Table 8: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Elderly patients	• 65 - 74 years: 20/166 (12.0%) • ≥75 years: 2/166 (1.2%)
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Hepatic impairment	Tofersen has not been studied in participants with hepatic impairment. Given the known PK of tofersen and the results of the clinical and non-clinical studies to date, hepatic effects are not anticipated.
Patients with relevant comorbidities: • Renal impairment	Tofersen has not been studied in participants with renal impairment. Given the known PK of tofersen and the results of the clinical and non-clinical studies to date, renal effects are not anticipated.
Patients with relevant comorbidities: • Cardiovascular impairment	Tofersen has not been studied in participants with cardiovascular impairment. Given the known PK of tofersen and the results of the clinical and non-clinical studies to date, cardiovascular effects are not anticipated.
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development programme.
Patients with relevant different ethnic origin	• Asian 10/166 (6.0%) • Black or African American 1/166 (0.6%) • Native Hawaiian or Other Pacific Islander 1/166 (0.6%) • White 102/166 (61.4%) • Not reported 50/166 (30.1%) • Other 2/166 (1.2%)
Subpopulations carrying relevant genetic polymorphisms	Other than a mutation in the SOD1 gene, which is a characteristic of the indication and target population, no other genetic polymorphisms were included in the clinical development programme.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

The US Food and Drug Administration (FDA) approved QALSODY™ (tofersen) 100 mg/15 mL injection on 25 Apr 2023 under the accelerated approval pathway for the indication of treatment of ALS in adults who have a mutation in the SOD1 gene. There is no post-authorisation data available as of 15 Jun 2023 (data lock point [DLP]).

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Tofersen, an ASO, does not cross the blood-brain-barrier; thus, there is no possibility of drug abuse potentially related to accidental or intentional intravenous or SC dose administration. Based on its reducing levels of the substrate for protein translation, tofersen is not likely to bind to receptors known to be involved in drug abuse. Because of the different targeted mechanism of action, no potential for drug abuse is anticipated, and no formal studies were conducted to examine drug abuse. In repeat dose toxicology studies in monkeys, neurobehavioural assessments were within normal limits, consistent with the lack of abuse potential.

Medical review of relevant AEs terms in the integrated dataset of tofersen (data cut: 28 Feb 2023) was performed to identify AEs potentially related to drug abuse: confusional state (2), mood swings (1), hallucination (1), agitation (1), and mental status changes (1). The frequencies of these terms were low (0.6% - 1.2%) and none of them were assessed as related to tofersen by the Investigator.

Thus, tofersen has a low potential for abuse and should not be considered a controlled substance.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable. This is the first EU RMP for tofersen.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

An identified risk is an undesirable clinical outcome for which there is sufficient scientific evidence of a causal association with the medicinal product. A potential risk is defined as an undesirable clinical outcome for which there is scientific evidence to suspect the possibility of a relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.

All identified and potential risks are followed within the framework of Biogen pharmacovigilance processes.

A summary of the rationale for not including identified or potential risks relevant for inclusion in the list of safety concerns (at the time of the initial tofersen marketing authorisation application) is presented below:

No potential risks have been classified for tofersen.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**
  - Identified risk(s):

    Aseptic meningitis: AE reports relating to aseptic meningitis have been observed in clinical study participants receiving tofersen. These events were not observed in participants receiving placebo. Most events were non-serious, however, 2 serious adverse events (SAEs) were reported and 1 of them led to discontinuation of tofersen after which the event resolved. The CSF profile in aseptic meningitis is frequently associated with pleocytosis and shifts from low or normal to high in CSF WBC and CSF protein were observed in the majority of participants receiving tofersen. Many of these abnormalities were not reported as AEs by the Investigators. In the non-clinical data, changes in CSF, total protein, and WBC were observed in animals receiving tofersen in the 9-month NHP study. These changes were not observed in the control animals. The preclinical findings, elevations of CSF WBC and CSF protein seen in the clinical development program, temporal relationship with tofersen exposure, and the resolution of the SAE of chemical meningitis with tofersen discontinuation all support a likely causal relationship between the events of aseptic meningitis and tofersen treatment. Drug-induced meningitis is generally monitorable, transient, and does not lead to permanent sequelae.
- **Other reasons for considering the risks not important:**

– Potential risk(s):

- Thrombocytopenia and Coagulation abnormalities: Thrombocytopenia and coagulation abnormalities have been observed after administration of some subcutaneously and intravenously administered ASOs. Whilst several different potential mechanisms for thrombocytopenic episodes have been proposed in the literature, there is no consensus of opinion on the mechanism causing such events, and it is proposed that these might differ between ASO treatments, pre-clinical test species, and in mild versus severe events observed during clinical use [Frazier 2014]. There were no AE reports relating to thrombocytopenia in the tofersen clinical studies. There were a total of 5 AEs related to coagulation studies [activated partial thromboplastin time prolonged (3), prothrombin time prolonged (1), and coagulation test abnormal (1)], of which none were treatment-limiting or serious. Based on class effects data, thrombocytopenia and coagulation abnormalities will be closely monitored.
- Renal toxicity: Renal toxicity has been observed after administration of some subcutaneously and intravenously administered ASOs. Data obtained in the pre-clinical setting indicate that most renal toxicities with ASOs are generally considered to be due to accumulation of oligonucleotides within lysosomes of the proximal tubule, resulting in physiologic perturbation of tubular absorptive capacity and in some cases, increased tubular proteinuria [Henry 2008]. Five events of acute kidney injury (Preferred Term [PT]) have been reported in the clinical studies overall, of which none was considered treatment-related. Four of them were nonserious and 1 was serious. Based on class effects data, renal toxicity will be closely monitored.
- Hydrocephalus: Hydrocephalus also has been reported with nusinersen, another IT administered ASO, in the post marketing setting. The proposed mechanisms of hydrocephalus include reduced absorption or impaired flow of CSF [Beni-Adani 2006]. There were no AE reports relating to hydrocephalus observed in the tofersen clinical studies. Based on these other reports, hydrocephalus will be closely monitored.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The rationale for considering the remaining risks relevant for inclusion in the current list of safety concerns at the time of initial MAA is presented in Table 9.

Table 9: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk category	Risk-benefit impact
Important Identified Risk: • Myelitis and/or radiculitis	Myelitis is a rare and clinically serious event with potentially serious outcomes. Symptoms of myelitis can overlap with ALS disease progression. When steroid treatment is provided, myelitis generally improves. In NHP studies of tofersen, there was evidence of mononuclear cell infiltrates in the meninges, perivacular cuffs, and nerve roots. No evidence of myelitis was seen in the non-clinical toxicology studies of tofersen. Based on the data from Studies 233AS101 and 233AS102 as of 28 Feb 2023, 6 participants receiving tofersen have experienced SAEs of myelitis and/or radiculitis (PTs Neurosarcoidosis, Myelitis (2), Myelitis transverse, Radiculopathy, and Lumbar radiculopathy). Two cases of myelitis were asymptomatic, and the other 2 cases of myelitis and 2 cases of radiculitis were symptomatic. All events resolved. The investigator considered 5 of the 6 events related to treatment. In 4 of the 6 events, treatment remained ongoing, and in the other 2 events treatment was discontinued. There is likely a causal relationship between these events and tofersen treatment.

Risk category	Risk-benefit impact
Important Identified Risk: • Increased intracranial pressure and/or papilloedema#	Papilloedema has been identified as a rare symptom of ALS presenting as a result of respiratory insufficiency. Ophthalmic examinations were conducted in the 13-week and 9-month NHP studies, and no abnormalities were noted. Reports of increased intracranial pressure and/or papilloedema have been observed in participants receiving treatment with tofersen, but not in placebo group. Based on the data from Studies 233AS101 and 233AS102 as of 28 Feb 2023, 4 SAEs in 4 participants were reported (PTs Intracranial pressure increased (3) and Papilloedema). All of the events were considered related to tofersen by the investigator. Elevated CSF protein and CSF WBC were observed in all 4 participants. CSF opening pressure was elevated in 3 participants and within the normal range in 1 participant. The confounders (weight gain and fourth ventricular mass) were present in 2 participants, respectively. Increased intracranial pressure and/or papilloedema has appeared at greater frequency than expected, and the hypothetical mechanism is related to CNS inflammation. There is temporal relationship with tofersen. As untreated papilloedema could lead to vision loss, it was assessed as an important identified risk.
Important Potential Risk	There are no important potential risks for tofersen.
Missing Information: • None	

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

Not applicable for initial marketing authorisation application submission.

SVII.2.2 Reclassification of existing safety concerns

Not applicable for initial marketing authorisation application submission.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks

Important Identified Risk: Myelitis and or radiculitis

Relevant MedDRA terms: HLT Spinal cord and nerve root disorders NEC; HLT Myelitis (incl infective); HLT Lumbar spinal cord and nerve root disorders.

Potential mechanisms

Immunostimulatory and proinflammatory effects have been associated with ASOs in multiple preclinical species. In rodents, activation of toll-like receptor 9 by ASOs can result in cytokine release, lymphoid hyperplasia, and lymphohistiocytic cell infiltrates in various organs. In monkeys, ASO-mediated inflammation results from complement activation and similarly can cause lymphoid hyperplasia and lymphohistiocytic infiltrates.

Evidence source(s) and strength of evidence

Events consistent with inflammation in the CNS, including myelitis and radiculitis, have occurred in participants receiving tofersen in clinical trials.

Whilst the mechanisms of these inflammatory events and the relationship between the laboratory abnormalities and these events are not well understood, myelitis in the general population is an uncommon clinical diagnosis. Therefore, the occurrence of these events in a relatively small population in the study is unusual and a possible causal relationship with tofersen cannot be excluded.

Characterisation of the risk

Four of 147 participants (2.7%) who received 100 mg tofersen in Study 233AS101 Part C or Study 233AS102 reported SAEs of myelitis (PTs Myelitis, Myelitis transverse, and Neurosarcoidosis), and 2 of 147 participants (1.4%) reported SAEs of radiculitis (PTs Radiculopathy and Lumbar radiculopathy).

Six participants receiving tofersen experienced SAEs of myelitis or radiculitis (PTs Neurosarcoidosis, Myelitis (2), Myelitis transverse, Radiculopathy, and Lumbar radiculopathy). All events resolved. The investigator considered 5 of the 6 events as related to treatment. In 4 of the 6 events, treatment remained ongoing, and in the other 2 cases treatment was discontinued. There is likely a causal relationship between these events and tofersen treatment.

Risk factors and risk groups

There are no known risk factors for the development of myelitis and/or radiculitis in tofersen-treated participants.

Preventability

The preventability of myelitis and/or radiculitis in participants treated with tofersen is currently unknown; however, symptoms of myelitis and/or radiculitis are clinically monitorable, and when appropriate, can be confirmed with magnetic resonance imaging. If symptoms occur, myelitis and/or radiculitis can be managed with standard of care.

Impact on the risk-benefit balance of the product

Tofersen is under evaluation for SOD1-ALS, a genetic subset of the orphan indication of ALS, a serious and rare life-limiting neurodegenerative disease with limited approved treatment options. Tofersen administration leads to early lowering of total CSF SOD1, an indirect marker of target engagement. These reductions are followed by clear reductions in neurofilament, a biomarker found to correlate with the rate of disease progression, as measured by the rate of decline on ALSFRS-R from symptom onset to the time of the neurofilament measurement [Brodovitch 2021; De Schaepdryver 2020; Gille 2019]. Thus, these neurofilament light chain reductions are reasonably likely to predict that people with SOD1-ALS who take tofersen are likely to have a slower functional decline and live longer than those who do not. Consistent with this hypothesis, these reductions in neuronal damage/injury led to demonstrable slowing of clinical disease progression with longer follow-up.

Whilst severe neurological conditions (including myelitis and/or radiculitis) if not recognized or managed appropriately may result in persistent or significant disability or incapacity, based on the information received to date, events of myelitis and/or radiculitis in tofersen-treated participants have been reversible. Given the considerable unmet medical need of the proposed patient population, the benefit-risk balance of tofersen treatment in the proposed indication remains positive.

Public health impact

Events of myelitis and/or radiculitis in tofersen-treated participants have been reported in a small number of cases and are considered to be manageable. Therefore, the public health impact is considered to be low.

Important Identified Risk: Increased intracranial pressure and/or papilloedema

Relevant MedDRA terms: SMQ Optic nerve disorders (Broad); PTs Intracranial pressure increased; CSF pressure increased.

Potential mechanisms

Papilloedema is optic disc swelling due to high intracranial pressure. Possible conditions causing papilloedema include intracerebral mass lesions, cerebral hemorrhage, head trauma, meningitis, hydrocephalus, and spinal cord lesions. Papilloedema from various causes of intracranial hypertension may develop at any age, in either sex, and in any racial or ethnic group. Papilloedema has been identified as a rare symptom of ALS presenting as a result of respiratory insufficiency [Leigh 2003; Wijesekera and Leigh 2009].

Evidence source(s) and strength of evidence

Reports of increased intracranial pressure and/or papilloedema have been observed in participants receiving treatment with tofersen, but not in the placebo group. The hypothetical mechanism is related to CNS inflammation. There is a temporal relationship with tofersen. Untreated, chronic papilloedema can lead to progressive visual field loss in the form of visual field defects, nerve fiber bundle defects, and even blindness [Pearson 1991; Wall 1983].

Characterization of the risk

The incidence of papilloedema in the general population is reported as 0.9 per 100,000 in the US and 1.56 per 100,000 in the United Kingdom [Rigi 2015]. No literature references were found reporting the frequency of papilloedema in ALS.

SAEs of increased intracranial pressure and/or papilloedema have been reported in 4 participants (2.7%) in the tofersen clinical development programme based on the data readout of Study 233AS101 and the open-label extension, Study 233AS102.

Based on the data from Studies 233AS101 and 233AS102, 4 SAEs (PTs Intracranial pressure increased [3] and Papilloedema [1]) in 4 participants were reported. All of the events were considered related to tofersen by the investigator. Elevated CSF protein and CSF WBC were observed in all 4 participants. CSF opening pressure was elevated in 3 participants and within the normal range in 1 participant. The confounders (weight gain and fourth ventricular mass) were present in 2 participants, respectively.

Risk factors and risk groups

All of the increased intracranial pressure and/or papilloedema events occurred in participants receiving 100 mg tofersen. None of them were from lower dosage cohorts. There were no patient-level risk factors that have been identified.

Preventability

The preventability of increased intracranial pressure and/or papilloedema in patients treated with tofersen is monitoring for symptoms suggestive of increased intracranial pressure. The symptoms of papilloedema are clinically monitorable, and it can be confirmed with OCT. If symptoms occur, increased intracranial pressure and/or papilloedema can be managed with standard of care, including treatment of the underlying disorder and/or decreasing intracranial pressure.

Impact on the risk-benefit balance of the product

Tofersen is under evaluation for SOD1-ALS, a genetic subset of the orphan indication of ALS, a serious and rare life-limiting neurodegenerative disease with limited approved treatment options. Tofersen has shown demonstrable benefits in patients for whom a considerable unmet medical need exists.

However, untreated, chronic increased intracranial pressure and/or papilloedema can lead to progressive visual field loss in the form of visual field defects, nerve fiber bundle defects, and even blindness [Pearson 1991; Wall 1983]. For specific clinical monitoring information for healthcare professionals, language was included in the Sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and in Sections 2 and 4 of the Patient Information Leaflet (PIL).

Given the considerable unmet medical need of the proposed patient population, the benefit-risk balance of tofersen treatment in the proposed indication remains positive.

Public health impact

Events of increased intracranial pressure and/or papilloedema in tofersen-treated participants have been reported in small number of cases and are considered to be manageable with standard of care. Therefore, the public health impact is considered to be low.

SVII.3.2 Presentation of the missing information

No missing information was identified.

PART II: MODULE SVIII – SUMMARY OF SAFETY CONCERNS

The tofersen safety specification includes the following important identified risks, important potential risks, and areas of missing information (Table 10).

Table 10: Summary of safety concerns

Important identified risks	• Myelitis and/or radiculitis • Increased intracranial pressure and/or papilloedema
Important potential risks	• None
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III. 1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed in order to provide further characterisation data for specific safety concerns:

Specific adverse reaction follow-up questionnaires for important identified risks of "Myelitis and/or radiculitis" and "Increased intracranial pressure and/or papilloedema": A targeted DCT for case reports of myelitis and/or radiculitis and increased intracranial pressure and/or papilloedema aims to collect detailed information relating to suspected events in a standardized fashion, to enable timely and robust collection of data and thereby optimize risk evaluation.

III. 2 Additional pharmacovigilance activities

Study name and title, including study design and population: Study 233AS102, An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation: This is a multicenter, long-term extension study of BIIB067. The study includes a 29-day Loading Dose Period, during which participants will receive 3 IT injections approximately every 2 weeks (on Days 1, 15, and 29). Participants who have completed Parts A or B of Study 233AS101 will have an unblinded Loading Dose Period, during which they will receive 3 doses of BIIB067. Participants who have completed Part C of Study 233AS101 will have a blinded Loading Dose Period, during which participants who received BIIB067 in Study 233AS101 will receive 2 doses of BIIB067, on Days 1 and 29, and placebo on Day 15, and participants who received placebo in Study 233AS101 will receive 3 doses of BIIB067, on Days 1, 15, and 29. For all participants, the Loading Dose Period will be followed by an unblinded maintenance dose portion of the study, during which participants will receive up to 90 doses of BIIB067, approximately every 4 weeks.

Rationale and study objectives: This study is an extension of Study 233AS101. The extension study will allow collection of PK and PD data during dose interruption and resumption, providing information on the dynamic behavior of the system. This information will supplement PK and PD data collected in Study 233AS101 for the purpose of creating models of the exposure-response relationship. These models will be used to simulate and assess the PD profiles under various dosing regimens and will inform the dose levels and frequencies to be tested in future studies. The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in participants with SOD1-ALS. The secondary objective is to evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and confirmed SOD1 mutation.

Milestones:

– Final Study Report: 30 September 2025

Study name and title, including study design and population: Study 233AS401, An observational registry-based Study to evaluate the long-term safety of tofersen in patients with *SOD1*-ALS (RMP Annex 3).

Rationale and study objectives:

Primary objectives:

- Describe demographic and clinical characteristics of SOD1-ALS participants at baseline, and stratified by tofersen treatment status
- Estimate the incidence of SAEs among all participants and stratified by tofersen treatment status, including serious neurologic events previously reported in clinical trial participants (e.g., myelitis, radiculitis, aseptic meningitis, increased intracranial pressure and/or papilloedema)

Secondary objectives :

- Disease progression measured by the ALSFRS-R as rate of change over time in total scores
- Occurrence of relevant clinical outcomes including permanent ventilation and feeding tube placement as well as changes in pulmonary function measured by FVC and SVC
- Variant-specific survival
- Reports of new comorbid conditions, pregnancy and pregnancy outcome, and hospitalizations (including reason for hospitalization) not reported as SAEs
- Treatment discontinuation

Milestones:

– Protocol submission: Within 6 months after the European Commission (EC) decision on this Marketing Authorisation (MA).

– Interim report*: 12 months after the Agency's approval of the final protocol and annually thereafter.

– Continued Evaluation: With annual reassessment

*Interim reports will be delivered annually with the submission of a standalone procedure

III. 3 Summary table of additional pharmacovigilance activities

A summary of the studies included in the pharmacovigilance plan are summarised in Table 11.

Table 11: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
<u>Category 1</u> – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
• None	• None	• None	• None	• None
<u>Category 2</u> – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
233AS401 An observational registry-based study to evaluate the long-term safety of tofersen in patients with SOD1 ALS **<u>Status:</u>** Planned	*<u>Primary Objective:</u>* • Describe demographic and clinical characteristics of SOD1-ALS participants at baseline, and stratified by tofersen treatment status • Estimate the incidence of SAEs among all participants and stratified by tofersen treatment status, including serious neurologic events previously reported in clinical trial participants (e.g., myelitis, radiculitis, aseptic meningitis, increased intracranial pressure and/or papilloedema) *<u>Secondary Objectives</u>:* • Disease progression measured by the ALSFRS-	• Myelitis and or radiculitis • Increased intracranial pressure and/or papilloedema	• Protocol submission • Interim progress report* • Continued evaluation	Within 6 months after the EC decision on this MAA 12 months after the Agency's approval of the final protocol and annually thereafter. With annual reassessment

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	R as rate of change over time in total scores • Occurrence of relevant clinical outcomes including permanent ventilation and feeding tube placement as well as changes in pulmonary function measured by FVC and SVC • Variant-specific survival • Reports of new comorbid conditions, pregnancy and pregnancy outcome, and hospitalizations (including reason for hospitalization) not reported as SAEs • Treatment discontinuation			
233AS102 An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation	*Primary Objective:* • Evaluate the long-term safety and tolerability of BIIB067 in participants with SOD1-ALS. *Secondary Objectives:* • Evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and confirmed SOD1 mutation.	• Myelitis and or radiculitis • Increased intracranial pressure and/or papilloedema	• Final report	30 September 2025

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Status: Ongoing				
Yearly updates on any new information concerning safety and efficacy of tofersen **Status:** Planned	In order to ensure adequate monitoring of safety and efficacy of Tofersen in the treatment of patients with SOD1-ALS, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tofersen.	• Any new information concerning safety and efficacy of tofersen	Annual report	Annually (with annual reassessment)
Category 3 – **Required additional pharmacovigilance activities**				
• None	• None	• None	• None	• None

*Interim reports will be delivered annually with the submission of a standalone procedure

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

A summary of the studies included in the post-authorisation efficacy studies plan are summarised in Table 12.

Table 12: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies that are conditions of the marketing authorisation				
• None	• None	• None	• None	• None
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
233AS303 A phase 3 randomized, placebo-controlled study in clinically presymptomatic adults with a confirmed SOD1 mutation **Status:** Ongoing	To investigate if initiation of tofersen in presymptomatic SOD1-ALS patients can delay or prevent emergence of clinically manifest ALS.	Long-term efficacy and safety Optimum timing of tofersen initiation	Last Patient Out	31 December 2027[a]
			Final report	31 December 2028
Integrated Analysis of Variant-Specific Survival **Status:** Planned	Descriptive analyses of disease duration (survival) by *SOD1* variant-type in tofersen-treated (Studies 101/102; disease registries vs. untreated patients (disease registries, natural history datasets/literature) Combined data from: • Study 101 (A, B, C) • Study 102 • Disease registries (ALS/MND-NHC and Precision-ALS) • Natural history datasets/literature	Long-term efficacy/effectiveness (survival)	Initial analysis and output	30 June 2027[b]

Error! Reference source not found. Dependent on enrollment timeline for Part B

[b] To be confirmed pending finalization of registry collaboration agreements and consolidation of available natural history dataset

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V: 1 Routine risk minimisation measures

A description of the routine risk minimisation measures per safety concern are discussed in Table 13.

Table 13: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Myelitis and/or radiculitis	***Routine risk communication:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Monitoring for symptoms suggestive of myelitis and/or radiculitis. ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Prescription only medicine
Increased intracranial pressure and/or papilloedema	***Routine risk communication:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Monitoring for symptoms suggestive of increased intracranial pressure and/or papilloedema. ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Prescription only medicine
Important Potential Risks	
None	None
Missing Information	
None	None

V. 2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 14: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Myelitis and/or radiculitis	***Routine risk minimisation measures:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4. • Legal status: Prescription only medicine. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • DCT for collection of additional information relating to reported events of myelitis and/or radiculitis ***Additional pharmacovigilance activities:*** • Study 233AS102 • Study 233AS401
Increased intracranial pressure and/or papilloedema	***Routine risk minimization measures:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4. • Legal status: Prescription only medicine ***Additional risk minimization measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • DCT for collection of additional information relating to reported events of papilloedema ***Additional pharmacovigilance activities:*** • Study 233AS102 • Study 233AS401
Important potential risks		
None	None	None
Missing information		
None	None	None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR QALSODY (TOFERSEN)

Summary of Risk Management Plan for Qalsody (tofersen)

This is a summary of the risk management plan (RMP) for Qalsody. The RMP details important risks of Qalsody, how these risks can be minimised, and how more information will be obtained about Qalsody's risks and uncertainties (missing information).

Qalsody's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Qalsody should be used.

This summary of the RMP for Qalsody should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Qalsody's RMP.

I. The medicine and what it is used for

Qalsody is authorised for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (see the SmPC for the full indication). It contains tofersen as the active substance, and it is given solution for intrathecal injection (one vial contains 100 mg tofersen).

Further information about the evaluation of Qalsody's benefits can be found in Qalsody's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Qalsody, together with measures to minimise such risks and the proposed studies for learning more about Qalsody's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of Qalsody is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Qalsody are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Qalsody. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine):

List of important risks and missing information	
Important identified risks	• Myelitis and/or radiculitis • Increased intracranial pressure and/or papilloedema
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risk(s)	
Myelitis and/or radiculitis	
Evidence for linking the risk to the medicine	Events consistent with inflammation in the central nervous system, including myelitis and radiculitis, have occurred in participants receiving tofersen in clinical trials. Whilst the mechanisms of these inflammatory events and the relationship between the laboratory abnormalities and these events are not well understood, myelitis in the general population is an uncommon clinical diagnosis. Therefore, the occurrence of these events in a relatively small population in the study is unusual and a possible causal relationship with tofersen cannot be excluded.
Risk factors and risk groups	There are no known risk factors for the development of myelitis and/or radiculitis in tofersen-treated participants.
Risk minimisation measures	***Routine risk minimisation measures:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4.

Important Identified Risk(s)	
	• Legal status: Prescription only medicine# ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 233AS102 • Study 233AS401 See Section II.C of this summary for an overview of the post-authorisation development plan.
Increased intracranial pressure and/or papilloedema	
Evidence for linking the risk to the medicine	Reports of increased intracranial pressure and/or papilloedema have been observed in participants receiving treatment with tofersen, but not in the placebo group. The hypothetical mechanism is related to CNS inflammation. There is a temporal relationship with tofersen. Untreated, chronic papilloedema can lead to progressive visual field loss in the form of visual field defects, nerve fiber bundle defects, and even blindness.
Risk factors and risk groups	All of the increased intracranial pressure and/or papilloedema events occurred in participants receiving 100 mg tofersen. None of them were from lower dosage cohorts. There were no patient-level risk factors that have been identified.
Risk minimisation measures	***Routine risk minimisation measures:*** • SmPC Sections 4.4 and 4.8 • PIL Sections 2 and 4 • Legal status: Prescription only medicine# ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 233AS102 • Study 233AS401 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk(s)
None

Missing Information
None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are specific obligations in the context of a marketing authorisation under exceptional circumstances:

233AS102: An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Purpose of the study: This study is an extension of Study 233AS101. The extension study will allow collection of PK and PD data during dose interruption and resumption, providing information on the dynamic behavior of the system. This information will supplement PK and PD data collected in Study 233AS101 for the purpose of creating models of the exposure-response relationship. These models will be used to simulate and assess the PD profiles under various dosing regimens and will inform the dose levels and frequencies to be tested in future studies. The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in participants with SOD1-ALS. The secondary objective is to evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and confirmed SOD1 mutation.

233AS401: An observational registry-based study to evaluate the long-term safety of tofersen in patients with SOD1-ALS.

Purpose of the study: The primary objectives of this study will be to describe demographic and clinical characteristics of SOD1-ALS patients at baseline and stratified by tofersen treatment status and estimate the incidence of SAEs among all participants and stratified by tofersen treatment status, including serious neurologic events previously reported in clinical trial participants (e.g., myelitis, radiculitis, aseptic meningitis, increased intracranial pressure and/or papilloedema).

233AS303 (ATLAS): A phase 3 randomized, placebo-controlled study in clinically presymptomatic adults with a confirmed SOD1 mutation.

Purpose of the study: This study is to investigate if initiation of tofersen in presymptomatic SOD1-ALS patients can delay or prevent emergence of clinically manifest ALS.

Integrated Analysis of Variant-Specific Survival

Purpose of the study: Descriptive analyses of disease duration (survival) by SOD1 variant-type in tofersen-treated (Studies 101/102; disease registries vs. untreated patients (disease registries, natural history datasets/literature)

Combined data from:

- Study 101 (A, B, C)
- Study 102
- Disease registries (ALS/MND-NHC and Precision-ALS)
- Natural history datasets/literature

II.C.2 Other studies in post-authorisation development plan

None.

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.